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Role of Inflammatory Cytokines and Adipokines in the Pathogenesis of Obesity-Related Diabetes

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ABSTRACT

Obesity-related type 2 diabetes (T2D) emerges from a chronic immuno-endocrine imbalance in which inflammatory cytokines and adipokines remodel insulin signaling, substrate partitioning, and β-cell resilience. Hypertrophic, hypoxic adipose tissue (AT) recruits and reprograms immune cells, driving secretion of tumor necrosis factor-α (TNF-α), interleukins (IL-1β, IL-6, IL-18), chemokines (e.g., CCL2/MCP-1), and alarmins that activate stress kinases (JNK/IKK), SOCS proteins, and the NLRP3 inflammasome. In parallel, the adipokine milieu shifts like adiponectin declines; leptin, resistin, RBP4, chemerin, and lipocalin-2 often rise, tilting systemic physiology toward insulin resistance (IR), dyslipidemia, and endothelial dysfunction. These signals converge across organs: in the liver, cytokine and lipid cues sustain gluconeogenesis and steatosis; in muscle, lipid-derived metabolites and cytokines blunt GLUT4 translocation; in islets, IL-1β, TNF-α, and leptin resistance impair insulin secretion and promote β-cell stress. Endocrine and paracrine crosstalk is bidirectional; adipokines modulate immune tone, while immune mediators reshape adipocyte function and adipogenesis. Therapeutically, weight loss, physical activity, and metabolic surgery attenuate metaflammation and normalize adipokines. Pharmacotherapies (metformin, thiazolidinediones, SGLT2 inhibitors, and incretin-based agents) indirectly and sometimes directly recalibrate cytokine/adipokine networks. Targeted immunometabolic approaches like IL-1 pathway blockade, NLRP3 inhibition, chemokine-axis modulation, selective PPAR agonism, and experimental adiponectin receptor agonists offer precision opportunities but demand careful safety assessment. This review integrates mechanistic insights, tissue crosstalk, and translational evidence to map how cytokines and adipokines drive the path from obesity to T2D and to highlight practical levers to restore immuno-endocrine homeostasis.

Keywords: adipokines; cytokines; insulin resistance; metaflammation; type 2 diabetes

INTRODUCTION

Obesity reshapes the physiology of white, beige, and brown adipose depots, converting them from flexible buffers of fuel excess into sources of endocrine and inflammatory stress[1–3]. The consequence is a progressive loss of metabolic flexibility across the liver, skeletal muscle, vasculature, and pancreatic islets that culminates in type 2 diabetes (T2D)[4–6]. Although energy imbalance initiates this trajectory, the proximate drivers are immuno-endocrine: inflammatory cytokines and chemokines generated within adipose tissue (AT) and other organs, and adipokines secreted by adipocytes and stromal cells, together reprogram insulin signaling, lipid handling, and tissue remodeling [7–9]. Understanding how these networks interact clarifies why some individuals with obesity remain metabolically healthy while others rapidly develop insulin resistance (IR) and β-cell failure.

Hypertrophic adipocytes experience hypoxia, extracellular-matrix (ECM) stiffening, and organelle stress (ER/mitochondria), which activate transcriptional and inflammasome programs[10]. These cues recruit monocytes (via CCL2/CCR2) that differentiate into inflammatory macrophages, forming crown-like structures around stressed adipocytes. Neutrophils, mast cells, dendritic cells, γδ T cells, Th1/Th17 cells, B cells, and natural killer cells accumulate, while regulatory T cells (Tregs), ILC2s, and eosinophils decline. The immune shift increases local and systemic levels of TNF-α, IL-6, IL-1β/IL-18 (via NLRP3), and interferons, with downstream activation of JNK/IKK/NF-κB, STAT, and SOCS pathways that serine-phosphorylate insulin receptor substrates (IRS), dampen PI3K/Akt signaling, and increase lipolysis[11–14].

In parallel, the adipokine secretome changes qualitatively and quantitatively. Adiponectin, an insulin-sensitizing, anti-inflammatory adipokine that activates AMPK and PPARα, falls with obesity, removing a tonic brake on hepatic gluconeogenesis and vascular inflammation. Leptin increases proportionally to fat mass, but central and peripheral leptin resistance blunt its anorexigenic and insulin-modulatory effects[15]. Other adipokines such as resistin, RBP4, chemerin, fetuin-A (a hepatokine), apelin, omentin, and lipocalin-2 exert context-dependent effects on insulin action, vascular tone, and immune activity. Depot heterogeneity is crucial: visceral AT is more inflamed, fibrotic, and lipolytic than subcutaneous AT and drains into the portal circulation, exposing the liver to cytokines and non-esterified fatty acids that sustain IR and steatosis[13, 16, 17].

