HSPI The Open Access Publisher

ABB ISSN 2639-6777 ARCHIVES OF BIOTECHNOLOGY AND BIOMEDICINE

Research Article

Adipose Tissue, Leptin Signaling, and Adiponectin in Obesity and Type 2 Diabetes Mellitus

Tihomir Rashev[1,2]* and Stefan Trifonov[1]

[1]Department of Anatomy, Histology, Cytology and Biology, Medical University – Pleven, Pleven, Bulgaria

[2]Scientific Research Laboratory, Medical University – Pleven, Pleven, Bulgaria

Abstract

The global rise in obesity represents a major public health challenge and is closely associated with the increasing prevalence of metabolic syndrome and type 2 diabetes mellitus (T2DM). Obesity is characterized by excessive accumulation of adipose tissue, which contributes to the development of insulin resistance, chronic low-grade inflammation, and multiple metabolic complications. T2DM accounts for the majority of diabetes cases and is a complex metabolic disorder involving both impaired insulin action and β-cell dysfunction. Its growing incidence parallels the increasing rates of obesity worldwide.

Adipose tissue is now recognized as a metabolically active endocrine organ rather than a passive energy reservoir. It plays a central role in energy homeostasis through lipid storage and the secretion of adipokines, including leptin and adiponectin, which are critical regulators of metabolic processes. Leptin is a key hormone involved in appetite regulation and energy expenditure, acting primarily through hypothalamic signaling pathways such as JAK/STAT, PI3K/Akt, MAPK, and AMPK. However, in obesity, elevated leptin levels fail to exert their expected physiological effects due to the development of leptin resistance, which is associated with disruptions in intracellular signaling, inflammation, and cellular stress responses.

In contrast, adiponectin exerts insulin-sensitizing, anti-inflammatory, and anti-atherogenic effects, primarily through activation of metabolic signaling pathways that enhance glucose utilization and fatty acid oxidation. Its circulating levels are inversely correlated with adiposity and are reduced in obesity and T2DM, contributing to metabolic dysregulation.

Understanding the molecular interplay between adipose tissue, leptin signaling, and adiponectin is essential for elucidating the pathogenesis of obesity-related metabolic disorders and for developing targeted therapeutic strategies.

More Information

***Corresponding author:** Tihomir Rashev, Department of Anatomy, Histology, Cytology and Biology, Medical University - Pleven, Pleven, Bulgaria, Email: t_rashev@mail.bg

Rashev T: https://orcid.org/0000-0001-5171-0297

Trifonov S: https://orcid.org/0000-0002-5186-0487

Submitted: May 01, 2026
Accepted: May 11, 2026
Published: May 12, 2026

Citation: Rashev T, Trifonov S. Adipose Tissue, Leptin Signaling, and Adiponectin in Obesity and Type 2 Diabetes Mellitus. Arch Biotechnol Biomed. 2026; 10(1): 16-19. Available from: https://dx.doi.org/10.29328/journal.abb.1001050

Keywords: Adipose tissue; Leptin signaling; Adiponectin; Insulin resistance; Type 2 diabetes mellitus

Introduction

The alarming rise in obesity prevalence has generated significant concern among developed nations. This condition is associated with a wide spectrum of metabolic disorders collectively referred to as metabolic syndrome, including insulin resistance, type 2 diabetes mellitus, cardiovascular complications, and liver disease [1]. The close relationship between obesity and T2DM arises primarily from insulin resistance, which represents a central pathogenic mechanism in both conditions [1].

Type 2 diabetes mellitus accounts for approximately 90–95% of all diabetes cases and encompasses a heterogeneous spectrum of metabolic disturbances, ranging from predominant insulin resistance with relative insulin deficiency to conditions characterized by impaired insulin secretion in combination with insulin resistance [2]. At present, approximately 317 million individuals worldwide are affected, with 9.9% of the adult population in Bulgaria, corresponding to approximately 519,300 individuals, diagnosed with T2DM [2]. This increase correlates strongly with the rapid rise in obesity rates observed in most countries [2].

