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UCP-1-Driven adipose tissue remodelling: Emerging insights for targeting visceral obesity and PCOS

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Abstract
Polycystic ovary syndrome (PCOS) is a prevalent endocrine-metabolic condition in reproductive-aged women and is frequently accompanied by ovulatory dysfunction and biochemical or clinical hyperandrogenism. The syndrome also increases susceptibility to metabolic complications such as insulin resistance, dyslipidemia, and fatty liver. Adipose tissue particularly visceral white adipose tissue (WAT) plays a central role in these abnormalities. Although traditionally viewed as an energy-storage depot, adipose tissue is now recognized as an active endocrine organ with pivotal functions in metabolic homeostasis.

In PCOS, disturbances in adipocyte biology, including altered fat distribution, increased visceral adiposity, and adipocyte hypertrophy, worsen insulin resistance and perpetuate hyperandrogenism. In contrast, brown adipose tissue (BAT) characterized by uncoupling protein 1 (UCP-1) supports energy expenditure and thermogenesis. BAT activity and mass are diminished in women with PCOS, contributing to impaired post-prandial thermogenesis and adverse metabolic profiles. The suppression of UCP-1 expression by excess androgens further links hyperandrogenism to disrupted mitochondrial function.

This review synthesizes current evidence on WAT and BAT dysfunction in PCOS, highlights the mechanistic relevance of UCP-1, and examines emerging therapeutic possibilities, including strategies aimed at activating BAT or promoting WAT browning.

Keywords: Insulin resistance, UCP-1, White adipose tissue, Brown adipose tissue, Visceral adiposity, PCOS, Thermogenesis

Introduction

Polycystic ovary syndrome (PCOS) represents the most common endocrine-metabolic disorder affecting women of reproductive age, with a global prevalence estimated between 6% and 10% [1]. It remains the leading cause of anovulatory infertility. Diagnostic confirmation typically relies on established criteria encompassing oligo- or anovulation, clinical or biochemical manifestations of hyperandrogenism, and ultrasonographic evidence of multifollicular ovarian morphology [2]. Although widely studied, the underlying pathophysiology of PCOS remains incomplete, likely involving complex interactions between genetic predisposition, epigenetic influences, and environmental factors.

A hallmark feature of PCOS is the high prevalence of insulin resistance affecting over 70% of affected individuals which is closely connected to compensatory hyperinsulinemia. Elevated insulin levels reduce hepatic production of sex hormone-binding globulin (SHBG) and stimulate androgen synthesis in ovarian thecal cells. Visceral white adipose tissue (WAT), located around intra-abdominal organs, appears to be a key contributor to these metabolic and endocrine disturbances. Increased visceral fat is associated with exacerbated insulin resistance, elevated androgen levels, and a heightened risk of metabolic syndrome, type 2 diabetes, and cardiovascular disease in women with PCOS [3, 4].

In contrast, brown adipose tissue (BAT) contains the thermogenic protein uncoupling protein 1 (UCP-1), which mediates adaptive heat production by diverting mitochondrial respiration away from ATP generation [5, 6]. BAT's contribution to energy expenditure and metabolic flexibility has gained attention for its potential relevance to PCOS, where reduced BAT mass and diminished UCP-1 activity have been observed.

This review provides an integrated overview of adipose tissue biology, the contrasting roles of WAT and BAT, and how dysfunction within these tissues contributes to the metabolic complexities of PCOS.

Adipose Tissue and its Function and General Characteristics

Adipose tissue is now widely regarded as a multifunctional endocrine organ rather than a passive energy reservoir. It plays a decisive role in regulating systemic metabolism, immune activity, and hormonal signaling. Adipocytes communicate through autocrine, paracrine, and endocrine pathways to influence whole-body energy balance.

Two primary adipose depots are recognized in humans: white adipose tissue (WAT) and brown adipose tissue (BAT), each displaying distinct cellular features and metabolic roles [7].