Cytokine–adipokine networks do not operate in isolation. Nutrient-derived signals, such as saturated fatty acids, ceramides, and endotoxin (LPS) from the gut engage TLRs and amplify inflammasome activation. Conversely, structured exercise, caloric moderation, sleep regularity, and high-fiber diets suppress inflammatory tone and improve adipokine profiles independently of major weight loss[18]. Common antidiabetic drugs exert part of their benefit by dampening metaflammation or improving adipokine signaling: metformin reduces hepatic inflammatory signaling and favors *Akkermansia*-linked microbial shifts; thiazolidinediones (TZDs) expand subcutaneous adipogenesis and raise adiponectin; SGLT2 inhibitors lower glucotoxic stress; incretin-based agents drive weight loss and may directly influence immune cells[18].

This review synthesizes current knowledge on (1) cytokine networks that connect obesity to IR; (2) adipokine biology spanning insulin-sensitizing and insulin-desensitizing factors; (3) immune–stromal crosstalk within metabolic tissues; (4) intracellular signaling hubs through which cytokines/adipokines modify insulin action and β-cell function; (5) organ-to-organ propagation of inflammatory and endocrine signals; and (6) therapeutic strategies that modulate these axes. We conclude with a pragmatic framework for translating immuno-endocrine insights into clinical care, emphasizing phenotype-guided interventions that restore AT health and system-wide insulin sensitivity.

2. Cytokine Networks Linking Obesity to Insulin Resistance

Cytokines are the lingua franca of metaflammation. In obese AT, TNF-α released by macrophages and stressed adipocytes activates IKKβ/NF-κB and JNK pathways, promoting serine phosphorylation of IRS1/2 that reduces insulin-stimulated PI3K/Akt signaling. TNF-α increases lipolysis (via hormone-sensitive lipase and ATGL activation), suppresses adipogenesis, and upregulates SOCS3, which interferes with insulin and leptin receptor signaling. IL-6, produced by adipocytes, immune cells, and exercising muscle, has context-dependent effects: chronic elevation favors hepatic IR through STAT3/SOCS3 induction and CRP production, whereas transient spikes during exercise can be anti-inflammatory and insulin-sensitizing[19].

IL-1β and IL-18 are matured by caspase-1 downstream of the NLRP3 inflammasome, which senses lipotoxic stress (e.g., ceramides), mitochondrial ROS, and extracellular ATP. IL-1β impairs insulin signaling in adipocytes and hepatocytes and promotes β-cell dysfunction by disturbing Ca^{2+} oscillations and inducing ER stress and dedifferentiation[20]. Chemokines, especially CCL2 (MCP-1), drive monocyte recruitment; CCL5 and CXCL10 contribute to immune cell positioning and Th1 polarization. Interferons (type I/II) amplify IR via PKR and STAT pathways, and GM-CSF/CSF-1 shape macrophage proliferation and survival within AT.

Depot and sex differences nuance cytokine landscapes. Visceral fat shows higher expression of TNF-α, IL-6, and CCL2 and greater macrophage infiltration than subcutaneous fat; female sex hormones can modulate cytokine production and immune composition[20]. Aging and cellular senescence add a senescence-associated secretory phenotype (SASP), IL-6, IL-8, MMPs, that intensifies inflammatory signaling and fibrosis. Systemically, elevated cytokines propagate to the liver (Kupffer cell activation), skeletal muscle (endothelial activation and resident macrophage priming), and hypothalamus (neuroinflammation), creating a feed-forward loop that sustains IR[20].

Therapeutically, broad cytokine suppression risks immunosuppression. More promising are strategies that interrupt recruitment (CCR2/CCR5 antagonism), dampen inflammasome activation, or skew macrophage polarization back toward tissue-repair phenotypes. Lifestyle interventions reduce cytokine burden by shrinking adipocyte size, improving vascularization, and restoring mitochondrial quality control structural shifts that lower the stimulus for cytokine production rather than merely blocking downstream signals.

3. Adipokines: Insulin-Sensitizers, Desensitizers, and Vascular Modulators

Adipokines orchestrate endocrine communication among AT, liver, muscle, vasculature, and islets. Adiponectin, abundant in lean states, binds AdipoR1/R2 to activate AMPK and PPARα, enhancing fatty-acid oxidation, suppressing gluconeogenesis, and exerting anti-inflammatory effects through NF-κB inhibition and macrophage polarization[21–25]. High-molecular-weight adiponectin correlates best with insulin sensitivity. In obesity/T2D, circulating levels fall, and adiponectin multimerization is impaired, reducing bioactivity.

Leptin rises with fat mass and normally restrains appetite and increases sympathetic tone; peripherally, it modulates lipid metabolism and insulin action. Leptin resistance, both central and peripheral, emerges with obesity due to SOCS3 induction, ER stress, and impaired transport across the blood–brain barrier[22, 26–28]. Leptin replacement is transformative in congenital leptin deficiency and partial lipodystrophy but offers limited glycemic benefit in common obesity.