The etiology of T2DM is multifactorial and includes genetic, environmental, and metabolic components. Advances in

genomics have enabled the identification of genes associated with increased susceptibility to obesity and T2DM, including those encoding leptin, its receptor, and adiponectin. These genes have been extensively studied through analyses of single nucleotide polymorphisms across different populations [1]. Obesity is characterized by excessive accumulation of fatty acids and adipose tissue and is closely associated with the development of insulin resistance in peripheral tissues such as skeletal muscle and liver [1].

Adipose tissue

Adipose tissue was initially considered a passive storage site for triacylglycerols; however, recent research has established it as a metabolically active and dynamic organ with significant endocrine function [3]. Its primary role is to store excess energy in the form of lipids, while simultaneously synthesizing and secreting a wide range of biologically active molecules involved in the regulation of metabolic homeostasis.

Structurally, adipose tissue is composed not only of adipocytes but also of a heterogeneous population of cells collectively referred to as the stromal vascular fraction, which includes immune cells, endothelial cells, pericytes, and adipocyte precursors [4,5]. This cellular diversity underlies the complex regulatory functions of adipose tissue, positioning it as an essential component of an integrated network controlling multiple physiological processes [6–8].

Adipogenesis represents the process by which pre-adipocytes differentiate into mature adipocytes. This process involves extensive morphological and functional changes driven by coordinated activation and repression of transcription factors, ultimately resulting in a phenotype specialized for lipid storage and endocrine activity [9,10]. Adipocytes retain the capacity for differentiation throughout life, enabling hyperplastic expansion of adipose tissue in response to increased energy demand. In addition to hyperplasia, adipocytes may undergo hypertrophy, increasing their size as lipid accumulation progresses. These adaptations are regulated by biochemical processes including lipid uptake, esterification, lipolysis, and cellular differentiation [11].

Adipose tissue in mammals is classified into white, brown, and beige adipose tissue, each characterized by distinct morphology and function. White adipose tissue represents the predominant form and serves as the principal site for energy storage, mechanical protection, and endocrine signaling. It is widely distributed throughout the body, including subcutaneous regions and visceral compartments surrounding internal organs [12]. In contrast, brown adipose tissue is specialized for thermogenesis and is characterized by multilocular lipid droplets and a high density of mitochondria containing uncoupling protein 1, which enables the dissipation of energy as heat through non-shivering thermogenesis [11]. Although brown adipose tissue is more prominent in infants, small depots persist in adults and contribute to metabolic regulation [13]. Beige adipose tissue represents an intermediate phenotype that arises within white adipose depots through a process known as "browning." Under specific stimuli such as cold exposure or β-adrenergic activation, beige adipocytes acquire thermogenic properties similar to those of brown adipose tissue, including expression of UCP1 [14,15].

The balance between energy storage and expenditure is further regulated by the opposing processes of lipogenesis and lipolysis. Lipogenesis involves the synthesis of triglycerides and is stimulated by carbohydrate intake and insulin, whereas lipolysis is the hydrolysis of stored lipids into free fatty acids and glycerol, mediated by enzymes such as hormone-sensitive lipase and monoacylglycerol lipase and stimulated by glucagon and catecholamines [8,16,17]. The coordinated regulation of these processes is essential for maintaining energy homeostasis.

Adipose tissue also functions as a major endocrine organ, secreting a wide array of adipokines, cytokines, and growth factors that influence metabolism, immunity, and vascular function [6,18]. In obesity, expansion of adipose tissue is accompanied by increased infiltration of macrophages and enhanced production of pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-6. This results in a state of chronic low-grade inflammation that contributes to the development of insulin resistance and metabolic syndrome [19,20].

Leptin

Leptin is a 16 kDa peptide hormone encoded by the *ob* gene and primarily secreted by adipocytes. It is structurally and functionally related to cytokines of the interleukin-6 family and plays a central role in the regulation of appetite and energy expenditure [1,21,22]. Circulating leptin levels correlate positively with adipose tissue mass and reflect the energy status of the organism.

Leptin exerts its effects through binding to the leptin receptor, a member of the class I cytokine receptor family. The long isoform of the receptor, ObRb, is responsible for intracellular signaling and is highly expressed in the hypothalamus, where it regulates appetite and energy balance [23]. Upon ligand binding, the receptor activates several intracellular signaling pathways, including the JAK/STAT, PI3K/Akt, MAPK, and AMPK pathways, which collectively modulate gene expression, neuronal activity, and metabolic processes [24,25].

