Review

Energy Restriction and Adipose Tissue Remodeling: From Inflammation to Thermogenesis

Penbe Mısırlıoğlu *

Posted Date: 31 July 2025

doi: 10.20944/preprints202507.2634.v1

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 doi:10.20944/preprints202507.2634.v1

Review

Energy Restriction and Adipose Tissue Remodeling: From Inflammation to Thermogenesis

Penbe Misirlioğlu

Faculty of Health Sciences, Department of Nutrition and Dietetics, Başkent University, Ankara, Turkey; ecemmisirlioglu@gmail.com

Abstract

Humans possess two primary types of adipose tissue: white and brown. Under specific conditions - such as cold exposure- white adipose depots may undergo remodeling, giving rise to metabolically active beige adipocytes in a process termed "browning." Recent evidence confirms that functional brown adipose tissue (BAT) persists in adult humans, playing a vital role in systemic energy expenditure through uncoupling protein-1 (UCP-1) mediated thermogenesis. Beyond its storage function, adipose tissue is a dynamic endocrine organ involved in inflammation and metabolic regulation. Energy restriction not only facilitates fat loss but also triggers favorable remodeling in adipose tissue, attenuates low-grade inflammation, and enhances metabolic flexibility. This review discusses how energy restriction influences adipose tissue dynamics, with a focus on inflammation, browning, adipokine secretion, and thermogenic capacity.

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Introductıon

Obesity has become a widespread public health concern globally and is recognized as a significant contributor to the development of numerous metabolic disorders, such as insulin resistance, type 2 diabetes, dyslipidemia, hypertension, non-alcoholic fatty liver disease, and atherosclerosis [1]. The condition typically arises when long-term caloric intake surpasses the body's energy demands, leading to an excessive buildup of white adipose tissue, characterized by abnormal lipid accumulation within adipocytes [2,3].

Adipose tissue plays a central role in maintaining energy balance in the body. In times of nutrient surplus, it acts as an energy reservoir by storing triglycerides, whereas during periods of caloric deficit, it undergoes lipolysis to release fatty acids, ensuring a continuous energy supply to peripheral tissues [4].

Recent studies have highlighted that adipose tissue is a dynamic organ, capable of remodeling in response to environmental, nutritional, and hormonal cues. This remodeling involves changes in adipocyte size and number, shifts in immune cell composition, and the transdifferentiation of white to beige adipocytes under specific stimuli [5].

In addition to its metabolic functions, adipose tissue is a potent endocrine organ that secretes a wide range of adipokines and pro-inflammatory cytokines. In obesity, adipose tissue expansion leads to chronic low-grade inflammation, which plays a pivotal role in the pathogenesis of metabolic disorders. Among these secreted factors, adipokines are key cytokines that regulate inflammation, metabolism, appetite, cardiovascular function, immunity, and other physiological processes [6].

Mammals possess two primary forms of adipose tissue: white adipose tissue (WAT) and brown adipose tissue (BAT). In humans, BAT is predominantly located in specific regions such as the supraclavicular area, the lower neck, the spine, and parts of the abdominal cavity [7].

From both evolutionary and experimental perspectives, BAT plays a vital role in heat production, enabling warm-blooded animals to maintain their core body temperature in cold

 doi:10.20944/preprints202507.2634.v1

environments [8]. In contrast to white adipocytes, brown fat cells contain a higher number of mitochondria and smaller lipid droplets. Notably, smaller mammals—such as mice and rats—possess proportionally more BAT than larger mammals, including adult humans [9].

Stimulating brown adipose tissue activity to enhance energy expenditure has emerged as a promising therapeutic strategy against obesity. Recent findings confirm that functionally active BAT exists in adult humans [10]. A key feature of this tissue is its expression of uncoupling protein-1 (UCP-1), which facilitates the dissipation of energy as heat [11].

With the increasing global burden of obesity and its related metabolic complications, non-pharmacological strategies such as caloric restriction have attracted substantial scientific interest for their ability to induce beneficial metabolic and structural changes in adipose tissue. This review provides a comprehensive overview of the mechanisms by which energy restriction modulates adipose tissue biology, with particular emphasis on inflammatory responses, tissue remodeling, and thermogenic adaptations.

Structure and Function of Adipose Tissue

Adipose tissue is a subtype of connective tissue predominantly composed of adipocytes—cells specialized in storing lipids. Historically, its primary role has been understood as conserving excess energy in the form of triglycerides and releasing this stored energy—in the form of free fatty acids and glycerol—during periods of caloric deficiency, such as fasting.