Table 1: Key Distinctions Between White and Brown Adipose Tissue

Characteristic	White Adipocytes (WAT)	Brown Adipocytes (BAT)
Relative abundance	Major adipose compartment	Present in smaller quantities
Primary function	Long-term energy storage	Heat production and elevated energy expenditure
Lipid droplet morphology	Dominantly unilocular	Multilocular with numerous small droplets
Mitochondrial density	Relatively low	Abundant mitochondria enriched with UCP-1
Common anatomical sites	Visceral and subcutaneous regions	Supraclavicular, cervico-thoracic, periaortic, peri-renal zones
UCP-1 expression	Essentially absent	Highly expressed
Age-related change	Proportion increases with age	Activity and volume decline across lifespan

White adipose tissue (WAT) consists of adipocytes containing a single large lipid droplet and relatively few mitochondria. Its main function is to sequester excess energy as triglycerides, releasing fatty acids during periods of energy deficit. WAT is composed not only of mature adipocytes but also stromal vascular elements such as fibroblasts, preadipocytes, endothelial cells, and resident immune cells. It produces numerous adipokines that modulate metabolic and inflammatory processes. Visceral WAT is particularly implicated in metabolic risk, as its anatomical position and secretory profile contribute disproportionately to cardiometabolic complications [8].

Brown adipose tissue (BAT), in contrast, is built from multilocular adipocytes containing abundant mitochondria enriched with UCP-1. This protein enables BAT to dissipate energy through heat production (non-shivering thermogenesis). BAT depots are heavily vascularized and densely innervated by sympathetic fibers, contributing to their distinctive brown coloration. BAT participates in whole-body energy regulation and communicates with other tissues via thermogenic and endocrine mechanisms [9, 10].

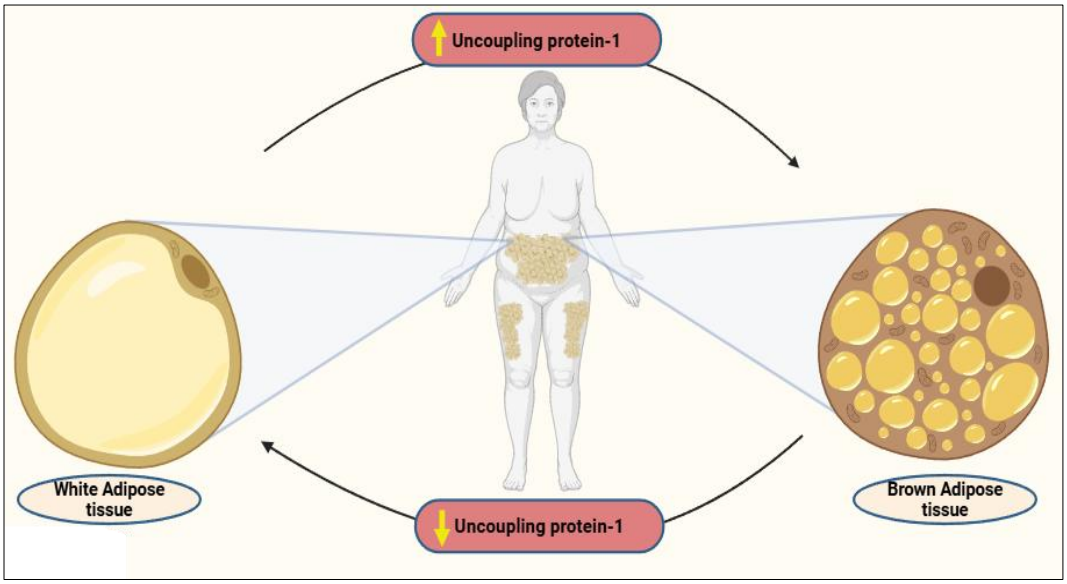

Fig 1: Conceptual representation of how UCP-1 activation facilitates the phenotypic conversion of white adipocytes toward a more thermogenically active, brown-like state, contributing to enhanced energy expenditure.