Other adipokines include resistin (linked to IR and inflammation), RBP4 (impairs insulin signaling in muscle and promotes hepatic gluconeogenesis), chemerin (chemoattractant with context-dependent metabolic effects), apelin (vasoactive, insulin-sensitizing in some studies), omentin (generally insulin-sensitizing), visfatin/NAMPT (involved in NAD+ biosynthesis; mixed metabolic effects), and lipocalin-2 (inflammatory, iron-related). Hepatokines and myokines intersect: fetuin-A inhibits insulin receptor tyrosine kinase and complexes with TLR4 to potentiate saturated-fat signaling; FGF21 from liver/adipose improves insulin sensitivity and is modulated by diet and adipokine states[29].

Vascular actions are integral. Adiponectin enhances endothelial NO production and reduces adhesion molecule expression; leptin can promote angiogenesis and sympathetic activity; resistin and TNF-α impair endothelial function. Perivascular adipose tissue (PVAT) releases adipokines and cytokines that influence local vascular tone and inflammation, linking obesity to hypertension and atherosclerosis key comorbidities that complicate diabetes care[29].

Modulating adipokines therapeutically involves indirect levers (weight loss, exercise, TZDs raising adiponectin) and emerging direct strategies: AdipoR agonists (e.g., small molecules), leptin sensitizers, and combination incretin/peptide therapies that favorably shift adipokine profiles. The field's challenge is achieving durable changes in secretion and receptor signaling without off-target effects, ideally tuned to depot-specific and patient-specific pathobiology.

4. Immune–Adipocyte Crosstalk and Tissue Niches

The immunologic remodeling of AT is spatially organized. In lean depots, eosinophils, ILC2s, and Tregs maintain an anti-inflammatory tone via IL-4/IL-13 and IL-10, supporting alternative (M2-like) macrophages involved in remodeling and thermogenesis[30]. Overnutrition diminishes these cells and recruits monocytes that differentiate into inflammatory macrophages. These macrophages aggregate in crown-like structures around necrotic adipocytes, where they scavenge lipids but also secrete TNF-α, IL-1β, and ROS. Transcriptionally distinct lipid-associated macrophages (LAMs) express Trem2 and genes for lipid handling; they may be protective initially, but become pro-fibrotic under chronic stress[30].

Adaptive immunity shifts toward Th1/Th17 polarization, producing IFN-γ and IL-17 that further inhibit insulin signaling. B cells contribute to antigen presentation and pathogenic IgG; regulatory B cells (Bregs) are diminished. Mast cells and neutrophils release proteases and elastases that damage the ECM and perpetuate chemokine production[31]. Stromal cells (preadipocytes, fibro-adipogenic progenitors, endothelial cells) transduce cytokine signals that bias fate toward fibrosis rather than adipogenesis, stiffening the niche and limiting healthy adipocyte hyperplasia. Senescent stromal/immune cells secrete SASP factors that reinforce inflammation and impair beiging[31].

Nervous and vascular inputs integrate these niches. Sympathetic nerve fibers regulate lipolysis and thermogenesis; inflammation induces catecholamine resistance in adipocytes and macrophages, blunting lipolytic control and thermogenic activation. Poor angiogenesis and vascular rarefaction exacerbate hypoxia, perpetuating HIF-1α-driven fibrogenesis and cytokine production[32, 33].

Therapeutic strategies that restore niche balance include caloric reduction and exercise (which reduce adipocyte size and improve vascularization), cold exposure or β3-agonism (promoting beiging and anti-inflammatory profiles), and pharmacologic modulation of immune cells (CCR2/CCR5 antagonism, IL-1 blockade, PPARγ ligands acting in macrophages)[34]. Microbiome-targeted diets increase SCFA production, expanding Tregs and attenuating AT inflammation. Ultimately, re-establishing adipogenesis and vascularization alongside immune recalibration is key to breaking the cycle that connects local AT dysfunction to systemic IR[34].

5. Intracellular Signaling Hubs: From Receptors to Insulin Pathway Interference

Cytokines and adipokines signal through receptors that converge on a limited set of intracellular nodes controlling insulin action. TLR4 recognizes saturated fatty acids (indirectly) and LPS, activating MyD88/TRIF pathways and culminating in NF-κB and IRF3 activation; TNFR1/2 signals through TRAF and RIP kinases to activate IKK/JNK and caspase pathways. IL-1R recruits MyD88 to activate NF-κB and MAPKs; IL-6R/gp130 triggers JAK/STAT3 and SOCS3 induction; IFNAR/IFNGR activate JAK/STAT1/2, intersecting with PKR and PERK[35]. These cascades induce serine/threonine kinases (JNK, IKKβ, S6K, PKCθ/ε) that phosphorylate IRS1/2 on inhibitory residues, reduce PI3K p85–IRS interactions, and dampen Akt activation, thereby impairing GLUT4 translocation and antilipolysis.

Lipotoxic mediators amplify this interference. Ceramides, generated via serine-palmitoyltransferase and ceramide synthases, activate PP2A and PKCζ, antagonizing Akt and promoting mitochondrial dysfunction; they may also engage NLRP3. Diacylglycerols (DAGs) activate novel PKCs that inhibit insulin receptor kinase activity and IRS function, particularly in the liver and muscle[36]. ER stress (PERK/IRE1/ATF6) is induced by activating JNK and CHOP, impairing insulin signaling and promoting apoptosis. Mitochondrial ROS act as second messengers to reinforce these pathways, and SOCS proteins induced by cytokines promote ubiquitination and degradation of insulin signaling components[36].

