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The Role of Brown and Beige Adipose Tissue Activation in Diabetes Prevention

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ABSTRACT

Brown and beige adipose tissues (BAT and BeAT) are thermogenic fat depots that dissipate energy as heat via uncoupling protein-1 (UCP1) and complementary UCP1-independent mechanisms. Their activation increases whole-body substrate oxidation, improves insulin sensitivity, and modulates hepatic and skeletal-muscle metabolism through endocrine "batokines." In humans, cold exposure and β-adrenergic stimulation acutely activate BAT, while repeated exposures drive the "browning" of white adipose tissue into beige adipocytes. Observational and interventional studies link higher BAT activity with lower fasting glucose, reduced triglycerides, and improved glucose tolerance, suggesting a role in preventing type 2 diabetes (T2D). This review summarizes the developmental origins and molecular control of BAT and beige fat, integrates evidence from animal and human studies on glucose homeostasis, and evaluates lifestyle, pharmacologic, and device-based strategies to activate thermogenic adipose tissue. We also address safety, feasibility, and knowledge gaps including heterogeneity of human BAT, durability of responses, and the need for clinically meaningful endpoints. Collectively, available data support BAT and beige adipose activation as a plausible, multifaceted approach to diabetes prevention, particularly when combined with diet and physical activity. However, translating mechanistic promise into population-level impact will require rigorous trials, standardized measurement, and long-term risk-benefit assessment.

Keywords: Brown Adipose Tissue; Beige Adipose Tissue; Thermogenesis; Type 2 Diabetes Prevention; Batokines

INTRODUCTION

Diabetes mellitus, encompassing both type 2 diabetes (T2D) and forms of dysglycemia that precede or accompany obesity, arises from a complex interplay between insulin resistance and impaired β-cell function[1, 2]. For decades, prevention strategies have focused primarily on reducing caloric intake, increasing physical activity, and prescribing insulin sensitizers. Yet the global incidence of T2D continues to climb, prompting renewed interest in energy-dissipating tissues that can counter positive energy balance while directly improving glucose homeostasis[3, 4]. Brown adipose tissue (BAT) and inducible beige adipocytes embedded within white adipose depots (collectively termed "thermogenic adipose") have emerged as compelling targets[5, 6]. Unlike white adipocytes, which store triglycerides, thermogenic adipocytes burn fuels to produce heat, largely through uncoupling protein-1 (UCP1) in mitochondria. Even modest activation of these tissues increases whole-body glucose uptake and fatty-acid oxidation, with measurable effects on circulating metabolites and insulin action[7–9].

In adult humans, metabolically active BAT is detectable in the supraclavicular, cervical, paravertebral, and perirenal regions, and its activity varies with age, sex, adiposity, and climate[10]. Cold exposure and β-adrenergic stimulation acutely activate BAT, while repeated stimuli recruit beige adipocytes within subcutaneous white fat, a process often termed "browning." Beyond heat production, thermogenic adipocytes are endocrine cells that secrete cytokines, lipokines, and peptides collectively "batokines" that influence the liver, skeletal muscle, pancreas, vasculature, and the central nervous system[11, 12]. Examples include neuregulin-4, 12,13-diHOME, and adiponectin-modulating signals, which together promote lipid clearance, enhance insulin-stimulated glucose uptake in muscle, suppress hepatic lipogenesis, and may preserve β-cell identity under metabolic stress[13].

Mechanistically, activating brown and beige fat improves glycemia through several converging routes. First, increased glucose uptake by thermogenic adipocytes directly lowers glycemic excursions and increases disposal of postprandial glucose. Second, oxidation of fatty acids reduces ectopic lipid accumulation in liver and muscle,

thereby alleviating lipotoxicity, a recognized driver of insulin resistance. Third, elevated resting energy expenditure creates a negative energy gap that facilitates weight loss or weight-neutral improvements in insulin sensitivity[14]. Importantly, thermogenic activation also reshapes adipose tissue immune tone—skewing macrophages toward anti-inflammatory phenotypes and reducing pro-inflammatory cytokines that impair insulin signaling. Neural circuits linking the hypothalamus with adipose depots integrate thermal, nutritional, and hormonal cues; these circuits can be harnessed by behavioral and pharmacologic interventions to sustain thermogenesis without intolerable cold exposure[14].