Despite elevated circulating leptin levels in obese individuals, its physiological effects are often diminished, a phenomenon known as leptin resistance. This condition arises from multiple mechanisms, including upregulation of suppressor of cytokine signaling 3, increased activity of protein tyrosine phosphatase 1B, endoplasmic reticulum stress, impaired transport of leptin across the blood–brain

barrier, and chronic inflammation. As a result, the central regulatory effects of leptin on appetite and energy expenditure are attenuated, contributing to the persistence of obesity.

Leptin signaling is further integrated with other metabolic and inflammatory pathways through extensive cross-talk. It interacts with insulin signaling via convergence on the PI3K pathway, while pro-inflammatory cytokines such as TNF-α and IL-6 modulate its activity. Additionally, leptin can transactivate growth factor receptors including EGFR and IGF-IR, linking metabolic regulation with cell proliferation and survival pathways.

Adiponectin

Adiponectin is an adipocyte-derived protein structurally related to the complement C1q family and is one of the most abundant circulating adipokines [26]. It exists in multiple oligomeric forms, ranging from low-molecular-weight trimers to high-molecular-weight complexes, which are considered the most biologically active forms [27].

In contrast to leptin, adiponectin levels are inversely correlated with adiposity, with reduced concentrations observed in obesity and T2DM [26]. This decrease is associated with impaired insulin sensitivity and increased metabolic risk. Adiponectin exerts its effects through binding to its receptors, AdipoR1 and AdipoR2, leading to activation of signaling pathways such as AMPK and PPARα, which enhance fatty acid oxidation, glucose uptake, and insulin sensitivity [28].

In skeletal muscle, adiponectin stimulates glucose uptake and fatty acid oxidation through AMPK activation, while in the liver it suppresses gluconeogenesis and improves metabolic efficiency [28,29]. The high-molecular-weight form of adiponectin appears to be particularly important for these metabolic effects, and reductions in this isoform are strongly associated with insulin resistance and T2DM [30].

Adiponectin also exhibits anti-inflammatory and vasculoprotective properties, further contributing to its beneficial role in metabolic regulation. Its secretion is tightly regulated at the level of adipocytes and involves endoplasmic reticulum chaperones such as ERp44 and Ero1-Lα, which control its folding, assembly, and release into circulation [31,32].

Conclusion

Adipose tissue is a complex and dynamic organ that plays a central role in the regulation of energy balance and metabolic homeostasis. The adipokines leptin and adiponectin are key mediators of these processes, exerting opposing effects on appetite, energy expenditure, and insulin sensitivity. Dysregulation of their signaling pathways, particularly the development of leptin resistance and reduced adiponectin levels, contributes significantly to the pathogenesis of obesity and T2DM.

A deeper understanding of the molecular mechanisms governing adipose tissue function and adipokine signaling may provide new therapeutic targets for the treatment and prevention of metabolic diseases.

Acknowledgment

We thank all participants who volunteered for the study. We gratefully acknowledge the assistance of Professor Vesela Dimova-Tomova from Medical University – Pleven for the selection of patients and collection of probes.

The authors declare that they have no conflict of interest.