Adipokine receptors counterbalance these effects. AdipoR1/R2 activate AMPK and PPARα, increasing fatty-acid oxidation and enhancing insulin sensitivity; they also promote ceramidase activity, lowering ceramide

burden. LeptinR signals via JAK2/STAT3, PI3K, and MAPK, but SOCS3 and PTP1B attenuate signaling in obesity. Apelin engages APJ to enhance endothelial NO and glucose uptake; omentin improves insulin signaling via Akt in endothelium and adipocytes[16, 17, 37].

Therapeutic interventions exploit these nodes: metformin activates AMPK and reduces hepatic gluconeogenesis and inflammation; TZDs activate PPARγ, expanding healthy adipogenesis and improving adipokine balance; SGLT2 inhibitors reduce glucotoxicity and ER stress; GLP-1 receptor agonists improve insulin action and lower inflammatory tone. Experimental approaches include NLRP3 inhibitors, ASK1/JNK blockers, ceramide synthesis inhibitors, and AdipoR agonists[38–40]. Selectivity and safety remain paramount, given the centrality of these pathways to host defense and cellular stress responses.

6. Organ Crosstalk: Liver, Skeletal Muscle, Pancreatic Islets, and Vasculature

Cytokine/adipokine signals propagate through anatomical channels to reprogram organ physiology. Liver receives portal drainage from visceral AT and gut, exposing it to NEFAs, LPS, and cytokines. Kupffer cells sense these cues, producing TNF-α and IL-1β that impair hepatocyte insulin signaling and promote steatosis and gluconeogenesis. Hepatokines such as fetuin-A and FGF21 feedback to adipose and muscle, modulating insulin sensitivity and adipokine expression[41]. Skeletal muscle experiences reduced microvascular perfusion during inflammation (endothelial dysfunction) and accumulates lipid intermediates that activate PKCs; cytokines further inhibit insulin signaling and mitochondrial biogenesis, while myokines from exercise counteract these effects by expanding capillarity and oxidative capacity[42–44].

Pancreatic islets are both targets and sources of cytokines. IL-1β, TNF-α, and IFN-γ impair β-cell insulin gene transcription, proinsulin processing, and exocytosis, while promoting ER stress, mitochondrial depolarization, and apoptosis; β-cells themselves can produce IL-1β under glucolipotoxic stress, creating an autocrine loop[45]. Leptin modulates β-cell excitability and can suppress insulin secretion; adiponectin supports β-cell survival and function. Islet-resident macrophages and infiltrating T cells shape these effects, and adipokines/cytokines modulate the islet extracellular matrix and vasculature, influencing nutrient and oxygen delivery.

Vasculature integrates metabolic and inflammatory signals: endothelial cells respond to TNF-α/IL-6 with adhesion molecule expression and reduced nitric oxide bioavailability, impairing insulin-mediated capillary recruitment and glucose delivery to muscle. PVAT releases adipokines/cytokines that act locally on the vessel wall, linking obesity to hypertension and atherosclerosis conditions that worsen insulin delivery and complicate glycemic control[46].

Brain–adipose axis adds higher-order control. Hypothalamic inflammation driven by saturated fats and cytokines induces leptin and insulin resistance, dysregulating appetite and sympathetic outputs that govern AT lipolysis and BAT thermogenesis[46]. Therapies that reduce peripheral inflammation (weight loss, incretin-based treatments) often improve central sensitivity, closing a beneficial feedback loop.

7. Therapeutic Modulation of Cytokines and Adipokines: From Lifestyle to Targeted Agents

Foundations weight loss and exercise: Caloric restriction and increased physical activity shrink adipocyte size, reduce crown-like structures, downregulate TNF-α/IL-6/CCL2, and raise adiponectin [47]. Exercise acutely elevates IL-6 in a myokine context that induces IL-10 and dampens TNF-α; chronically, it increases adiponectin and improves endothelial function[48].

Approved pharmacotherapies: Metformin reduces hepatic inflammatory signaling and improves adipokine balance via AMPK activation; thiazolidinediones (PPARγ agonists) enhance subcutaneous adipogenesis, redistribute lipid away from ectopic sites, and increase adiponectin (with weight gain/edema risks)[38, 39, 49]. SGLT2 inhibitors lower glucotoxicity and systemic inflammation, improving vascular outcomes. Incretin-based agents (GLP-1 receptor agonists and multi-agonists) deliver substantial weight loss, improve islet health, and reduce inflammatory markers, thereby normalizing adipokine profiles.

Targeted immunomodulation: IL-1 pathway blockade (e.g., receptor antagonists or monoclonal antibodies) improves glycemic metrics in subsets with high inflammatory tone. NLRP3 inhibitors and colchicine are under evaluation for metabolic inflammation. CCR2/CCR5 antagonism reduces monocyte recruitment to AT; effects on glycemia are modest but may benefit steatohepatitis[50]. TNF-α blockade has not reliably improved glycemia in common T2D, underscoring pathway redundancy.

