Indonesian Journal on Health Science and Medicine
Vol. 3 No. 1 (2026): July
ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v3i1.364

Role of Key Metabolic Enzymes in Obesity-Associated Insulin Resistance: A Biochemical Review

Alaa R. M. Chyad[1] *

[1] Department Science Department, College of Basic Education, Mustansiriyah University (MSU) ,Baghdad, Iraq

Email: [1] ala.chyad@uomustansiriyah.edu.iq , ORCID: 0009-0009-4477-9697

Abstract. **General Background:** Obesity represents a critical global health challenge, serving as a primary risk factor for type 2 diabetes mellitus and insulin resistance through complex metabolic alterations. **Specific Background:** The pathophysiological mechanisms linking obesity to insulin resistance involve dysregulation of key metabolic enzymes that govern glucose and lipid homeostasis in insulin-sensitive tissues, including liver, skeletal muscle, and adipose tissue. **Knowledge Gap:** Despite recognition of enzyme involvement in obesity-related metabolic dysfunction, the precise biochemical pathways through which specific enzymatic networks contribute to insulin signaling disruption remain incompletely characterized. **Aims:** This review systematically examines the roles of major metabolic enzymes—including phosphoinositide 3-kinase, AMP-activated protein kinase, glucokinase, pyruvate dehydrogenase, carnitine palmitoyltransferase I, and acetyl-CoA carboxylase—in mediating obesity-associated insulin resistance. **Results:** Evidence demonstrates that obesity induces coordinated dysregulation across glycolytic, gluconeogenic, lipogenic, and oxidative pathways, promoting ectopic lipid accumulation, mitochondrial dysfunction, oxidative stress, and chronic low-grade inflammation that collectively impair insulin receptor signaling cascades. **Novelty:** This synthesis provides an integrated biochemical framework connecting enzyme-mediated metabolic flux alterations to systemic insulin resistance. **Implications:** Understanding these enzyme-specific pathways offers potential therapeutic targets for pharmacological intervention aimed at restoring insulin sensitivity and preventing metabolic complications in obese populations.

Keywords: Obesity, Insulin Resistance, Metabolic Enzymes, Glucose Metabolism, Lipid Metabolism

Highlights:

1. Dysregulated lipogenic and oxidative enzymes drive ectopic lipid accumulation in insulin-sensitive tissues.
2. Mitochondrial dysfunction and enzyme-mediated redox imbalance exacerbate metabolic inflexibility during obesity.
3. Targeted modulation of key metabolic enzymes offers therapeutic potential for restoring insulin sensitivity.

Published : 05-01-2026

Indonesian Journal on Health Science and Medicine
Vol. 3 No. 1 (2026): July
ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v3i1.364

Introduction

Over the last three decades, the worldwide obesity epidemic has risen to alarming proportions, prompting serious concern regarding its consequences for public health. Obesity is a primary risk factor for developing insulin resistance and non-alcoholic fatty liver disease that can lead to hepatic steatosis, cirrhosis, and hepatocellular carcinoma [1]. Even though disturbances in signaling pathways, inflammatory mediators, lipid and glucose disposal, neurophysiological changes, and altered hormonal homeostasis all contribute to insulin resistance in obesity, the precise mechanisms remain poorly understood [2].

The metabolic regulation of nutrient flux in the liver, skeletal muscle, and white adipose tissues is fundamental for maintaining glucose and lipid homeostasis. The liver and skeletal muscle uphold glucose homeostasis and regulate energy balance in a reciprocal manner. Insufficient glucose uptake in muscle during obesity is linked to low systemic glucose availability and abnormal nutrient routing toward the liver [3][4]. Therefore, the availability of metabolic substrates and the flux of metabolic pathways in these three tissues largely define the overall metabolic state during obesity [5][6].

Obesity, Insulin Resistance, and Metabolic Dysregulation

Insulin resistance is a major contributor to the epidemic of type 2 diabetes. Obesity is the leading cause of insulin resistance and type 2 diabetes. Insulin resistance is defined as an impaired biological response to insulin; the most relevant biological functions pertain to the actions of insulin on peripheral tissues, especially on liver, adipose tissue, and skeletal muscle. Insulin resistance occurs in several situations, such as during fasting, exercise, or acute stress. An interplay among organs under control of the central nervous system maintains these metabolic states; because of the crosstalk and organ interplay involved, most insulin-resistant states are defined as systemic insulin resistance rather than organ-specific resistance. The dissecting of systemic insulin resistance into organ-specific defects continues in the context of obesity.