Translational data support a protective role of BAT and beige recruitment in humans. Individuals with greater BAT activity exhibit lower odds of T2D and dyslipidemia, independent of body mass index, and demonstrate improved insulin sensitivity during cold exposure or pharmacologic activation[15]. Although the absolute mass of human BAT is small compared with white fat, its high perfusion, dense mitochondria, and rapid fuel turnover magnify systemic effects. Moreover, beige adipocyte recruitment within abundant subcutaneous white fat may scale thermogenic capacity beyond classical BAT depots[16]. Together, these insights position brown and beige adipose activation as a promising adjunct to lifestyle modification and incretin-based therapies for diabetes prevention, particularly in high-risk individuals with obesity, prediabetes, or cardiometabolic syndrome[16].

The emerging view positions thermogenic adipose tissue as both a metabolic sink and an endocrine node that coordinates multi-organ crosstalk. For prevention, this matters because early disease is characterized by subtle impairments in insulin action that are reversible if energetic balance and tissue lipid handling are corrected. Interventions that safely and sustainably raise thermogenic tone by lifestyle, environment, or pharmacology could therefore tilt physiology away from diabetogenesis without relying solely on weight loss[17, 18]. This is especially appealing for individuals who struggle to lose weight, older adults with sarcopenic obesity, and people in cold climates where traditional exercise is difficult.

At the same time, there are important caveats. Thermogenic activation increases sympathetic nervous system drive and may elevate blood pressure or cardiac workload in susceptible patients; compensatory hyperphagia could offset energy dissipation; and the plasticity of human BAT declines with age and obesity, potentially limiting effect size[19]. Furthermore, the field still debates the relative contributions of UCP1-dependent uncoupling versus UCP1-independent pathways such as creatine-futile cycling, Ca2+-cycling via SERCA, and triglyceride/fatty-acid cycling. These mechanistic uncertainties influence biomarker selection, imaging readouts, and how clinical endpoints are interpreted[19]. This review synthesizes current knowledge on the role of brown and beige adipose tissue activation in diabetes prevention. We first outline the cellular and molecular mechanisms that link thermogenesis to glucose homeostasis. We then survey modifiable triggers cold, diet, exercise, and circadian cues and emerging therapeutics that recruit or activate thermogenic adipocytes. Finally, we discuss human evidence, safety considerations, and research gaps that must be addressed before large-scale prevention programs can be implemented. Together, these perspectives suggest that targeted activation of brown and beige fat, integrated with established lifestyle measures and cardiometabolic medications, represents a realistic and potentially powerful strategy to blunt the trajectory from insulin resistance to overt diabetes.

Mechanisms of Thermogenic Activation

Brown and beige adipocytes exert their unique metabolic role through specialized mechanisms that dissipate chemical energy as heat. At the core of this process lies uncoupling protein 1 (UCP1), a mitochondrial inner membrane protein that disrupts the proton gradient normally used for ATP synthesis[20]. Instead of driving ATP production, protons leak back across the inner mitochondrial membrane, releasing energy as heat. This mechanism, known as non-shivering thermogenesis, enables thermogenic adipocytes to act as metabolic sinks for glucose and fatty acids, thus influencing systemic energy and glucose homeostasis[20].

The sympathetic nervous system (SNS) is the primary activator of BAT. Environmental stimuli such as cold exposure, diet-induced thermogenesis, or even psychological stress trigger SNS outflow to adipose depots[21]. Norepinephrine, released from sympathetic nerve endings, binds to β3-adrenergic receptors (β3-ARs) on adipocyte membranes. This activates adenylyl cyclase, elevates cyclic AMP (cAMP), and stimulates protein kinase A (PKA). PKA phosphorylates downstream effectors, including hormone-sensitive lipase (HSL) and perilipin, thereby promoting lipolysis[22]. The liberated fatty acids serve a dual role: providing substrate for mitochondrial β-oxidation and directly binding to UCP1, allosterically activating proton leak and heat generation.

In addition to UCP1-driven uncoupling, UCP1-independent pathways contribute significantly, especially in beige adipocytes. These include the creatine-phosphate futile cycle, where ATP is repeatedly consumed and regenerated without network, dissipating energy as heat; SERCA2b-mediated Ca^{2+} cycling, in which calcium ions are continually pumped into the sarco/endoplasmic reticulum and leak back, costing ATP and generating thermogenesis; and triglyceride/fatty acid cycling, where repeated esterification and hydrolysis of fatty acids consumes ATP[23]. These diverse pathways broaden the repertoire of thermogenic mechanisms beyond UCP1, offering therapeutic potential even in individuals with low UCP1 expression.