Due to the body's limited capacity to store energy as glycogen, prolonged imbalances between energy intake and expenditure result in the accumulation of triacylglycerols within adipose cells, which, over time, contributes to the development of obesity [12].

Emerging evidence indicates that adipose tissue serves not only as an energy reservoir but also as an active endocrine organ, producing a variety of signaling molecules collectively referred to as adipokines or adipocytokines [13].

In obesity, the expansion of adipose tissue is associated with increased secretion of inflammatory mediators, including cytokines and chemokines such as TNF-α, IL-1, IL-6, along with acute-phase reactants like C-reactive protein. These proinflammatory factors, elevated in the bloodstream, are thought to originate primarily from adipose tissue itself.

As a result, the persistent, low-grade inflammation characteristic of obese adipose tissue is considered a key contributor to the elevated risk of metabolic and cardiovascular complications, including insulin resistance, type 2 diabetes, hypertension, metabolic syndrome, and coronary artery disease [14].

Adipose tissue is known to secrete over 50 hormones, with proteomic analyses suggesting that many more remain to be identified [15]. Among the most extensively studied adipokines are leptin, adiponectin, and resistin.

Leptin levels are proportional to the amount of adipose tissue and are influenced by dietary intake. It exerts anorectic effects and promotes increased energy expenditure [16]. However, in obesity, leptin resistance and hyperleptinemia are common, which limits the efficacy of leptin-based therapies. Interestingly, recent research suggests that lowering leptin levels in obese individuals may offer therapeutic benefits [17].

Adiponectin enhances glucose uptake in muscle, suppresses hepatic glucose production, and exerts anti-inflammatory effects [18]. In contrast, resistin—named for its role in promoting insulin resistance—is associated with inflammatory pathways and an increased risk of cardiometabolic disorders [19].

Functional Classification of Adipose Tissue: White, Brown, and Beige Fat

Body fat depots are categorized into three types: brown, white, and beige adipose tissue.

WAT: Storage and Endocrine Functions

 doi:10.20944/preprints202507.2634.v1

WAT serves as the primary site for energy storage in the human body and also functions as a dynamic endocrine organ involved in regulating metabolic balance and immune activity [20]. It is categorized into two major types based on anatomical location: subcutaneous and visceral fat.

Subcutaneous fat lies beneath the skin across various regions of the body and accounts for approximately 80% of total fat mass. In contrast, visceral adipose tissue, which surrounds internal organs, comprises a smaller proportion — around 20% in men and 5–8% in women [21].

The distribution of these fat depots has important clinical implications due to their differing metabolic profiles. Visceral adiposity is strongly associated with insulin resistance and a higher risk of cardiometabolic diseases, whereas subcutaneous fat may exert a more protective role against metabolic syndrome [22].

In humans, metabolically flexible fat depots are primarily located in the abdominal and thigh regions. The main visceral compartments include mesenteric and omental fat stores [23,24]. On a cellular level, white adipocytes are characterized by a single, large lipid droplet and relatively few mitochondria. By contrast, BAT is specialized for thermogenesis, producing heat and thereby increasing energy expenditure, particularly under conditions of cold exposure [20].

BAT: Thermogenesis and Energy Expenditure

While WAT primarily serves as a lipid storage site and exhibits metabolic activity, BAT functions as a thermogenic organ with high oxidative capacity. In both humans and rodents, BAT activation can be induced by short-term cold exposure or pharmacological stimulation via β-adrenergic receptor agonists. Upon activation, BAT enhances systemic energy expenditure by promoting the oxidation of fatty acids [21]. Anatomically, BAT is located in specific regions, including the supraclavicular and cervical areas, the abdominal cavity, and along the spinal column.

Brown adipocytes, characterized by high mitochondrial content and numerous small lipid droplets, are specialized for heat production. Early anatomical studies showed that BAT is abundant in newborns, leading to the belief that it largely diminishes after infancy. In human neonates, BAT constitutes approximately 5% of total body weight and is primarily located in the interscapular region at birth.

Although BAT was long thought to be present only in infants and Arctic indigenous populations, recent functional imaging studies have demonstrated its existence in adults as well, with metabolically active depots identified in regions such as the supraclavicular, thoracic, and abdominal areas [4]. Furthermore, advanced imaging techniques such as positron emission tomography/computed tomography (PET/CT) have confirmed that BAT persists into adulthood in certain individuals, although it is generally more abundant in children than in adults [25].