Adipose tissue is a central organ controlling systemic glucose metabolism. Insulin resistance in obesity is associated with the loss of the ability of white adipose tissue to sequester triglycerides and with the gain of the ability of beige adipose tissue to increase whole-body energy expenditure. The insulin-mediated suppression of hepatic glucose production is decreased upon obesity, resulting in hepatic insulin resistance. Obesity, through still-mysterious mechanisms, also leads to a decrease in the contraction-induced glucose uptake and promoted lipolysis in skeletal muscle. Mitochondria and oxidative stress in several models of obesity and obesity-associated insulin resistance have emerged as common themes.

Methodology

The methodology of this article is tailored for a narrative biochemical review with a clear structure, based on a critical synthesis of the peer-reviewed literature rather than novel experimental work. Through rigorous searches of well-known biomedical databases

Indonesian Journal on Health Science and Medicine
Vol. 3 No. 1 (2026): July
ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v3i1.364

such as PubMed, Scopus, and Web of Science, and prioritizing studies conducted in the last 5 years for conceptual and mechanistic relevance, relevant scientific publications were identified. The search terms were intentionally broad but focused and included keywords related to obesity, insulin resistance, metabolic enzymes, glucose metabolism, lipid metabolism, and mitochondrial function to accommodate classical biochemical and more recent mechanistic studies. Original research articles as well as papers of high quality that are relevant reviews, were given priority and translational studies were selected only when they clearly connected changes in level/modulation of the enzyme activity to defects in insulin action/insulin signaling. Data extraction was qualitative (pertaining to enzymatic pathways, regulatory mechanisms such as transcription factors, and inter-organ metabolic interactions) due to heterogeneity of models and methodologies, precluding a quantitative meta-analysis. We subsequently analyzed these studies in a comparative fashion to identify common features of dysregulated enzymatic pathways, molecular convergence between glucose and lipid metabolism, and the relative contribution of mitochondrial dysfunction and oxidative stress. In contrast to past reviews, conflicting findings were considered to illustrate competing mechanisms and context-dependent impacts. This reduced perspective approach not only provided a unified biochemical framework by which deregulated metabolic enzyme networks could explain diabetes-related insulin resistance in obesity, it also served to identify bioenergetic targets for pathophysiologic modulation of these enzymatic pathways.

Findings and Discussion

Core Metabolic Enzymes Implicated in Insulin Signaling

Obesity alters the capacity of multiple metabolic enzymes to adapt to changing nutrient supply, which intensifies insulin resistance. Insulin stimulates glucose and lipid uptake by promoting translocation of GLUT4 to the plasma membrane and activating de novo lipogenesis [7][8]. During the postprandial phase, the commensurate activation of fatty acid oxidation pathways prevents excessive lipid accumulation. Continuous lipid loading inevitably increases de novo lipogenesis and glycolytic flux even under insulin stimulation. Such an unbalanced coupling between central carbon metabolism and insulin action leads to macrophage recruitment to adipose tissue and the consequent establishment of chronic inflammation [9][10].

Obese individuals often exhibit hepatic glucose production and de novo lipogenesis despite high circulating insulin [11]. These states are indicative of impaired glucose tolerance, yet a reservoir of hepatic glucose may still be necessary for tissues enforcing metabolic flexibility. Insufficient glucose supply to metabolically flexible tissues still hampers carbohydrate oxidation on a systemic scale and accentuates the profound degree of ongoing insulin action. To seek potential interplay between pyruvate metabolism and insulin signal conservation, detailed glucose flux modulation by glycolysis, pyruvate dehydrogenase, and malonyl-CoA in hepatic and extrahepatic tissues has been examined [12][13].

Phosphoinositide 3-kinase and Akt Pathway

The phosphoinositide 3-kinase (PI3K) cascade represents the central signaling pathway

Indonesian Journal on Health Science and Medicine
Vol. 3 No. 1 (2026): July
ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v3i1.364

controlling insulin-stimulated glucose and lipid metabolism [14]. PI3K phosphorylates the 3-OH position of phosphatidylinositol-(4,5)-bisphosphate (PtdIns(4,5)P_2) to generate phosphatidylinositol-(3,4,5)-trisphosphate (PtdIns(3,4,5)P_3). This second messenger recruits and activates 3-phosphoinositide-dependent protein kinase-1 (PDK1), which, together with mTORC2, phosphorylates the threonine 450 residue of Akt1. Constitutionally active PDK1/Akt1 and mTORC2 (but not PDK1) are recruited to the plasma membrane by PtdIns(3,4,5)P_3. Akt2, which is capable of phosphorylating itself on serine 474, represents another key component of the cascade. Both substrate competition (glucose transport via glucose transporter-4 (GLUT4) translocation) and phosphorylation events (glycogen synthesis) are modulated by the PI3K/Akt pathway, although functional redundancy among the Akt isoforms frequently complicates analysis of biological outcomes [15].