At the transcriptional level, several master regulators orchestrate thermogenic programming. Peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) enhances mitochondrial biogenesis and oxidative capacity. PRDM16, a zinc-finger transcription factor, directs progenitor cells toward brown/beige

adipocyte fate[24]. PPARγ, a central regulator of adipogenesis, in concert with PGC-1α, drives the thermogenic gene network. Together, these transcriptional regulators ensure robust mitochondrial density, increased vascularization, and a phenotype optimized for rapid fuel mobilization and oxidation[24].
Importantly, thermogenic adipocytes secrete batokines, signaling molecules that influence systemic metabolism. Neuregulin-4 (NRG4) suppresses hepatic lipogenesis; 12,13-diHOME enhances skeletal muscle fatty acid uptake; and adiponectin-modulating factors improve insulin sensitivity[25]. These endocrine outputs extend the impact of BAT beyond heat production, positioning thermogenic adipocytes as central hubs of metabolic regulation with profound implications for glucose homeostasis and diabetes prevention.

Lifestyle and Environmental Modulators

The activation and recruitment of thermogenic adipose tissue are strongly shaped by lifestyle and environmental exposures. Among these, cold exposure is the most potent physiological activator of brown fat. Repeated mild cold acclimation typically maintaining ambient temperatures of 16–19 °C for 1–2 hours daily significantly enhances BAT activity as measured by glucose uptake and mitochondrial density[26]. Prolonged cold also recruits beige adipocytes within subcutaneous white fat, a process termed "browning." This adaptation increases total thermogenic capacity and can persist beyond the exposure period, highlighting the feasibility of intermittent protocols in everyday life[26].
Exercise**,** although not a direct BAT activator in humans, plays a key role in promoting browning of white adipose tissue [27]. Contracting skeletal muscle secretes myokines such as irisin and meteorin-like, as well as natriuretic peptides, which signal to adipocytes to upregulate thermogenic genes and mitochondrial biogenesis. These signals expand beige adipocyte populations, indirectly increasing energy expenditure and improving systemic glucose metabolism. In animal models, exercise enhances both BAT vascularization and responsiveness to adrenergic stimulation, though human data remain less robust[27].
Dietary factors also influence thermogenesis. Protein-rich diets exert a thermogenic effect via diet-induced thermogenesis, increasing SNS tone and fuel oxidation. Polyphenols, including catechins in green tea and resveratrol in grapes, activate AMP-activated protein kinase (AMPK) and PGC-1α, promoting browning and mitochondrial activity[28]. Capsaicin**,** a bioactive compound in chili peppers, stimulates TRPV1 receptors, mimicking cold exposure by triggering SNS outflow to BAT. Although these nutritional modulators produce modest effects compared with cold, they represent accessible adjuncts for individuals unable to tolerate cold exposure. Circadian rhythms and sleep exert additional control over thermogenic tone. The SNS exhibits diurnal variation, with sympathetic activity and BAT glucose uptake peaking at specific circadian phases. Misalignment—such as shift work or sleep deprivation—attenuates BAT function and increases risk of insulin resistance. Conversely, aligning feeding and activity with circadian cycles optimizes thermogenic efficiency and may enhance glucose handling[29].
Environmental and lifestyle modulators are attractive because they leverage natural physiological pathways with minimal pharmacological intervention. However, individual responses vary based on genetics, age, sex, adiposity, and prior cold exposure. Integrating cold acclimation, structured exercise, and dietary strategies with circadian health may synergistically enhance thermogenesis[30]. Together, these approaches demonstrate that environmental manipulation and lifestyle behaviors can serve as non-pharmacologic tools to activate brown and beige fat, improving energy balance and reducing diabetes risk in a sustainable and accessible manner[30].