References

1. Galic S, Oakhill JS, Steinberg GR. Adipose tissue as an endocrine organ. Molecular and Cellular Endocrinology [Internet]. 2010 [cited 2024 May 11];316(2):129–139. Available from: https://doi.org/10.1016/j.mce.2009.08.018
2. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Research and Clinical Practice [Internet]. 2018 [cited 2025 Nov 19]; 138:271–281. Available from: https://doi.org/10.1016/j.diabres.2018.02.023
3. Ottaviani E, Malagoli D, Franceschi C. The evolution of the adipose tissue: A neglected enigma. General and Comparative Endocrinology [Internet]. 2011 [cited 2024 July 25];174(1):1–4. Available from: https://doi.org/10.1016/j.ygcen.2011.06.018
4. Ahima RS, Flier JS. Adipose Tissue as an Endocrine Organ.Trends Endocrinol Metab. 2000 Oct;11(8):327-32. Available from: https://doi.org/10.1016/s1043-2760(00)00301-5
5. Saely CH, Geiger K, Drexel H. Brown versus White Adipose Tissue: A Mini-Review. Gerontology [Internet]. 2012 [cited 2025 Nov 19];58(1):15–23. Available from: https://doi.org/10.1159/000321319
6. Costa JV, Duarte JS. [Adipose tissue and adipokines]. Acta Med Port. 2006;19(3):251–256. Available from: https://pubmed.ncbi.nlm.nih.gov/17234088/
7. Fonseca-Alaniz MH, Takada J, Alonso-Vale MIC, Lima FB. [The adipose tissue as a regulatory center of the metabolism]. Arq Bras Endocrinol Metabol. 2006;50(2):216–229. Available from: https://doi.org/10.1590/s0004-27302006000200008
8. Kiess W, Petzold S, Töpfer M, Garten A, Blüher S, Kapellen T, et al. Adipocytes and adipose tissue. Best Pract Res Clin Endocrinol Metab. 2008;22(1):135–153. Available from: https://doi.org/10.1016/j.beem.2007.10.002
9. Gray SL, Vidal-Puig AJ. Adipose Tissue Expandability in the Maintenance of Metabolic Homeostasis. Nutrition Reviews [Internet]. 2008 [cited 2025 Nov 20];65:S7–S12. Available from: https://doi.org/10.1111/j.1753-4887.2007.tb00331.x
10. Seale P, Bjork B, Yang W, Kajimura S, Chin S, Kuang S, et al. PRDM16 controls a brown fat/skeletal muscle switch. Nature [Internet]. 2008 [cited 2026 Apr 23];454(7207):961–967. Available from: https://doi.org/10.1038/nature07182
11. Cannon B, Nedergaard J. Brown Adipose Tissue: Function and Physiological Significance. Physiological Reviews [Internet]. 2004 [cited 2026 Apr 23];84(1):277–359. Available from: https://doi.org/10.1152/physrev.00015.2003
12. Kajimura S, Spiegelman BM, Seale P. Brown and Beige Fat: Physiological Roles beyond Heat Generation. Cell Metabolism [Internet]. 2015 [cited 2026 Apr 23];22(4):546–559. Available from: https://doi.org/10.1016/j.cmet.2015.09.007
13. Bartelt A, Heeren J. Adipose tissue browning and metabolic health. Nat

Rev Endocrinol [Internet]. 2014 [cited 2026 Apr 23];10(1):24–36. Available from: https://doi.org/10.1038/nrendo.2013.204

14. Wu J, Boström P, Sparks LM, Ye L, Choi JH, Giang AH, et al. Beige Adipocytes Are a Distinct Type of Thermogenic Fat Cell in Mouse and Human. Cell [Internet]. 2012 [cited 2026 Apr 23];150(2):366–376. Available from: https://doi.org/10.1016/j.cell.2012.05.016

15. Harms M, Seale P. Brown and beige fat: development, function and therapeutic potential. Nat Med [Internet]. 2013 [cited 2026 Apr 23];19(10):1252–1263. Available from: https://doi.org/10.1038/nm.3361

16. Kersten S. Mechanisms of nutritional and hormonal regulation of lipogenesis. EMBO Reports [Internet]. 2001 [cited 2025 Nov 20];2(4):282–286. Available from: https://doi.org/10.1093/embo-reports/kve071

17. Laclaustra M, Corella D, Ordovas JM. Metabolic syndrome pathophysiology: The role of adipose tissue. Nutrition, Metabolism and Cardiovascular Diseases [Internet]. 2007 [cited 2025 Nov 20];17(2):125–139. Available from: https://doi.org/10.1016/j.numecd.2006.10.005

18. Matsuzawa Y. Therapy Insight: adipocytokines in metabolic syndrome and related cardiovascular disease. Nat Rev Cardiol [Internet]. 2006 [cited 2026 Apr 9];3(1):35–42. Available from: https://doi.org/10.1038/ncpcardio0380