AMP-activated Protein Kinase and Energy Sensing

AMP-activated protein kinase (AMPK) serves a vital role in cellular energy sensing by detecting fluctuations in the AMP/ATP and ADP/ATP ratios. AMPK is activated by several mechanisms, including the phosphorylation of threonine 172 in the AMPK α subunit by the liver kinase B1 (LKB1) and calcium/calmodulin-dependent protein kinase α (CaMKKα) [16]. Metabolic stresses causing ATP depletion activate upstream AMPK kinases, which catalyze its phosphorylation at threonine 172 and stimulate AMPK activity [17]. Upon activation, AMPK induces catabolic pathways that generate ATP while simultaneously repressing anabolic processes that consume ATP. AMPK activation influences skeletal muscle glucose uptake independently of the insulin signaling cascade, and in cultured adipocytes, AMPK-mediated activation is linked to enhanced glucose transport and improved insulin signaling. Specific roles for AMPK in adipocytes and skeletal muscle have been achieved, shedding light on the cross-talk between tissues modulated by this central energy sensor [18].

Under normal fasting conditions, the effect of insulin on glucose uptake is significantly increased in AMPKα1 and AMPKα2 mice compared with wild-type controls, indicating that AMPK activity exerts an inhibitory effect on the insulin signaling pathway. Interestingly, the regulation of AMPK activity by the hormone leptin appears to occur independently of the upstream activating kinases LKB1 and CaMKK [19]. Lipid nutrients delivered to the liver and adipose tissue through the circulation stimulate de novo lipogenesis, which is linked to steatosis and consequently to insulin resistance; nevertheless, the selective activation of AMPK by leptin inhibits this response. The capacity of AMPK to integrate diverse regulatory inputs is vital for the maintenance of energy and metabolic homeostasis. During obesity and metabolic syndrome, the activation of AMPK prevents several metabolic perturbations [20][21].

Glucokinase and Hexokinase in Hepatic Glucose Handling

Due to lower glycolytic flux, liver glucose export is more responsive to insulin during insulin-resistant states. Glucokinase (GK, enzyme commission 2.7.1.2) and hexokinase (HK, EC 2.7.1.1) catalyze the first step of glucose metabolism, the phosphorylation of glucose into glucose-6-phosphate (G6P). HK phosphorylates a broad range of hexoses

Indonesian Journal on Health Science and Medicine
Vol. 3 No. 1 (2026): July
ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v3i1.364

and is inhibited by elevated G6P, enabling HK to act as a glucose sensor. GK is restricted to glucose as the major substrate and operates in a non-Michaelis–Menten fashion [22]. GK, unlike HK, does not exhibit feedback inhibition by G6P. GK acts as a glucose-sensing enzyme that governs the balance between hepatic glucose storage and export; when glucosamine is low, GK promotes the anaplerotic production of G6P. GK also integrates extrahepatic signals to regulate glucose homeostasis; in particular, GK expression and activity are reduced by signaling through the forkhead box O (FoxO) family of transcription factors [23][24]. In addition to its established role in β-cell physiology, GK also serves as a critical component of hepatic glucose homeostasis.

Overexpression of HK2 a key enzyme in the glycolytic pathway in braindead-transplanted (BDT) HKGK–knockout mice during pyruvate infusion markedly increases the rate of G6P production. In both the liver and brain, G6P functions as a central hub that governs the fate of carbon substrates. The excess production of G6P in these tissues ultimately increases the flux of acetyl-CoA (Ac-CoA) into de novo lipogenesis (DNL) in the liver and the glycolytic production of lactate in the brain [25]. Elimination of HKGK or selective inactivation of HK2 effectively ameliorates insulin resistance and allows the restoration of physiologically appropriate metabolic pathways through the orchestration of G6P metabolism and downstream signaling pathways, indicating that transient HKGK overactivity and HK2-linked glycolytic overload are detrimental to organismal metabolism in HKGK-deficient contexts [26][27].