PCOS and White Adipose Tissue: WAT Malfunction

Dysregulation of white adipose tissue is a prominent and mechanistically important contributor to both the metabolic and reproductive manifestations of PCOS. WAT dysfunction in this context encompasses impaired adipogenesis, diminished glucose uptake, altered adipokine release, and the development of a chronic low-grade inflammatory state all of which reinforce systemic insulin resistance and promote hyperandrogenism [11, 12].

Under normal physiological conditions, expansion of adipose tissue occurs primarily through hyperplasia (formation of new adipocytes). However, in PCOS, adipocyte hypertrophy predominates, particularly within the subcutaneous depot. Although the early phases of insulin signaling remain relatively intact, insulin-stimulated glucose transport is consistently diminished in women with PCOS. This impaired glucose handling contributes to circulating metabolic derangements through effects on lipid flux and adipokine secretion.

A decline in mitochondrial respiration and a reduction in thermogenic efficiency further exacerbate WAT dysfunction in PCOS, perpetuating a cycle of reduced energy expenditure and aggravated insulin resistance [13-15].

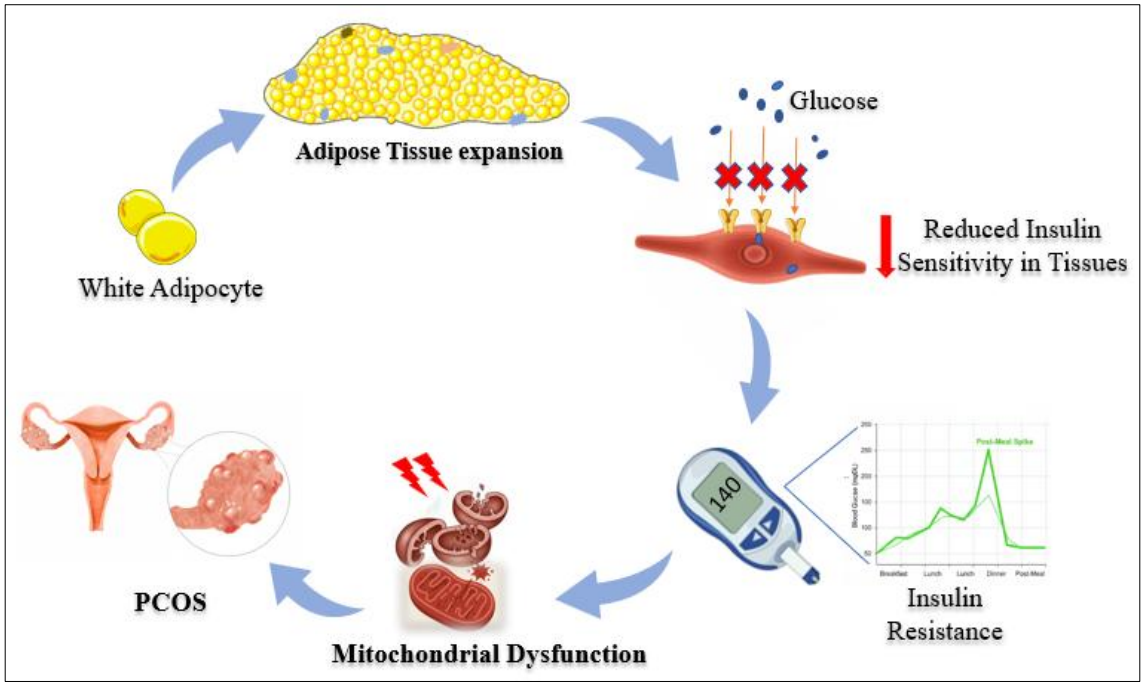

Fig 2: Schematic representation of the progressive disturbances occurring within white adipose tissue in PCOS, highlighting impaired adipogenesis, altered adipokine profiles, inflammatory signaling, and metabolic inflexibility that collectively contribute to systemic insulin resistance.

Insulin Resistance in PCOS and WAT Malfunction: Are There Emerging Therapeutic Targets?