19. Seneff S, Wainwright G, Mascitelli L. Is the metabolic syndrome caused by a high fructose, and relatively low fat, low cholesterol diet? Arch Med Sci. 2011;7(1):8–20. Available from: https://doi.org/10.5114/aoms.2011.20598

20. Stepień M, Rosniak-Bak K, Paradowski M, Misztal M, Kujawski K, Banach M, et al. Waist circumference, ghrelin and selected adipose tissue-derived adipokines as predictors of insulin resistance in obese patients: Preliminary results. Med Sci Monit [Internet]. 2011 [cited 2025 Nov 21];17(11):PR13–PR18. Available from: https://doi.org/10.12659/msm.882030

21. Trzeciak-Ryczek A, Tokarz-Deptuła B, Niedźwiedzka-Rystwej P, et al. Adipose tissue - Component of the immune system. Central-European Journal of Immunology. 2011; 36:95–99.

22. Itoh M, Suganami T, Hachiya R, Ogawa Y. Adipose Tissue Remodeling as Homeostatic Inflammation. Int J Inflam [Internet]. 2011 [cited 2025 Nov 21]; 2011:720926. Available from: https://doi.org/10.4061/2011/720926

23. Tartaglia LA. The leptin receptor. J Biol Chem. 1997;272(10):6093–6096. Available from: https://doi.org/10.1074/jbc.272.10.6093

24. Banks AS, Davis SM, Bates SH, Myers MG, Jr. Activation of downstream signals by the long form of the leptin receptor. J Biol Chem. 2000;275(19):14563–14572. Available from: https://doi.org/10.1074/jbc.275.19.14563

25. Ghilardi N, Ziegler S, Wiestner A, Stoffel R, Heim MH, Skoda RC. Defective STAT signaling by the leptin receptor in diabetic mice. Proc Natl Acad Sci U S A. 1996;93(13):6231–6235. Available from: https://doi.org/10.1073/pnas.93.13.6231

26. Hu E, Liang P, Spiegelman BM. AdipoQ Is a Novel Adipose-specific Gene Dysregulated in Obesity. Journal of Biological Chemistry [Internet]. 1996 [cited 2025 Dec 16];271(18):10697–10703. Available from: https://doi.org/10.1074/jbc.271.18.10697

27. Barré L, Richardson C, Hirshman MF, et al. Genetic model for the chronic activation of skeletal muscle AMP-activated protein kinase leads to glycogen accumulation. American Journal of Physiology-Endocrinology and Metabolism [Internet]. 2007 [cited 2025 Dec 17];292(3):E802–E811. Available from: https://doi.org/10.1152/ajpendo.00369.2006

28. Yamauchi T, Kamon J, Waki H, Brozinick J, Fiering S, Kemp BE, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med. 2001;7(8):941–946. Available from: https://doi.org/10.1152/ajpendo.00369.2006

29. Combs TP, Berg AH, Obici S, Scherer PE, Rossetti L. Endogenous glucose production is inhibited by the adipose-derived protein Acrp30. J Clin Invest [Internet]. 2001 [cited 2025 Dec 18];108(12):1875–1881. Available from: https://doi.org/10.1172/jci14120

30. Kobayashi H, Ouchi N, Kihara S, Walsh K, Kumada M, Abe Y, et al. Selective suppression of endothelial cell apoptosis by the high molecular weight form of adiponectin. Circ Res. 2004;94(4):e27-31. Available from: https://doi.org/10.1161/01.res.0000119921.86460.37

31. Wang Y, Lam KSL, Chan L, Chan KW, Lam JBB, Lam MC, et al. Post-translational Modifications of the Four Conserved Lysine Residues within the Collagenous Domain of Adiponectin Are Required for the Formation of Its High Molecular Weight Oligomeric Complex*. Journal of Biological Chemistry [Internet]. 2006 [cited 2025 Dec 17];281(24):16391–16400. Available from: https://doi.org/10.1074/jbc.m513907200

32. Qiang L, Wang H, Farmer SR. Adiponectin Secretion Is Regulated by SIRT1 and the Endoplasmic Reticulum Oxidoreductase Ero1-Lα. Mol Cell Biol [Internet]. 2007 [cited 2025 Dec 17];27(13):4698–4707. Available from: https://doi.org/10.1128/mcb.02279-06