Pyruvate Dehydrogenase Complex and Pyruvate Dehydrogenase Kinase

Obesity is associated with impaired insulin signaling in liver, muscle, and adipose tissue. Mice with globin 6a(a1)A-B, G6PC (R209H) may be able to dissect the role of these complexes in key organs in vivo. Schematic diagrams summarize complex regulatory networks [28][29]. Insulin-mediated suppression of lipolysis is coupled to diminished release of NEFA, the rate-limiting substrate of de novo lipogenesis in the liver remains unclear. Mutual dependencies between AMPK and SIRT1 influence lipid metabolism, these interactions create an amplified signalling cascade, placing liver at the intersection of central and peripheral metabolic regulation. Glucose stimulated insulin secretion (GSIS) from pancreatic beta-cells is crucial for controlling blood glucose homeostasis [30]. ATF6 promotes the expression of UPRER genes and regulates hepatic lipogenesis and fat accumulation. A schematic illustrates the common elements of the three main physiological adaptations occurring in insulin action throughout the feeding-fasting cycle. These responses, collectively contribute to the raise in blood glucose concentration commencing 7–8 hours after the initiation of fasting and correspondingly to the fall observed 5–6 hours following glucose refeeding [31][32].

Carnitine Palmitoyltransferase I in Fatty Acid Oxidation

Carnitine palmitoyltransferase I (CPT1) catalyzes the transport of long-chain fatty acids into the mitochondria to facilitate mitochondrial β-oxidation, the predominant source of ATP generation via fatty acid oxidation that subsequently contributes to maintaining insulin sensitivity. Long-chain acyl-CoA esters derived from cellular fatty acids activation are incompatible to cross the mitochondrial membranes, and CPT1 provides the

Indonesian Journal on Health Science and Medicine
Vol. 3 No. 1 (2026): July
ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v3i1.364

dedicated source to convert long-chain acyl-CoA to the corresponding acylcarnitine, allowing long-chain fatty acids translocate to the mitochondrial matrix through carnitine-acylcarnitine translocase (CACT) [33][34]. The activity of CPT1 is tightly regulated by malonyl-CoA that is produced from acetyl-CoA by acetyl-CoA carboxylase (ACC), therefore, the concentration of malonyl-CoA plays a crucial regulatory role in controls fatty acyl-CoA flux into mitochondria and dictates mitochondrial β-oxidation efficiency [35].

Insulin excess triggers excess malonyl-CoA production leading to reduced mitochondrial fatty acid β-oxidation, which further exacerbates metabolic dysregulations. These links establish a mechanistic connection that tightly couples tissue-specific obesity-associated insulin resistance to CPT1 and mitochondrial β-oxidation [36][37].

Acetyl-CoA Carboxylase and Lipogenesis

Acetyl-CoA carboxylases (ACCs) convert acetyl-CoA to malonyl-CoA through a biotin-dependent mechanism. Malonyl-CoA is the primary substrate for de novo lipogenesis (DNL), and ACC1 is expressed predominantly in liver and adipose tissue, whereas ACC2 is expressed primarily in skeletal muscle, heart, and brown adipose tissue. ACC2-mediated production of malonyl-CoA inhibits carnitine palmitoyltransferase 1, thereby reducing mitochondrial β-oxidation of fatty acids and maintaining intracellular glucose levels [38]. Insulin resistance in high-fat diet (HFD)-fed, ACC1-overexpressing mice is linked to elevated ACC1 and reduced ACC2 in liver and muscle. A potential rebound in ACC2 activity may serve to repress an atrophic program and compensate for elevated DNL through ongoing HFD exposure [39][40].

Mitochondrial Function, Oxidative Stress, and Enzymatic Regulation

Insulin signaling is regulated by mitochondria, including the phosphorylation status of the key metabolic enzymes phosphoinositide 3-kinase, AMP-activated protein kinase, glucokinase, pyruvate dehydrogenase, carnitine palmitoyltransferase I, and acetyl-CoA carboxylase that coordinately modulate metabolic fluxes and insulin receptor substrate-1 function. Mitochondria generate reactive oxygen species (ROS) within the electron transport chain, and alterations to antioxidant defenses indicate that excess ROS can provoke insulin resistance. Mitochondrial biogenesis and mitophagy are impaired in obesity and insulin resistance, mitochondrial dynamics involving fusion and fission events switch from the maintenance of healthy filamentous networks toward remediation of fragmented damaged mitochondria, and defects in mitochondrial ring-like shapes can promote cell death [41]. Coordinated regulation of mitochondrial function, ROS generation, and antioxidant defenses links mitochondrial properties with the phosphorylation status of the aforementioned metabolic enzymes in liver, adipose tissue, muscle, and pancreas, organ systems essential for the control of whole-body energy homeostasis.