Pharmacologic and Nutraceutical Approaches

While lifestyle strategies hold promise, pharmacologic and nutraceutical interventions aim to harness thermogenesis more consistently and independently of environmental limitations. The most studied agents are β3-adrenergic receptor agonists, which mimic sympathetic stimulation of BAT[31]. These drugs, such as mirabegron, have been shown to increase BAT glucose uptake, elevate resting energy expenditure, and improve insulin sensitivity in humans. However, widespread use has been limited by side effects, including tachycardia and hypertension, due to off-target activation of β1- and β2-receptors in the heart and vasculature. Lower, carefully titrated doses may offer metabolic benefits with acceptable safety profiles, but long-term trials are needed[31].
Beyond β3 agonists, several compounds emulate cold-induced signaling**.** Capsaicin and capsinoids activate TRPV1 receptors, stimulating catecholamine release and indirectly engaging BAT thermogenesis. Nutraceuticals such as green tea catechins and resveratrol activate AMPK-PGC-1α pathways, increasing mitochondrial biogenesis and promoting beige adipocyte formation[32]. Although their thermogenic effect is modest, they are generally safe and can be incorporated into broader dietary interventions. Thyroid hormone analogs, particularly those selective for thyroid hormone receptor-β (TRβ), stimulate mitochondrial metabolism and BAT activity but carry risks of arrhythmia, bone resorption, and muscle wasting when used chronically[33].
Emerging pharmacotherapies target molecular drivers of beige adipogenesis and batokine secretion. Agents that modulate PPARγ not only enhance insulin sensitivity but also promote beige cell recruitment. Fibroblast growth factor 21 (FGF21) analogs, already in clinical development for obesity and diabetes, enhance energy expenditure and BAT activity while improving lipid metabolism[34]. Neuregulin-4 (NRG4) mimetics and bone morphogenetic proteins (BMP7/8) are being explored for their ability to enhance thermogenic programming at

the transcriptional level. Additionally, approaches that enhance mitochondrial creatine cycling or calcium handling represent novel therapeutic frontiers for UCP1-independent thermogenesis[35].
Interestingly, incretin-based multi-agonists, including GLP-1/GIP/GCGR triagonists, primarily reduce body weight by suppressing appetite and enhancing insulin secretion. However, preclinical studies suggest these agents may also upregulate BAT activity and beige recruitment, providing dual benefits for both weight control and glucose homeostasis[36–38]. This synergy positions them as potential cornerstone therapies in diabetes prevention when combined with lifestyle strategies.
Overall, pharmacologic and nutraceutical approaches represent a rapidly expanding area of research. The challenge lies in balancing efficacy with safety, given the cardiovascular sensitivity of BAT pathways. Carefully designed trials, particularly those integrating pharmacologic agents with lifestyle-based activation, may yield synergistic outcomes that are both potent and sustainable for diabetes prevention.

Clinical Evidence and Prevention Potential

The translation of BAT and beige adipose activation into clinical diabetes prevention depends on robust human evidence. Observational studies using PET-CT imaging consistently demonstrate that individuals with higher BAT activity exhibit lower fasting glucose, reduced triglycerides, improved insulin sensitivity, and lower prevalence of type 2 diabetes (T2D). Importantly, these associations are independent of body mass index, suggesting that BAT confers metabolic advantages beyond weight regulation[39]. Individuals with active BAT also tend to exhibit better lipid profiles and reduced incidence of cardiovascular disease, reinforcing its systemic impact[39]. Interventional trials have provided causal evidence. Short-term cold acclimation protocols (e.g., daily exposure to 17–19 °C for 2–6 weeks) improve whole-body insulin sensitivity, increase glucose disposal, and reduce hepatic fat content, even without significant changes in body weight[40]. In overweight men with T2D, cold acclimation improved peripheral glucose uptake, while in prediabetic individuals it enhanced postprandial lipid clearance. These results underscore the potential of non-pharmacological interventions to augment metabolic health through BAT recruitment[40].
Nonetheless, the magnitude of effect varies widely. Age and obesity are major determinants: BAT activity declines with advancing age and higher adiposity, partly due to reduced sympathetic responsiveness and increased white fat infiltration. Genetic background, sex hormones, and environmental acclimatization also modulate responsiveness. This heterogeneity emphasizes the need for personalized approaches that account for individual variability in BAT mass and activity[41].
In terms of prevention, BAT activation holds promise as a complement to established strategies such as diet, exercise, and pharmacologic weight loss therapies. Combining cold-induced thermogenesis with weight-reducing medications (e.g., GLP-1 receptor agonists) may yield additive or synergistic improvements in glucose homeostasis[42]. This is particularly relevant in high-risk groups such as individuals with prediabetes, gestational diabetes history, or metabolic syndrome, where early interventions are crucial to delaying or preventing disease progression. Long-term studies remain limited. While short-term benefits on insulin sensitivity and lipid metabolism are clear, the durability of BAT activation and its impact on diabetes incidence remain untested in large-scale trials. Furthermore, imaging-based assessments of BAT are expensive and impractical for routine use, highlighting the need for non-invasive biomarkers (e.g., circulating batokines, lipid metabolites, or wearable thermography) to track activity in prevention programs[43].
Clinical evidence strongly supports BAT and beige adipose activation as beneficial for metabolic health, but the field is still at an early translational stage. The challenge moving forward is to establish clinically meaningful endpoints, demonstrate long-term safety and efficacy, and integrate thermogenic activation into scalable, population-level diabetes prevention strategies.