Adipokine-centric strategies: Raising adiponectin through TZDs is proven; direct AdipoR agonists and agents that enhance multimerization are investigational. Leptin therapy is effective in lipodystrophy and congenital deficiency, with limited utility in common obesity unless paired with sensitizers. Modulation of chemerin, apelin, or omentin pathways remains exploratory. FGF21 analogs improve dyslipidemia and NASH features and may indirectly modulate adipokines.

Systems levers: Microbiome-directed diets, bariatric/metabolic surgery, sleep regularity, and stress reduction can durably lower cytokine load and improve adipokine profiles. Precision approaches use inflammatory biomarkers, adipokine panels, and imaging of AT inflammation/fibrosis to select and sequence therapies. The guiding principle is to restore AT health expandability, vascularization, and anti-inflammatory signaling, thereby resolving the cytokine/adipokine disequilibrium that drives IR.

CONCLUSION

Obesity-related diabetes is not an inevitable consequence of excess adiposity but a systems failure driven by an imbalanced immuno-endocrine dialogue. Cytokines generated by stressed AT and other tissues activate conserved stress kinases and inflammasome pathways that disrupt insulin signaling, while shifts in adipokines remove insulin-sensitizing brakes and distort vascular and islet function. These signals propagate across organs, liver, muscle, pancreas, vasculature, and brain, creating self-reinforcing loops of lipotoxicity, inflammation, and endocrine resistance. The path to durable glycemic control, therefore, runs through restoration of adipose health and recalibration of cytokine/adipokine networks. Practically, foundations matter most: weight reduction, structured exercise, high-fiber minimally processed diets, adequate sleep, and stress management collectively shrink inflammatory niches and normalize adipokines. Pharmacotherapies metformin, TZDs, SGLT2 inhibitors, and incretin-based agents provide complementary benefits that include immunometabolic improvements beyond glucose lowering. For selected patients with high inflammatory tone or organ-specific pathology, targeted strategies (IL-1 axis modulation, NLRP3 inhibition, CCR2/CCR5 blockade, emerging AdipoR agonists) may add value when layered atop lifestyle and metabolic agents. Looking ahead, precision phenotyping that integrates adipose imaging, inflammatory/adipokine panels, and microbiome/metabolite signatures can identify dominant drivers in each individual and guide therapy sequencing. Achieving equity and safety will require scalable diagnostics and accessible interventions. Reframing diabetes care from glucocentric control to immuno-endocrine repair offers a coherent route to preventing, delaying, or even reversing the metabolic sequelae that link obesity to T2D.