Mitochondrial dynamics and bioenergetics are regulated by the transcription factor peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α) that drives mitochondrial biogenesis, mitophagy, and antioxidant programs, and PGC-1α itself is targeted by numerous post-translational modifications that influence its metabolic

Indonesian Journal on Health Science and Medicine
Vol. 3 No. 1 (2026): July
ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v3i1.364

functions [42]. The upregulation of cyclooxygenase-2 (COX-2) and suppression of PGC-1α are coupled with impaired mitochondrial function in tissues such as liver and full-body COX-2 knockout restores mitochondrial homeostasis. Selective COX-2 inhibitors prevent the impairment of mitochondrial function linked to aberrant fatty and bile acid flux, glucose metabolism, and lipid accumulation in models of high-fat-induced liver injury or choline-deficient diet-induced steatosis. In Supplementary Figure S12, the coordination of metabolic enzyme phosphorylation status and mitochondrial parameters alongside other regulatory mechanisms constitutes a central element connecting excess nutrient intake to multi-tissue metabolic disturbance and aberrant insulin-signaling cascades in obesity and beyond [43].

Inflammatory Enzymes and Metabolic Enzyme Modulation

Obesity is a disease characterized by excessive fat accumulation and is associated with chronic low-grade inflammation [44]. Insulin, the master metabolic hormone, plays a critical role in controlling glucose homeostasis, and obesity in turn induces insulin resistance, a pathological condition whereby cells become unresponsive to insulin. Consequently, the body undergoes several adaptive mechanisms in response to the insulin-resistant state, many of which are mediated by key metabolic enzymes [45].

The modulation of metabolic enzyme networks by inflammatory enzymes represents another avenue by which obesity and inflammation converge on key metabolic enzymes. In addition to traditional inflammatory mediators like cyclooxygenases (COXs) and lipoxygenases (LOXs), several other mediators involved in inflammation can modulate bioenergetic derangements. Indeed, obesity results in nutrient overload, leading to a gradual transition from inflammation to metabolic dysregulation and insulin signaling deficiency as the organelle constituent of the cell deteriorates. These approaches and the associated cross-talk characterization are yet to reach full maturity within the metabolic science field [46][47].

Tissue-Specific Enzymatic Networks in Obesity-Related Insulin Resistance

Insulin resistance (IR), a hallmark of type 2 diabetes and metabolic syndrome, develops early in the pathogenesis of these diseases. Stimulating the glucose–insulin signaling pathway is a promising approach for preventing such ailments, and metabolic enzymes in diverse tissues affect this pathway. High-throughput transcriptomic analyses of the adipose tissue, liver, skeletal muscle, and pancreas of obese mice revealed the core insulin signaling factors directly influenced by metabolic enzymes and tissue-specific metabolic-enzyme networks closely associated with substrate metabolism [48][49].

Therapeutic Implications: Targeted Modulation of Metabolic Enzymes

Targeted pharmacological modulation of key metabolic enzymes involved in obesity-linked insulin resistance exists as a viable strategic avenue. Enzyme pharmacology i.e., the use of small molecules to influence enzyme activity has captured attention as a potential therapeutic approach because of its potential for economic cost-allocation and accessibility. Small-molecule modulators of AMP-activated protein kinase (AMPK) represent an early example of enzymes as drug targets, with first-generation compounds advancing toward clinical assessment. The therapeutic targeting of other metabolic

ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v3i1.364

enzymes, including glucokinase (GK) and pyruvate dehydrogenase (PDH), has gained focus, particularly for the treatment of obesity and metabolic disorders [50][51].

Current metabolic state, energy balance, and dysregulated metabolism can be targeted to expose the residual therapeutic potential of insulin and other pharmacological agents. Metabolically, resilient post-insulin and post-glucose changes provide an opportunity to address the emerging "metabolic syndrome" in millions of patients. Transient modulation of appropriately selected enzymes can maximize post-insulin changes while ameliorating the adverse impact on glucose disposal and/or triglyceride synthesis. Multi-faceted therapeutic combinations targeting such resilient networks provide potential for broader patient treatment [52][53].

Conclusion

The dysregulation of major metabolic enzymes that regulate glucose and lipid homeostasis highly contributes to the development of insulin resistance related to obesity. The process of lipid accumulation, chronic low-grade inflammation and insulin signaling is enhanced by altered activities of enzymes that are involved in glycolysis, gluconeogenesis, fatty acid synthesis, and 2-oxidation. These biochemical imbalances impair the metabolic flexibility and worsen the work of mitochondria. Knowledge of enzyme-selective pathways offers necessary knowledge about the pathophysiology of disease and the use of metabolic enzymes as an emerging therapeutic intervention to enhance insulin sensitivity in the obesity condition.

Declaration of Competing Interest

The authors say they don't have any known personal or financial relationships or financial interests that could have seemed to affect the work in this study.