Insulin resistance is present in approximately 70% of women with PCOS, cutting across both obese and normal-weight phenotypes [16-18]. When insulin responsiveness declines, compensatory hyperinsulinemia develops, amplifying the risk of type 2 diabetes and accelerating metabolic deterioration. Abnormal accumulation of white adipose tissue particularly in visceral regions is recognized as a major precursor to dysglycemia and cardiometabolic dysfunction [19, 20]. Indeed, elevated waist-to-hip ratio has been linked to reduced insulin sensitivity and higher circulating androgen levels, underscoring a close association between fat distribution patterns and hormonal imbalance [21]. Evidence from Indian populations further emphasizes this relationship. In a cohort comparing women with PCOS to age- and BMI-matched controls, individuals with PCOS exhibited substantially greater total fat mass, truncal fat content, and visceral adipose tissue. Insulin resistance was observed in roughly 80% of obese women with PCOS and approximately 20% of non-obese women with PCOS. Importantly, even after adjusting for BMI, an increased adipose-to-lean mass ratio remained independently correlated with adverse fasting insulin and HOMA-IR profiles [22-24].

These findings point to visceral adiposity and the accompanying dysfunction of WAT as a central driver of insulin resistance in PCOS. The metabolic and endocrine consequences of altered fat distribution reinforce the urgency of exploring therapies that can meaningfully modulate adipose biology.

Therapeutic Investigations

Several pharmacologic and nonpharmacologic strategies have been explored to favorably modify adipose tissue behavior in PCOS, with varying degrees of success in clinical and pre-clinical settings**.**

Metformin

Metformin remains widely used for addressing metabolic abnormalities and reducing androgen excess in PCOS. However, despite its favorable influences on insulin sensitivity and lipid parameters, metformin has not consistently produced significant reductions in body weight or visceral fat volume. In a randomized, double-blind study, 12 weeks of metformin therapy did not yield meaningful changes in visceral adiposity, although improvements in lipid markers were documented [25, 26].

GLP-1 Receptor Agonists

GLP-1 receptor agonists, originally developed for type 2 diabetes and obesity, have recently been investigated for their potential benefits in PCOS [27, 28]. Women with PCOS exhibit approximately a 31% reduction in GLP-1 secretion, with levels particularly suppressed in those with obesity [29]. A landmark 2018 randomized clinical trial demonstrated that 26 weeks of GLP-1 agonist therapy significantly reduced intrahepatic fat content and visceral adipose tissue in PCOS participants [30, 31]. These findings suggest that GLP-1 agonists may address both metabolic and reproductive facets of PCOS by enhancing satiety, improving weight-related outcomes, and potentially influencing adipose tissue remodeling.

SGLT2 Inhibitors

SGLT2 inhibitors represent another class of agents being evaluated for metabolic benefits in PCOS. Preclinical work in a female rat model showed that three weeks of SGLT2 inhibition resulted in reduced adiposity, although mitochondrial defects and oxidative stress within WAT

were not reversed [32]. Currently, lifestyle interventions particularly sustained increases in physical activity remain the cornerstone of PCOS management and the most reliable approach for modulating adipose tissue distribution [33].

Thiazolidinediones (TZDs)

Thiazolidinediones like pioglitazone enhance insulin sensitivity by activating PPAR-γ, promoting adipocyte differentiation and shifting lipid storage toward subcutaneous depots. Trials in PCOS show improvements in insulin resistance, menstrual function, and androgen excess [34-36]. Their use is limited by side effects such as weight gain and edema, making them suitable mainly for women with significant insulin resistance.

Inositols (Myo-inositol and D-chiro-inositol)

Inositols act as insulin second messengers and regulate ovarian steroidogenesis. Myo-inositol (MI), alone or with D-chiro-inositol (DCI), improves insulin resistance, ovulation, androgen levels, and central adiposity markers in PCOS [37-40]. Combination MI+DCI is particularly effective in younger obese phenotypes [41]. While their direct role in BAT activation is unclear, inositols appear to favorably influence adipose distribution.