BAT activity is influenced by several factors, including age, sex, and body composition. It tends to be more active in lean, young individuals and is typically reduced in older or obese populations [24]. Some studies suggest that males exhibit higher BAT activity than females, and an inverse relationship has been observed between body mass index (BMI) or fat mass and BAT activation [26].

During cold exposure, brown adipose tissue contributes to overall energy metabolism by facilitating thermogenesis through the oxidation of fatty acids. In both humans and rodent models, cold exposure has been shown to enhance insulin sensitivity and improve glucose metabolism, suggesting that BAT may serve as a promising target to increase systemic energy expenditure and mitigate obesity and its related metabolic disorders. Experimental studies in animals demonstrate that BAT activation reduces weight gain, improves insulin responsiveness, enhances glucose tolerance, and lowers circulating free fatty acid levels, highlighting its critical role in metabolic regulation [27].

A key protein underlying BAT's thermogenic function is uncoupling protein-1 (UCP-1), which dissipates the mitochondrial proton gradient by bypassing ATP synthesis and releasing stored energy as heat [28]. This thermogenic process also contributes to the reduction of elevated triglycerides and cholesterol levels, thereby offering protection against atherosclerosis and other

 doi:10.20944/preprints202507.2634.v1

metabolic diseases. To sustain thermogenesis, BAT requires substantial metabolic inputs and utilizes multiple fuel sources, including glucose, circulating fatty acids, and intracellular triglycerides [25,29].

Emerging evidence also suggests that long-term dietary patterns may influence BAT activity. For instance, mice on a low-protein, high-carbohydrate diet demonstrated increased resting energy expenditure linked to enhanced BAT thermogenesis [30]. Likewise, rodents consuming a high-fat diet displayed improved cold adaptation, greater survival, and elevated mitochondrial density within BAT. Additionally, findings from ketogenic diet models support these observations, indicating a rise in total BAT mass and UCP-1 expression [31]. Overall, both white and brown fat depots contribute to the regulation of energy balance through complementary roles in storage and expenditure.

Beige Adipose Tissue: The Browning Process and Thermogenic Potential

Under certain stimuli, most notably, cold exposure-thermogenic beige adipocytes can emerge within WAT depots, including areas such as the suprascapular, subcutaneous anterior, and inguinal regions. This adaptive transformation is known as the "browning" process [31]. Beige adipocytes share functional similarities with classical brown fat cells, particularly in their metabolic response to cold, which includes elevated uptake of glucose and free fatty acids. Despite being present in lower abundance, beige cells also express UCP-1 and possess mitochondria capable of supporting thermogenesis [32,33].

	UCP-1 presence	Mitochondrial density	Lipid droplet	Basic function
White	-	Low	Single lipid droplet	Energy storage and endocrine
Beige	+	Medium	Multilocular lipid droplet	Thermogenesis and endocrine
Brown	+++	High	Multilocular lipid droplet	Thermogenesis and endocrine

Figure 1. Adipose Tissue Function and Location. Comparison of white, beige, and brown adipose tissues based on UCP-1 presence, mitochondrial density, lipid droplet morphology, and primary functions. White adipose tissue primarily serves as energy storage and has endocrine roles, characterized by low mitochondrial density and a single large lipid droplet. Beige adipose tissue exhibits intermediate mitochondrial density and multilocular lipid droplets, contributing to both thermogenesis and endocrine functions. Brown adipose tissue is highly thermogenic, with abundant mitochondria, high UCP-1 expression, and multilocular lipid droplets.

Mechanisms of Adipose Tissue Remodeling Under Energy Restriction

Energy restriction (ER) is a dietary approach characterized by a sustained reduction in caloric intake while maintaining adequate essential nutrient consumption. In human studies, this approach

 doi:10.20944/preprints202507.2634.v1

has been associated with numerous health benefits, including a lower risk of cardiovascular disease, hypertension, obesity, type 2 diabetes, chronic inflammation, and certain cancers [34]. As such, ER is widely recognized as a primary lifestyle intervention for the management of obesity. Long-term energy restriction has been demonstrated to reduce adipocyte size and promote beneficial remodeling of adipose tissue, notably by shifting fat distribution away from metabolically detrimental visceral white adipose tissue (vWAT) towards metabolically protective subcutaneous white adipose tissue (sWAT) [35,36]. In addition to this quantitative change, ER promotes qualitative remodeling of adipose tissue by enhancing vascularization, reducing fibrosis, and altering immune cell composition toward anti-inflammatory phenotypes—such as M2 macrophages and regulatory T cells (Tregs)—thus supporting tissue homeostasis and metabolic flexibility [36].