Safety, Equity, and Implementation Challenges

While the metabolic benefits of activating brown and beige adipose tissue are promising, practical implementation is tempered by safety concerns and social inequities. Cold exposure, the most physiological activator, is not universally tolerated. For elderly individuals, those with cardiovascular disease, or hypertensive patients, cold can acutely increase blood pressure and cardiac workload, raising the risk of adverse events. Similarly, chronic activation of the sympathetic nervous system may exacerbate arrhythmias or impair sleep quality. β-adrenergic agonists, though effective in stimulating BAT, often elevate heart rate and blood pressure, limiting their suitability for chronic use[44]. Thyroid hormone analogs, while thermogenic, risk bone loss, muscle wasting, and arrhythmias, underscoring the need for cautious dosing and monitoring.
Socio-environmental barriers also shape the feasibility of thermogenic interventions. Cold acclimation protocols are less practical in tropical or low-income settings where access to climate control or cooling technologies is limited. Housing quality, occupational exposures, and cultural preferences regarding comfort temperatures all influence adherence. For many, intentionally lowering home temperatures is economically or socially impractical. Similarly, wearable cooling devices or cold-water immersion therapies may not be accessible or culturally acceptable across all populations[45]
Equity considerations extend to pharmacologic interventions. Many emerging agents are costly and may not be available in low-resource settings where diabetes incidence is rising most rapidly. Without strategies for equitable access, therapies targeting thermogenesis risk widening health disparities[46]. Ethical deployment

therefore demands low-cost, culturally acceptable strategies such as modest indoor cooling, intermittent cold showers, or dietary adjuncts (e.g., capsaicin-rich foods) that can be adapted across diverse environments.

From an implementation perspective, monitoring and safety frameworks are essential. Standardized protocols for cold exposure, pharmacologic dosing, and biomarker tracking need to be established to ensure benefits outweigh risks. Development of batokine-based blood tests or wearable thermographic devices could provide accessible ways to monitor activity and tailor interventions. Additionally, guidelines must emphasize contraindications for high-risk populations, ensuring that interventions are personalized and safe[47].

Future research should focus on long-term outcomes, testing whether BAT activation reduces incident diabetes and cardiovascular events over years rather than weeks. Moreover, implementation science is needed to evaluate scalable interventions in real-world settings such as workplaces, schools, and clinics. Addressing cultural diversity, socioeconomic status, and health equity will be central to ensuring thermogenic activation strategies are not only effective but also inclusive. Ultimately, the successful translation of BAT-based diabetes prevention will hinge on balancing efficacy, safety, and accessibility, ensuring that metabolic innovation benefits all populations equitably.

CONCLUSION

Several priorities could accelerate translation. First, develop simple biomarkers of thermogenic tone, circulating batokines, lipid signatures, or wearable-derived thermography, to replace costly PET-CT. Second, test combination regimens pairing browning stimuli with GLP-1 receptor agonists or SGLT2 inhibitors to leverage complementary mechanisms: appetite reduction, natriuresis, and enhanced oxidation. Third, deepen focus on UCP1-independent heat production that may persist in aged or UCP1-low tissue. Fourth, embrace precision: genetics, sex, ethnicity, and microbiome composition shape responses to cold or β-agonism, implying that targeted selection will raise benefit-to-risk ratios. Finally, implementation science is essential; pragmatic trials in workplaces, schools, and clinics can identify scalable, climate-appropriate protocols that fit daily life without stigma.

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