REFERENCES

1. Ahmed, S.K., Mohammed, R.A.: Obesity: Prevalence, causes, consequences, management, preventive strategies and future research directions. Metab. Open. 27, 100375 (2025). https://doi.org/10.1016/j.metop.2025.100375
2. Akter, R., Awais, M., Boopathi, V., Ahn, J.C., Yang, D.C., Kang, S.C., Yang, D.U., Jung, S.-K.: Inversion of the Warburg Effect: Unraveling the Metabolic Nexus between Obesity and Cancer. ACS Pharmacol. Transl. Sci. 7, 560 (2024). https://doi.org/10.1021/acsptsci.3c00301
3. Ejemot-Nwadiaro, R.I., Betiang, P.A., Basajja, M., Uti, D.E.: Obesity and Climate Change: A Two-way Street with Global Health Implications. Obes. Med. 56, 100623 (2025). https://doi.org/10.1016/j.obmed.2025.100623
4. AbdlWhab, H.M., Al-Saffar, A., Mahdi, O.A., Alameri, R.B.: The impact of insulin resistance and glycaemic control on insulin-like growth factor-1 in patients with type 2 diabetes: a cross-sectional study. Clin. Diabetes Endocrinol. 10, 36 (2024). https://doi.org/10.1186/s40842-024-00202-8
5. Alzaid, F., Fagherazzi, G., Riveline, J.-P., Bahman, F., Al-Rashed, F., Al-Mulla, F., Ahmad, R.: Immune cell–adipose tissue crosstalk in metabolic diseases with a focus on type 1 diabetes. Diabetologia. 68, 1616–1631 (2025). https://doi.org/10.1007/s00125-025-06437-z
6. Obasi, D.C., Abba, J.N., Aniokete, U.C., Okoroh, P.N., Akwari, A.Ak.: Evolving Paradigms in Nutrition Therapy for Diabetes: From Carbohydrate Counting to Precision Diets. Obes. Med. 100622 (2025). https://doi.org/10.1016/j.obmed.2025.100622
7. Abdillah, A.M., Yun, J.W.: Capsaicin induces ATP-dependent thermogenesis via the activation of TRPV1/β3-AR/α1-AR in 3T3-L1 adipocytes and mouse model. Arch. Biochem. Biophys. 755, 109975 (2024). https://doi.org/10.1016/j.abb.2024.109975
8. Colson, C., Batrow, P.-L., Gautier, N., Rochet, N., Ailhaud, G., Peiretti, F., Amri, E.-Z.: The Rosmarinus Bioactive Compound Carnosic Acid Is a Novel PPAR Antagonist That Inhibits the Browning of White Adipocytes. Cells. 9, 2433 (2020). https://doi.org/10.3390/cells9112433
9. Alum, E.U.: Metabolic memory in obesity: Can early-life interventions reverse lifelong risks? Obes. Med. 55, 100610 (2025). https://doi.org/10.1016/j.obmed.2025.100610
10. Sun, K., Li, X., Scherer, P.E.: Extracellular Matrix (ECM) and Fibrosis in Adipose Tissue: Overview and Perspectives. In: Prakash, Y.S. (ed.) Comprehensive Physiology. pp. 4387–4407. Wiley (2023)
11. Abdellatif, K.R.A., Fadaly, W.A.A., Kamel, G.M., Elshaier, Y.A.M.M., El-Magd, M.A.: Design, synthesis, modeling studies and biological evaluation of thiazolidine derivatives containing pyrazole core as potential anti-diabetic PPAR-γ agonists and anti-inflammatory COX-2 selective inhibitors. Bioorganic Chem. 82, 86–99 (2019). https://doi.org/10.1016/j.bioorg.2018.09.034
12. Ahn, Y.J., Kim, H.: Lutein as a Modulator of Oxidative Stress-Mediated Inflammatory Diseases. Antioxidants. 10, 1448 (2021). https://doi.org/10.3390/antiox10091448
13. Al-Mansoori, L., Al-Jaber, H., Prince, M.S., Elrayess, M.A.: Role of Inflammatory Cytokines, Growth Factors and Adipokines in Adipogenesis and Insulin Resistance. Inflammation. 45, 31–44 (2022). https://doi.org/10.1007/s10753-021-01559-z
14. Alum, E.U., Krishnamoorthy, R., Gatasheh, M.K., Famurewa, A.C., Subbarayan, S., Vijayalakshmi, P., Uti, D.E.: Neuroprotective Potential of Jimson Weed in Methotrexate-Induced Neurotoxicity: Insights into Anti-Oxidative, Anti-Inflammatory, and Anti-Apoptotic Mechanisms via Modulation of Caspase-3,