Recent research shows that inflammation-driven changes in adipose tissue are reversible and closely linked to insulin sensitivity and fat accumulation. In both obese humans and mouse models, increased levels of pro-inflammatory markers and macrophage infiltration correlate with insulin resistance. However, after weight loss induced by calorie restriction, the immune environment shifts: pro-inflammatory M1 macrophages decrease while anti-inflammatory M2 macrophages increase, helping to restore insulin sensitivity [5].

The role of adipose tissue in mediating the beneficial effects of ER is particularly evident in the context of surgical interventions. Bariatric procedures, especially Roux-en-Y gastric bypass, are among the most effective strategies for sustained weight loss and metabolic improvement in individuals with obesity. In a study involving 13 obese, non-diabetic women undergoing gastric bypass surgery, weight loss was associated with decreased adipose tissue inflammation, alleviation of endoplasmic reticulum stress, and enhanced antioxidant defense mechanisms [37].

ER refers to a 20–50% decrease in calorie intake compared to typical unrestricted (ad libitum) levels, implemented without causing nutrient deficiencies [38]. This intervention has been widely observed to enhance metabolic health and extend lifespan across multiple species, particularly during aging. One prominent effect of ER is a notable reduction in body fat. Since adipose tissue serves as a key endocrine organ, this fat loss may play a substantial role in mediating the metabolic benefits associated with calorie reduction.

By reducing excess fat and restoring adipose tissue functionality, ER helps counteract age-related metabolic disturbances, including hormonal imbalances and inflammation. Specifically, it lowers levels of leptin, resistin, and insulin, contributing to a decreased risk of chronic metabolic diseases [39]. Aging is often accompanied by hepatic insulin resistance, elevated insulin levels, and excessive white fat accumulation, especially in visceral regions [40].

In rodent models, calorie restriction for 12–20 weeks has been shown to lower metabolic rate, decrease brown fat mass, and reduce body temperature. Long-term restriction (40% reduction for 6–26 months) in rats led to brown fat enlargement without significantly changing UCP-1 gene expression [41].

In human studies, a structured diet intervention comprising an initial phase of very low-calorie intake (approximately 780–1000 kcal/day) followed by a six-month maintenance period was associated with decreased thermogenic activity in abdominal white fat, although changes in brown fat thermogenesis were not assessed. In another clinical trial, calorie restriction over 2 years was linked to reduced inflammatory gene expression in adipose tissue and improvements in metabolic markers such as fasting insulin and triglycerides [42].

A recent study examined how short-term dietary protein reduction influences metabolic outcomes in both young and aged mice. In older animals, limiting protein intake appeared to alleviate certain metabolic impairments commonly associated with aging. This improvement was linked to elevated circulating levels of fibroblast growth factor 21 (FGF21), increased browning activity in subcutaneous white adipose tissue, higher core temperature, and enhanced energy expenditure. Interestingly, despite these changes, glucose regulation and insulin sensitivity remained unaffected. The researchers concluded that temporary dietary protein restriction might improve metabolic function during aging, potentially through FGF21-related mechanisms without compromising

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skeletal muscle performance. Additionally, studies in FGF21 knockout mice confirmed that the absence of this hormone abolishes the metabolic benefits of protein restriction, further highlighting its central role in adaptation to nutrient availability [34].

Table 1. Energy restriction effects on adipose tissue: studies.

Study	Year	Topic	Key Findings	Source
Calcium Restriction and Adipose Thermogenesis	2025	Effects of caloric restriction on calcium levels and thermogenesis in white adipose tissue	Caloric restriction increases calcium levels in white adipose tissue, enhancing thermogenic activity	[43]
Time-Restricted Feeding and Metabolic Syndrome	2025	Impact of time-restricted feeding on brown adipose tissue thermogenesis	Time-restricted feeding activates thermogenesis in brown adipose tissue, improving metabolic syndrome	[44]
Protein Restriction and FGF21 Levels	2025	Dietary protein restriction effects on FGF21 and energy expenditure	Protein restriction increases FGF21 levels and boosts energy expenditure	[45]
Long-term (40%) caloric restriction in rats	2021	Effects of long-term caloric restriction on brown adipose tissue mass and ucp-1 expression in rats	Long-term (40%) caloric restriction in rats increased brown adipose tissue mass but did not change UCP-1 expression. Metabolic adaptations and thermoregulation were assessed.	[46]
Caloric Restriction and Diet-Induced Weight Loss on Browning of Subcutaneous WAT in Obese Adults	2018	Effect of caloric restriction and weight loss on browning of subcutaneous white adipose tissue in obese adults	No significant browning or increase in thermogenic markers in subcutaneous WAT after caloric restriction and weight loss in obese adults.	[47]
FGF21 regulates PGC-1α and browning of white adipose tissues in adaptive thermogenesis	2012	Role of FGF21 in browning of white adipose tissue and adaptive thermogenesis	FGF21 promotes browning of white fat and boosts energy expenditure during calorie restriction and cold.	[48]
Metabolic and thermogenic adaptation to energy restriction in aging	2011	Impact of long-term energy restriction on BAT function and metabolic health in aged mice	Energy restriction improved mitochondrial function and partially reversed age-related metabolic dysfunctions. BAT activity and thermogenesis were enhanced in aged mice.	[49]