Collectively, these therapeutic strategies highlight a shift toward modifying adipose tissue biology rather than focusing solely on weight reduction.

Future clinical investigations should determine how each treatment influences the WAT-BAT-UCP-1 axis across different PCOS phenotypes and ethnic populations.

Brown Adipose Tissue and its characteristics

Brown adipose tissue (BAT) is a metabolically active organ central to thermoregulation, especially during infancy and early life. Its physiological relevance in adults became clearer only with the advent of advanced imaging techniques such as PET-CT, which facilitated reliable identification of metabolically active BAT depots [42, 43].

BAT generates heat through a specialized mitochondrial mechanism mediated by uncoupling protein 1 (UCP-1). This protein enables mitochondria to dissipate the electrochemical gradient as heat rather than synthesizing ATP, thereby promoting energy expenditure through non-shivering thermogenesis. BAT relies on both glucose and fatty acids as fuel substrates, reflecting its role at the crossroads of carbohydrate-lipid metabolism [44, 45].

Beyond thermogenesis, BAT secretes a diverse array of adipokines sometimes referred to as “batokines” which exert autocrine, paracrine, and endocrine effects. These mediators enhance BAT activity itself, improve systemic metabolic parameters, and may induce the browning of white adipose tissue (WAT) [45, 46]. Clinical observations highlight the importance of BAT: individuals with functional BAT tend to exhibit lower central adiposity and better cardiometabolic profiles.

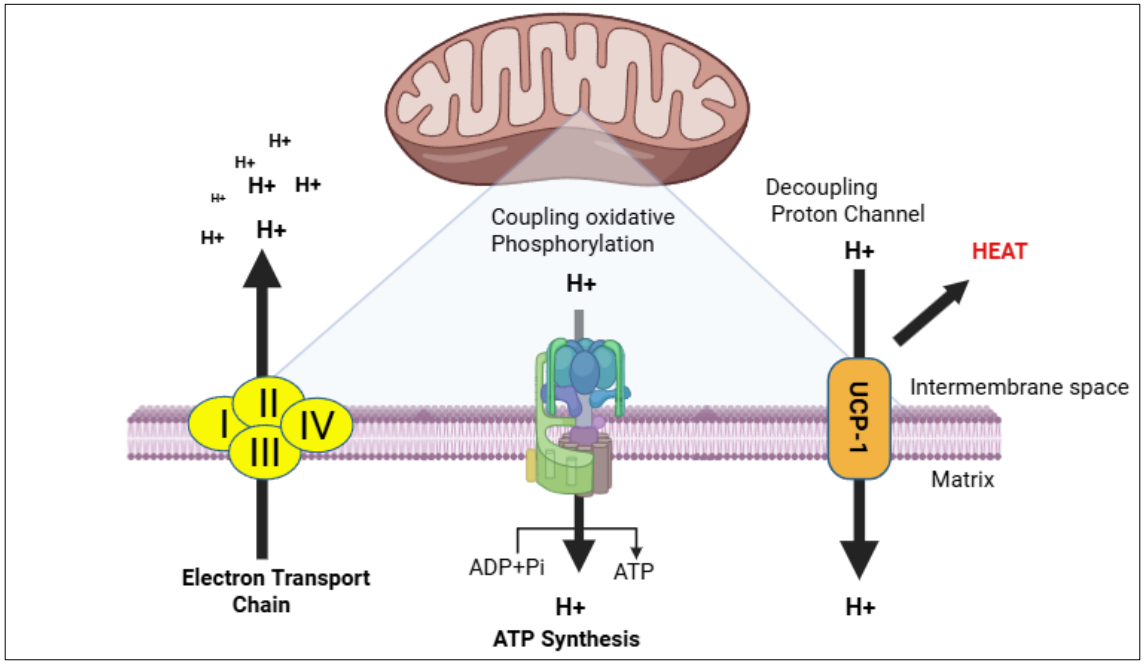

Fig 3: Illustration of the thermogenic machinery within brown adipocytes, underscoring the role of UCP-1 in uncoupling mitochondrial respiration to facilitate heat generation at the expense of ATP synthesis.