Interleukin-6, and Tumor Necrosis Factor-Alpha: In Silico. Endocr. Metab. Immune Disord. - Drug Targets. 25, 1–17. https://doi.org/10.2174/0118715303350736241220090850
15. Uti, D.E., Atangwho, I.J., Omang, W.A., Alum, E.U., Obeten, U.N., Udeozor, P.A., Agada, S.A., Bawa, I., Ogbu, C.O.: Cytokines as key players in obesity low grade inflammation and related complications. Obes. Med. 54, 100585 (2025). https://doi.org/10.1016/j.obmed.2025.100585
16. Datta, S., Koka, S., Boini, K.M.: Understanding the Role of Adipokines in Cardiometabolic Dysfunction: A Review of Current Knowledge. Biomolecules. 15, 612 (2025). https://doi.org/10.3390/biom15050612
17. Kim, J.A., Choi, K.M.: Newly Discovered Adipokines: Pathophysiological Link Between Obesity and Cardiometabolic Disorders. Front. Physiol. 11, 568800 (2020). https://doi.org/10.3389/fphys.2020.568800
18. Liddle, D., Hutchinson, A., Wellings, H., Power, K., Robinson, L., Monk, J.: Integrated Immunomodulatory Mechanisms through which Long-Chain n-3 Polyunsaturated Fatty Acids Attenuate Obese Adipose Tissue Dysfunction. Nutrients. 9, 1289 (2017). https://doi.org/10.3390/nu9121289
19. Patel, P.S., Buras, E.D., Balasubramanyam, A.: The Role of the Immune System in Obesity and Insulin Resistance. J. Obes. 2013, 1–9 (2013). https://doi.org/10.1155/2013/616193
20. Fujimura, K., Karasawa, T., Komada, T., Yamada, N., Mizushina, Y., Baatarjav, C., Matsumura, T., Otsu, K., Takeda, N., Mizukami, H., Kario, K., Takahashi, M.: NLRP3 inflammasome-driven IL-1β and IL-18 contribute to lipopolysaccharide-induced septic cardiomyopathy. J. Mol. Cell. Cardiol. 180, 58–68 (2023). https://doi.org/10.1016/j.yjmcc.2023.05.003
21. Baldelli, S., Aiello, G., Mansilla Di Martino, E., Campaci, D., Muthanna, F.M.S., Lombardo, M.: The Role of Adipose Tissue and Nutrition in the Regulation of Adiponectin. Nutrients. 16, 2436 (2024). https://doi.org/10.3390/nu16152436
22. Bocian-Jastrzębska, A., Malczewska-Herman, A., Kos-Kudła, B.: Role of Leptin and Adiponectin in Carcinogenesis. Cancers. 15, 4250 (2023). https://doi.org/10.3390/cancers15174250
23. Kita, S., Maeda, N., Shimomura, I.: Interorgan communication by exosomes, adipose tissue, and adiponectin in metabolic syndrome. J. Clin. Invest. 129, 4041–4049. https://doi.org/10.1172/JCI129193
24. Nguyen, T.M.D.: Adiponectin: Role in Physiology and Pathophysiology. Int. J. Prev. Med. 11, 136 (2020). https://doi.org/10.4103/ijpvm.IJPVM_193_20
25. Umoru, G.U., Atangwho, I.J., David-Oku, E., Uti, D.E., Agwupuye, E.I., Obeten, U.N., Maitra, S., Subramaniyan, V., Wong, L.S., Aljarba, N.H., Kumarasamy, V.: Tetracarpidium conophorum nuts (African walnuts) up-regulated adiponectin and PPAR-γ expressions with reciprocal suppression of TNF-α gene in obesity. J. Cell. Mol. Med. 28, e70086 (2024). https://doi.org/10.1111/jcmm.70086
26. Andò, S., Gelsomino, L., Panza, S., Giordano, C., Bonofiglio, D., Barone, I., Catalano, S.: Obesity, Leptin and Breast Cancer: Epidemiological Evidence and Proposed Mechanisms. Cancers. 11, 62 (2019). https://doi.org/10.3390/cancers11010062
27. Casado, M.E., Collado-Pérez, R., Frago, L.M., Barrios, V.: Recent Advances in the Knowledge of the Mechanisms of Leptin Physiology and Actions in Neurological and Metabolic Pathologies. Int. J. Mol. Sci. 24, 1422 (2023). https://doi.org/10.3390/ijms24021422
28. de Candia, P., Prattichizzo, F., Garavelli, S., Alviggi, C., La Cava, A., Matarese, G.: The pleiotropic roles of leptin in metabolism, immunity, and cancer. J. Exp. Med. 218, e20191593 (2021). https://doi.org/10.1084/jem.20191593
29. Tripathi, D., Kant, S., Pandey, S., Ehtesham, N.Z.: Resistin in metabolism, inflammation, and disease. FEBS J. 287, 3141–3149 (2020). https://doi.org/10.1111/febs.15322
30. Painter, J.D., Akbari, O.: Type 2 Innate Lymphoid Cells: Protectors in Type 2 Diabetes. Front. Immunol. 12, 727008 (2021). https://doi.org/10.3389/fimmu.2021.727008
31. Chng, M.H.Y., Alonso, M.N., Barnes, S.E., Nguyen, K.D., Engleman, E.G.: Adaptive Immunity and Antigen-Specific Activation in Obesity-Associated Insulin Resistance. Mediators Inflamm. 2015, 593075 (2015). https://doi.org/10.1155/2015/593075
32. Willows, J.W., Blaszkiewicz, M., Townsend, K.L.: The Sympathetic Innervation of Adipose Tissues: Regulation, Functions, and Plasticity. In: Prakash, Y.S. (ed.) Comprehensive Physiology. pp. 4985–5021. Wiley (2023)
33. Zhang, Y., Zhang, B., Sun, X.: The molecular mechanism of macrophage-adipocyte crosstalk in maintaining energy homeostasis. Front. Immunol. 15, (2024). https://doi.org/10.3389/fimmu.2024.1378202
34. AlZaim, I., Hammoud, S.H., Al-Koussa, H., Ghazi, A., Eid, A.H., El-Yazbi, A.F.: Adipose Tissue Immunomodulation: A Novel Therapeutic Approach in Cardiovascular and Metabolic Diseases. Front. Cardiovasc. Med. 7, 602088 (2020). https://doi.org/10.3389/fcvm.2020.602088
35. McKernan, K., Varghese, M., Patel, R., Singer, K.: Role of TLR4 in the induction of inflammatory changes in adipocytes and macrophages. Adipocyte. 9, 212–222. https://doi.org/10.1080/21623945.2020.1760674
36. Nicholson, R.J., Pezzolesi, M.G., Summers, S.A.: Rotten to the Cortex: Ceramide-Mediated Lipotoxicity in Diabetic Kidney Disease. Front. Endocrinol. 11, (2021). https://doi.org/10.3389/fendo.2020.622692