Metabolic Effects of Energy Restriction and the Role of Inflammation

ER, when applied without inducing malnutrition, has been shown to extend lifespan and lower the risk of age-related diseases through multiple biological pathways. A consistent observation in ER models is the reduction of chronic low-grade inflammation, which may partly explain the decreased incidence of conditions such as osteoporosis, Alzheimer's disease, cardiovascular diseases, and

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certain cancers. This suggests that excessive energy storage may play a key role in initiating chronic inflammation.

Recent insights from obesity research reinforce this idea, indicating that chronic inflammation is often a consequence of energy surplus. Emerging evidence proposes that inflammatory signaling promotes energy expenditure as a feedback mechanism to counteract energy overload. However, when this feedback system is disrupted—a condition referred to as "inflammation resistance"—energy expenditure decreases, leading to further energy storage and the development of obesity.

Thus, inflammation may act as a regulatory mechanism for energy homeostasis: elevated inflammation in obesity encourages energy dissipation, whereas reduced inflammation during ER helps conserve energy [35].

Thermogenic Adaptations Induced by Energy Restriction

Energy restriction (ER) triggers a range of metabolic and cellular adaptations that support thermogenesis and help maintain energy homeostasis. A key mechanism involves the activation of brown adipose tissue (BAT) and the browning of white adipose tissue (WAT), largely driven by enhanced activity of the sympathetic nervous system (SNS). Through the release of catecholamines—particularly norepinephrine—ER stimulates β3-adrenergic receptors on adipocytes, activating signaling cascades that promote lipolysis and the expression of thermogenic genes, most notably Ucp1. This protein is central to heat generation by uncoupling mitochondrial respiration from ATP synthesis [25].

Beyond this classical pathway, ER also enhances mitochondrial biogenesis and function, with upregulation of critical regulators such as PGC-1α, NRF1/2, and TFAM, leading to increased mitochondrial number and efficiency [50].

Importantly, recent studies indicate that thermogenic responses are not solely dependent on Ucp1. Under conditions of low Ucp1 expression or genetic knockout, alternative pathways—such as creatine cycling, calcium handling, and lipid cycling—can also drive thermogenesis. These mechanisms operate by elevating substrate turnover and ATP consumption, ultimately producing heat independently of Ucp1 [51].

Additionally, ER contributes to the immune remodeling of adipose tissue. A shift toward an anti-inflammatory immune profile, including increased M2 macrophages and regulatory T cells (Tregs), fosters a tissue environment that supports metabolic flexibility and enhances thermogenic potential [52].

Energy restriction triggers a multifaceted physiological response involving neural and hormonal signals, as well as mitochondrial and immune adaptations, which collectively enhance the thermogenic capacity of adipose tissue. These coordinated mechanisms help sustain energy expenditure and support metabolic health during periods of reduced caloric intake.

Conclusion and Future Directions

In both humans and rodents, BAT can be activated by short-term cold exposure or β-adrenergic receptor stimulation, resulting in increased energy expenditure and fatty acid oxidation. Caloric restriction—when implemented without compromising nutritional adequacy—remains a widely utilized strategy for managing obesity and related metabolic disorders. The most effective outcomes are often achieved when dietary interventions are combined with regular physical activity.

Adipose tissue regulates thermogenesis through both Ucp1-dependent and Ucp1-independent pathways, supporting energy balance under varying physiological conditions. Furthermore, individual variability, genetic predispositions, and environmental factors play crucial roles in modulating BAT activity and the metabolic adaptations to energy restriction.

Although much of our current understanding is derived from animal studies, additional research is needed to elucidate the underlying mechanisms in humans. Advancing this knowledge

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will be essential for developing innovative and targeted strategies to prevent and treat obesity and its associated complications.

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