BAT and Its Role in Endocrine and Metabolic Disorders in PCOS

BAT is the principal tissue responsible for adaptive thermogenesis heat production triggered by cold exposure or food intake. In women with PCOS, BAT function is impaired, leading to a marked reduction in postprandial thermogenesis. This phenomenon was first reported in 1992 and remains a significant insight into the metabolic abnormalities of PCOS [47].

A practical, non-invasive indicator of BAT activity is the temperature measured over the supraclavicular region, where a substantial BAT depot is located. Studies consistently show that women with PCOS have supraclavicular skin temperatures approximately 0.6°C to 0.7°C lower than healthy controls, suggesting diminished BAT activation. Lower BAT activity correlates inversely with BMI, waist circumference, and the degree of hyperandrogenism [48, 49]. Moreover, PCOS is associated

with a reduced overall volume of BAT, compounding thermogenic deficits.

The mechanistic link between androgen excess and BAT dysfunction is increasingly evident. Androgens suppress the transcriptional coactivator PGC-1α, a critical driver of UCP-1 expression in brown adipocytes. Reduced UCP-1 expression limits mitochondrial heat production and compromises thermogenic capacity. Additionally, sex hormones such as testosterone influence sympathetic innervation of adipose tissue, further impairing BAT responsiveness to physiological stimuli [50, 51]. The combined effect of diminished BAT mass, reduced UCP-1 activity, and altered autonomic signaling helps explain the impaired post-meal energy dissipation observed in women with PCOS. These disturbances may also contribute to weight gain, metabolic rigidity, and increased central adiposity.

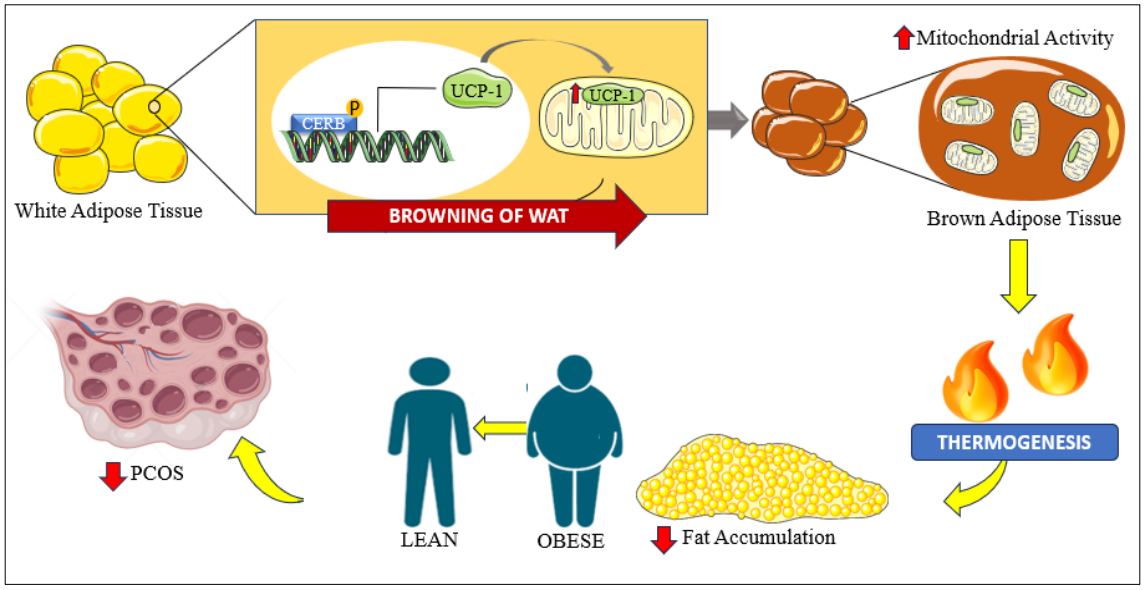

Fig 4: Overview of brown adipose tissue as a prospective therapeutic avenue, illustrating how enhanced BAT activity or induction of beige adipocytes may help reduce visceral adiposity and improve metabolic outcomes in PCOS.