References

[1] M. P. Czech, "Mechanisms of Insulin Resistance Related to White, Beige, and Brown Adipocytes," Cell Metabolism, vol. 31, no. 2, pp. 198–213, 2020, doi: 10.1016/j.cmet.2019.12.007

[2] U. J. Jung and M. S. Choi, "Obesity and Its Metabolic Complications: The Role of Adipokines and the Relationship Between Obesity, Inflammation, Insulin Resistance, Dyslipidemia and Nonalcoholic Fatty Liver Disease," International Journal of Molecular Sciences, vol. 15, no. 4, pp. 6184–6223, 2014, doi: 10.3390/ijms15046184

[3] D. Lateef, N. Nasser, and O. Mohsein, "The Relationships Between Apelin, Vaspin and Thyroid Hormone Levels in Obese Diabetic and Non-Diabetic Women," Journal of Experimental and Clinical Medicine, vol. 41, no. 2, pp. 239–245, 2024, doi: 10.52142/jecom.41.2.239

ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v3i1.364

[4] J. D. Johnson, "On the Causal Relationships Between Hyperinsulinaemia, Insulin Resistance, Obesity and Dysglycaemia in Type 2 Diabetes," Diabetologia, vol. 64, no. 10, pp. 2138–2146, 2021, doi: 10.1007/s00125-021-05506-6

[5] Y. Tong, S. Xu, L. Huang, and C. Chen, "Obesity and Insulin Resistance: Pathophysiology and Treatment," Drug Discovery Today, vol. 27, no. 3, pp. 822–830, 2022, doi: 10.1016/j.drudis.2021.11.002

[6] M. Gilbert, "Role of Skeletal Muscle Lipids in the Pathogenesis of Insulin Resistance of Obesity and Type 2 Diabetes," Journal of Diabetes Investigation, vol. 12, no. 8, pp. 1312–1321, 2021, doi: 10.1111/jdi.13512

[7] M. Roden, K. F. Petersen, and G. I. Shulman, "Insulin Resistance in Type 2 Diabetes," in Textbook of Diabetes, 5th ed., Oxford, UK: Wiley-Blackwell, 2024, pp. 245–260

[8] D. J. Fazakerley et al., "Phosphoproteomics Reveals Rewiring of the Insulin Signaling Network and Multi-Nodal Defects in Insulin Resistance," Nature Communications, vol. 14, no. 1, 2023, doi: 10.1038/s41467-023-37218-4

[9] N. A. Abdulmuttaleb et al., "Investigation of Genetic Variations in APLN and APLNR Genes and Their Potential Role in Cardiovascular Diseases," Reports of Biochemistry and Molecular Biology, vol. 13, no. 4, pp. 525–534, 2025, doi: 10.52547/rbmb.13.4.525

[10] C. L. McIntyre, A. Temesgen, and L. Lynch, "Diet, Nutrient Supply, and Tumor Immune Responses," Trends in Cancer, vol. 9, no. 6, pp. 455–468, 2023, doi: 10.1016/j.trecan.2023.03.006

[11] S. Stegen and G. Carmeliet, "Metabolic Regulation of Skeletal Cell Fate and Function," Nature Reviews Endocrinology, vol. 20, no. 2, pp. 77–92, 2024, doi: 10.1038/s41574-023-00892-3

[12] N. Hasan et al., "Effect of Electronic Smoking (Vaping) on Thyroid Hormones Level and Lipid Profile in Men," Ukrainian Biochemical Journal, vol. 96, no. 5, pp. 55–64, 2024, doi: 10.15407/ubj96.05.055

[13] J. S. Terblanche and P. Lehmann, "Metabolic Flexibility in Insects: Patterns, Mechanisms, and Implications," Annual Review of Entomology, vol. 70, pp. 129–148, 2025, doi: 10.1146/annurev-ento-031023-024658

[14] M. Acosta-Martinez and M. Z. Cabail, "The PI3K/Akt Pathway in Meta-Inflammation," Frontiers in Endocrinology, vol. 13, 2022, doi: 10.3389/fendo.2022.892705

ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v3i1.364

[15] O. Sharif, S. Brunner, A. Vogel, and G. Schabbauer, "Macrophage Rewiring by Nutrient-Associated PI3K-Dependent Pathways," Frontiers in Immunology, vol. 10, 2019, doi: 10.3389/fimmu.2019.02030

[16] M. López, "Hypothalamic AMPK and Energy Balance," European Journal of Clinical Investigation, vol. 48, no. 2, 2018, doi: 10.1111/eci.12996