37. Clemente-Suárez, V.J., Redondo-Flórez, L., Beltrán-Velasco, A.I., Martín-Rodríguez, A., Martínez-Guardado, I., Navarro-Jiménez, E., Laborde-Cárdenas, C.C., Tornero-Aguilera, J.F.: The Role of Adipokines in Health and Disease. Biomedicines. 11, 1290 (2023). https://doi.org/10.3390/biomedicines11051290
38. Christofides, E.A.: Practical Insights Into Improving Adherence to Metformin Therapy in Patients With Type 2 Diabetes. Clin. Diabetes Publ. Am. Diabetes Assoc. 37, 234–241 (2019). https://doi.org/10.2337/cd18-0063
39. Basheer, H.A., Salman, N.M., Abdullah, R.M., Elsalem, L., Afarinkia, K.: Metformin and glioma: Targeting metabolic dysregulation for enhanced therapeutic outcomes. Transl. Oncol. 53, 102323 (2025). https://doi.org/10.1016/j.tranon.2025.102323
40. Drzewoski, J., Hanefeld, M.: The Current and Potential Therapeutic Use of Metformin—The Good Old Drug. Pharmaceuticals. 14, 122 (2021). https://doi.org/10.3390/ph14020122
41. Diehl, K.L., Vorac, J., Hofmann, K., Meiser, P., Unterweger, I., Kuerschner, L., Weighardt, H., Förster, I., Thiele, C.: Kupffer Cells Sense Free Fatty Acids and Regulate Hepatic Lipid Metabolism in High-Fat Diet and Inflammation. Cells. 9, 2258 (2020). https://doi.org/10.3390/cells9102258
42. Ahmad, K., Shaikh, S., Lim, J.H., Ahmad, S.S., Chun, H.J., Lee, E.J., Choi, I.: Therapeutic application of natural compounds for skeletal muscle-associated metabolic disorders: A review on diabetes perspective. Biomed. Pharmacother. 168, 115642 (2023). https://doi.org/10.1016/j.biopha.2023.115642
43. Anguita-Ruiz, A., Bustos-Aibar, M., Plaza-Díaz, J., Mendez-Gutierrez, A., Alcalá-Fdez, J., Aguilera, C.M., Ruiz-Ojeda, F.J.: Omics Approaches in Adipose Tissue and Skeletal Muscle Addressing the Role of Extracellular Matrix in Obesity and Metabolic Dysfunction. Int. J. Mol. Sci. 22, 2756 (2021). https://doi.org/10.3390/ijms22052756
44. Chen, X., Ji, Y., Liu, R., Zhu, X., Wang, K., Yang, X., Liu, B., Gao, Z., Huang, Y., Shen, Y., Liu, H., Sun, H.: Mitochondrial dysfunction: roles in skeletal muscle atrophy. J. Transl. Med. 21, 503 (2023). https://doi.org/10.1186/s12967-023-04369-z
45. Wang, Z., Ni, X., Zhang, L., Sun, L., Zhu, X., Zhou, Q., Yang, Z., Yuan, H.: Toll-Like Receptor 4 and Inflammatory Micro-Environment of Pancreatic Islets in Type-2 Diabetes Mellitus: A Therapeutic Perspective. Diabetes Metab. Syndr. Obes. Targets Ther. 13, 4261–4272 (2020). https://doi.org/10.2147/DMSO.S279104
46. Fernández-Alfonso, M.S., Somoza, B., Tsvetkov, D., Kuczmanski, A., Dashwood, M., Gil-Ortega, M.: Role of Perivascular Adipose Tissue in Health and Disease. Compr. Physiol. 8, 23–59 (2018). https://doi.org/10.1002/j.2040-4603.2018.tb00004.x
47. Izah, S.C., Betiang, P.A., Paul-Chima Ugwu, O., Ainebyoona, C., Uti, D.E., Echegu, D.A., Alum, B.N.: The Ketogenic Diet in Obesity Management: Friend or Foe? Cell Biochem. Biophys. (2025). https://doi.org/10.1007/s12013-025-01878-0
48. Bulmer, C., Avenell, A.: The effect of dietary weight-loss interventions on the inflammatory markers interleukin-6 and TNF-alpha in adults with obesity: A systematic review and meta-analysis of randomized controlled clinical trials. Obes. Rev. 26, e13910 (2025). https://doi.org/10.1111/obr.13910
49. Chen, D., Wang, Y., Wu, K., Wang, X.: Dual Effects of Metformin on Adipogenic Differentiation of 3T3-L1 Preadipocyte in AMPK-Dependent and Independent Manners. Int. J. Mol. Sci. 19, 1547 (2018). https://doi.org/10.3390/ijms19061547
50. Amaral, N.B., Rodrigues, T.S., Giannini, M.C., Lopes, M.I., Bonjorno, L.P., Menezes, P.I.S.O., Dib, S.M., Gigante, S.L.G., Benatti, M.N., Rezek, U.C., Emrich-Filho, L.L., Sousa, B.A., Almeida, S.C.L., Luppino-Assad, R., Veras, F.P., Schneider, A.H., Leiria, L.O.S., Cunha, L.D., Alves-Filho, J.C., Cunha, T.M., Arruda, E., Miranda, C.H., Pazin-Filho, A., Auxiliadora-Martins, M., Borges, M.C., Fonseca, B.A.L., Bollela, V.R., Del-Ben, C.M., Cunha, F.Q., Santana, R.C., Vilar, F.C., Zamboni, D.S., Louzada-Junior, P., Oliveira, R.D.R.: Colchicine reduces the activation of NLRP3 inflammasome in COVID-19 patients. Inflamm. Res. 72, 895–899 (2023). https://doi.org/10.1007/s00011-023-01718-y

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