Does Brown Adipose Tissue and UCP-1 Represent a Viable Target for Therapeutic Intervention?

Growing interest in brown adipose tissue (BAT) as a metabolic regulator has prompted extensive research into its therapeutic potential for obesity and related endocrine disorders [52]. In animal studies, obesity is associated with diminished BAT thermogenic activity, which limits energy dissipation and glucose utilization. The inverse association between BAT mass and BMI in humans further supports the relevance of BAT to central adiposity and metabolic dysfunction, creating a strong rationale for exploring BAT-centered interventions in PCOS [53, 54].

Compelling experimental evidence comes from xenotransplantation models. In a notable study, transplantation of functional BAT from young donor rats into PCOS mice restored ovarian function including improvements in fertility, oocyte quality, and expression of critical reproductive genes while simultaneously enhancing insulin sensitivity and elevating adiponectin levels for up to 10 months [55]. These results highlight an intricate cross-talk between adipose tissue and reproductive physiology.

However, human studies have thus far been less conclusive. In a randomized controlled trial, metformin administered at 1,500 mg/day for 60 days did not significantly modify BAT activity relative to placebo in women with PCOS [56]. These findings suggest that conventional insulin-sensitizing therapies may have limited direct impact on thermogenic adipose tissue.

An alternative therapeutic concept involves inducing browning of white adipose tissue (WAT). Cold exposure, a well-established activator of BAT, can also trigger beige adipocyte formation in WAT. In a PCOS rat model, exposure to 4°C for 20 days improved BAT activity and increased UCP-1-positive adipocyte populations, accompanied by favorable metabolic effects [57]. This underscores the potential of environmental and behavioral interventions to modulate adipose tissue phenotype.

Lifestyle-based strategies such as structured exercise and dietary modification remain powerful modulators of BAT activation. Exercise has been shown to increase UCP-1 expression in classical BAT depots, while both cold and exercise stimulate thermogenic pathways that may help prevent obesity and metabolic syndrome [58, 59]. The ongoing ACTIBATE trial is investigating the specific contribution of exercise-induced BAT activation to metabolic health outcomes in young adults, though similar targeted trials in PCOS populations have not yet been undertaken [60].

Altogether, these insights point toward BAT activation and WAT browning as promising therapeutic approaches for mitigating insulin resistance, reducing visceral adiposity, and improving reproductive function in PCOS. Nonetheless, most evidence remains preliminary, and clinical translation requires robust trials designed specifically for PCOS cohorts.

Conclusion

Adipose tissue plays a far more dynamic role in metabolic regulation than previously appreciated, and its dysfunction contributes substantively to the pathophysiology of polycystic ovary syndrome (PCOS). Disturbances within white adipose tissue (WAT) including disproportionate visceral fat accumulation, impaired adipocyte differentiation, hypertrophy, and chronic low-grade inflammation drive insulin resistance and amplify hyperandrogenic signaling. These alterations not only

worsen metabolic outcomes but also impair reproductive physiology.

Growing attention has turned toward brown adipose tissue (BAT) and its thermogenic mediator UCP-1, given their capacity to enhance energy expenditure and modulate metabolic homeostasis. Evidence from experimental models suggests that activating BAT or inducing WAT browning may offer innovative therapeutic opportunities. Early findings indicate potential benefits in insulin sensitivity, reproductive function, and adipose tissue remodeling in PCOS.

Despite these promising observations, clinical applications remain limited. Metformin does not appear to significantly influence BAT in PCOS, and lifestyle interventions though beneficial have not been extensively studied for BAT-specific effects in this population. As research advances, targeted strategies aimed at enhancing BAT activity or inducing browning may become integral to comprehensive PCOS management frameworks.

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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.

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