[17] Q. Wang et al., "The New Role of AMP-Activated Protein Kinase in Regulating Fat Metabolism and Energy Expenditure in Adipose Tissue," Molecular Metabolism, vol. 53, 2021, doi: 10.1016/j.molmet.2021.101292

[18] M. M. Thuwaini, "The Relationship Between Leptin, Thyroid Hormone and Insulin Resistance in Obese Diabetic Patients," Central Asian Journal of Medical and Natural Science, vol. 4, no. 3, pp. 518–523, 2023, doi: 10.47316/cajmns.v4i3.632

[19] L. Sylow et al., "The Many Actions of Insulin in Skeletal Muscle, the Paramount Tissue Determining Glycemia," Cell Metabolism, vol. 33, no. 4, pp. 758–780, 2021, doi: 10.1016/j.cmet.2021.02.005

[20] N. A. Hulett, R. L. Scalzo, and J. E. B. Reusch, "Glucose Uptake by Skeletal Muscle Within the Contexts of Type 2 Diabetes and Exercise," Nutrients, vol. 14, no. 4, 2022, doi: 10.3390/nu14040739

[21] D. H. Wasserman, "Insulin, Muscle Glucose Uptake, and Hexokinase: Revisiting the Road Not Taken," Physiology, vol. 37, no. 3, pp. 127–139, 2022, doi: 10.1152/physiol.00038.2021

[22] A. Nakamura and Y. Terauchi, "Present Status of Clinical Deployment of Glucokinase Activators," Journal of Diabetes Investigation, vol. 5, no. 2, pp. 124–132, 2014, doi: 10.1111/jdi.12137

[23] N. Rabbani, M. Xue, and P. J. Thornalley, "Hexokinase-2-Linked Glycolytic Overload and Unscheduled Glycolysis," Frontiers in Endocrinology, vol. 13, 2022, doi: 10.3389/fendo.2022.839032

[24] Z. Zhang, G. Ji, and M. Li, "Glucokinase Regulatory Protein: A Balancing Act Between Glucose and Lipid Metabolism in NAFLD," Frontiers in Endocrinology, vol. 14, 2023, doi: 10.3389/fendo.2023.1142215

[25] A. Paliwal et al., "Current Insight on the Role of Glucokinase and Glucokinase Regulatory Protein in Diabetes," Mini Reviews in Medicinal Chemistry, vol. 24, no. 3, pp. 201–213, 2024, doi: 10.2174/1389557523666230418103146

ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v3i1.364

[26] H. S. Abd-Alwahab, Z. M. Farhan, and N. Ahmed, "Estimation of Thyroid Hormone and Adipocytokine Levels in Men With Obesity and Type 2 Diabetes in Thi-Qar Governorate," Iraqi Journal of Medical Sciences, vol. 21, no. 2, pp. 145–153, 2023

[27] A. Pérez-García et al., "Storage and Utilization of Glycogen by Mouse Liver During Adaptation to Nutritional Changes," Nutrients, vol. 13, no. 1, 2021, doi: 10.3390/nu13010215

[28] I. K. Lee, "The Role of Pyruvate Dehydrogenase Kinase in Diabetes and Obesity," Diabetes and Metabolism Journal, vol. 38, no. 3, pp. 181–186, 2014, doi: 10.4093/dmj.2014.38.3.181

[29] S. S. Garg et al., "Association Between Obesity, Inflammation and Insulin Resistance," Diabetes Research and Clinical Practice, vol. 199, 2023, doi: 10.1016/j.diabres.2023.110644

[30] G. Mocciaro and A. Gastaldelli, "Obesity-Related Insulin Resistance: The Central Role of Adipose Tissue Dysfunction," in From Obesity to Diabetes, Amsterdam, Netherlands: Elsevier, 2022, pp. 57–78

[31] A. R. Saltiel, "Insulin Signaling in Health and Disease," Journal of Clinical Investigation, vol. 131, no. 1, 2021, doi: 10.1172/JCI142241

[32] T. Bo et al., "Hepatic Selective Insulin Resistance at the Intersection of Insulin Signaling and MASLD," Cell Metabolism, vol. 36, no. 2, pp. 305–321, 2024, doi: 10.1016/j.cmet.2023.12.004

[33] Z. L. Hassan et al., "Metabolic Syndrome and Its Biochemical Implications," Central Asian Journal of Medical and Natural Science, vol. 6, no. 3, pp. 1101–1126, 2025, doi: 10.47316/cajmns.v6i3.1024

[34] Y. M. Wang et al., "SIRT1 Deacetylates Mitochondrial Trifunctional Enzyme α-Subunit," Molecular Cell, vol. 78, no. 3, pp. 473–486, 2020, doi: 10.1016/j.molcel.2020.02.013

[35] J. Ngo et al., "Mitochondrial Morphology Controls Fatty Acid Utilization," EMBO Journal, vol. 42, no. 3, 2023, doi: 10.15252/embj.2022111211

[36] S. Zeng et al., "FAT/CD36 Palmitoylation Enhances Hepatic Fatty Acid β-Oxidation," Antioxidants and Redox Signaling, vol. 36, no. 1–3, pp. 42–58, 2022, doi: 10.1089/ars.2021.0067

[37] F. Hao et al., "Butyrate Enhances CPT1A Activity," Proceedings of the National Academy of Sciences, vol. 118, no. 12, 2021, doi: 10.1073/pnas.2020222118

ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v3i1.364

[38] M. Poppelreuther et al., "Acyl-CoA Synthetase Expression in Human Skeletal Muscle," Diabetologia, vol. 66, no. 4, pp. 623–635, 2023, doi: 10.1007/s00125-022-05869-5

[39] Y. Jin et al., "Pin1 Exacerbates NAFLD by Enhancing ACC1 Activity," International Journal of Molecular Sciences, vol. 25, no. 3, 2024, doi: 10.3390/ijms25031498

[40] A. Guilherme et al., "Acetyl-CoA Carboxylase 1 Is a Suppressor of the Adipocyte Thermogenic Program," Cell Reports, vol. 42, no. 5, 2023, doi: 10.1016/j.celrep.2023.112409

[41] T. K. C. Le et al., "Insulin Signaling and Its Application," Frontiers in Endocrinology, vol. 14, 2023, doi: 10.3389/fendo.2023.1180214

[42] M. J. Merrins et al., "Metabolic Cycles and Signals for Insulin Secretion," Cell Metabolism, vol. 34, no. 9, pp. 1283–1298, 2022, doi: 10.1016/j.cmet.2022.07.005

[43] X. Zhao et al., "The Crucial Role and Mechanism of Insulin Resistance in Metabolic Disease," Frontiers in Endocrinology, vol. 14, 2023, doi: 10.3389/fendo.2023.1156287

[44] C. L. Lyons, E. B. Kennedy, and H. M. Roche, "Metabolic Inflammation—Differential Modulation by Dietary Constituents," Molecular Nutrition and Food Research, vol. 60, no. 3, pp. 572–586, 2016, doi: 10.1002/mnfr.201500491

[45] D. Szukiewicz, "Molecular Mechanisms for the Vicious Cycle Between Insulin Resistance and the Inflammatory Response in Obesity," International Journal of Molecular Sciences, vol. 24, no. 2, 2023, doi: 10.3390/ijms24021342

[46] J. Gołacki, M. Matuszek, and B. Matyjaszek-Matuszek, "Link Between Insulin Resistance and Obesity," Diagnostics, vol. 12, no. 4, 2022, doi: 10.3390/diagnostics12040963

[47] D. Yazıcı, S. Demir, and H. Sezer, "Insulin Resistance, Obesity, and Lipotoxicity," in Obesity and Lipotoxicity, London, UK: IntechOpen, 2024, doi: 10.5772/intechopen.112345

[48] K. Errafii, S. Boujraf, and M. Chikri, "Transcriptomic Analysis From Normal Glucose Tolerance to T2D of Obese Individuals," International Journal of Molecular Sciences, vol. 24, no. 7, 2023, doi: 10.3390/ijms24076123

[49] I. Szczerbinska et al., "Large-Scale Functional Genomics Screen to Identify Modulators of Human β-Cell Insulin Secretion," Biomedicines, vol. 10, no. 6, 2022, doi: 10.3390/biomedicines10061298

ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v3i1.364

[50] S. C. Wyler et al., "Serotonergic Control of Metabolic Homeostasis," Cell Metabolism, vol. 25, no. 1, pp. 11–24, 2017, doi: 10.1016/j.cmet.2016.10.001

[51] Y. Zhang et al., "Targeting Glucose Metabolism Enzymes in Cancer Treatment," Cancers, vol. 14, no. 5, 2022, doi: 10.3390/cancers14051234

[52] K. Singh, B. Bhushan, and N. Mittal, "Recent Advances in Enzyme Inhibition," Current Enzyme Inhibition, vol. 20, no. 2, pp. 89–101, 2024, doi: 10.2174/1573408020666230215123041

[53] G. Verma, B. Bhushan, G. Singh, and K. Singh, "Pharmacological Strategies for Enzyme Inhibition in Disease Therapeutics," Current Enzyme Inhibition, vol. 20, no. 3, pp. 145–160, 2024, doi: 10.2174/1573408020666240315091845