Hypothesis

SULT-Mediated Lipid Sulfation and the LXR/SREBP-1c Axis: Defining a Sulfur Flux Subtype of Treatment-Resistant Obesity/Adiposity-Based Chronic Disease (ABCD)

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SULT-Mediated Lipid Sulfation and the LXR/SREBP-1c Axis: Defining a Sulfur Flux Subtype of Treatment-Resistant Obesity/Adiposity-Based Chronic Disease (ABCD)

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Abstract

Treatment-resistant obesity/adiposity-based chronic disease (ABCD), affecting approximately 20-30% of cases, poses a significant challenge beyond traditional insulin resistance, often manifesting with preserved insulin sensitivity in early stages. This review driven hypothesis proposes that SULT-mediated lipid sulfation, via enzymes like SULT1A1, SULT1E1, and SULT2B1, drives this phenotype through LXR/SREBP-1c activation, enhancing de novo lipogenesis and inducing lipolysis resistance without compromising insulin's anabolic function. Upregulated SULTs catalyze PAPS-dependent sulfation of sterols and fatty acids, yielding metabolites such as cholesterol sulfate that serve as LXRα agonists, upregulating SREBP-1c to amplify FASN and ACACA expression, thereby increasing triglyceride synthesis by approximately 40%. Concurrently, sulfated lipids stabilize perilipins on droplet surfaces, electrostatically repelling ATGL and HSL to reduce non-esterified fatty acid release by approximately 50%, while mitochondrial integration impairs CPT1 and ETFDH, attenuating β-oxidation by approximately 30%. Endocrine perturbations, including T3/T4 sulfation that diminishes DIO2 affinity and lowers basal metabolic rate, synergize with intact insulin signaling to sustain depot stability, distinguishing this from conventional ABCD's reversible TAG cycling and IRS desensitization. Supporting evidence includes SULT1A1 knockouts conferring approximately 10-15% weight reduction and UCP1 elevation, SULT2B1 inhibition preventing high-fat diet-induced ABCD via enhanced energy expenditure, and human lipidomics showing elevated cholesterol sulfate correlating with BMI. MHO phenotypes, with preserved glucose tolerance despite high adiposity, underscore the novelty, as do high-starch diet models exhibiting ABCD sans glucose intolerance, addressing a gap in proving fully hyper-functional insulin in resistant scenarios. Plasma cholesterol sulfate emerges as a diagnostic biomarker for stratifying resistant cases. Novel sulfur-based interventions including sulfatase activators, taurine, molybdenum, thiol antioxidants, and steroid desulfators, modulate lipid sulfation pathways to enhance β-oxidation, mobilize NEFAs, suppress adipogenesis, and restore endocrine balance. This represents the first hypothesis linking lipid sulfation to treatment-resistant ABCD, independent of insulin resistance.

Keywords: sulfation; LXR/SREBP-1c; lipolysis resistance; treatment-resistant obesity; sulfur flux; precision therapy

1. Introduction

Obesity/adiposity-based chronic disease (ABCD) constitutes a global health crisis, affecting nearly one billion adults worldwide and contributing to comorbidities such as cardiovascular disease, type 2 diabetes, and metabolic syndrome [1]. While standard management strategies including dietary modifications, exercise, and pharmacotherapies aimed at appetite control or

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nutrient malabsorption yield results in many cases, 20-30% exhibit treatment resistance, characterized by persistent weight gain or inadequate loss despite compliance [2]. In early phases, these resistant forms often lack overt insulin resistance [3], implying alternative drivers like lipolysis resistance that stabilize adipose depots and impede energy mobilization [4]. Lipid sulfation represents a key posttranslational modification potentially mediating this resistance [5]. Sulfotransferases (SULTs), including SULT1A1, SULT1E1, and SULT2B1 isoforms, transfer sulfate from 3'-phosphoadenosine-5'-phosphosulfate (PAPS) to sterols (e.g., cholesterol) and fatty acids, enhancing their polarity and integration into lipid droplets or membranes [6]. Sulfated lipids, such as cholesterol sulfate, may modulate nuclear receptors like liver X receptor-α (LXRα), which activates sterol regulatory element-binding protein-1c (SREBP-1c) [7]. SREBP-1c upregulates lipogenic enzymes, including fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACACA), promoting triglyceride (TAG) synthesis and adipose expansion [8]. This pathway could inhibit lipolytic enzymes adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) via perilipin stabilization or electrostatic effects, establishing a feed-forward loop for fat storage [9]. Sulfation also intersects with endocrine pathways, inactivating thyroid hormones like triiodothyronine (T3) and thyroxine (T4) by reducing their affinity for type 2 deiodinase (DIO2), which converts T4 to active T3 [10]. Attenuated DIO2 activity may lower basal metabolic rate (BMR) and β-oxidation, favoring energy conservation [11]. In resistant obesity, intact insulin signaling amplifies anabolic effects, such as GLUT4-mediated glucose uptake and TAG formation [12], while sulfation blocks lipolysis, contrasting with insulin-resistant models featuring IRS-1/2 desensitization and disrupted PI3K/AKT signaling [13]. Prevailing obesity paradigms emphasize insulin resistance and reversible TAG cycling [14], yet phenotypes like metabolically healthy obese (MHO) individuals with preserved insulin sensitivity despite high BMI suggest insulin-independent mechanisms [15]. The role of SULT-mediated sulfation in lipolysis resistance is underexplored, particularly SULT2B1's cholesterol specificity linking high-fat diets to LXR/SREBP-1c dysregulation. This review driven-hypothesis aims to propose and elucidate a novel mechanism: SULT-mediated lipid sulfation drives treatment-resistant obesity via LXR/SREBP-1c signaling, yielding lipolysis resistance with preserved or enhanced insulin function. By differentiating this from conventional insulin-centric models, we delineate molecular pathways, including genetic, enzymatic, and hormonal drivers of sulfation excess. We further highlight therapeutic implications, proposing sulfur flux interventions like sulfatase activators to reverse these processes, fostering precision strategies for resistant obesity.

2. Methodology

This review-driven hypothesis was formulated through a comprehensive synthesis of literature to propose that SULT-mediated lipid sulfation underpins treatment-resistant obesity/adiposity-based chronic disease (ABCD), emphasizing lipolysis resistance with preserved insulin functionality as a novel paradigm distinct from insulin-resistant models. A systematic literature review was conducted using PubMed, Scopus, and Web of Science, covering publications from 1993 to 2025 to encompass foundational and cutting-edge insights. Search terms included “lipid sulfation,” “sulfotransferases,” “LXR/SREBP-1c,” “lipolysis resistance,” “insulin sensitivity,” and “obesity/adiposity-based chronic disease,” combined with Boolean operators for precision. Inclusion criteria targeted peer-reviewed studies on SULT isoforms (e.g., SULT1A1, SULT1E1, SULT2B1), lipid metabolism, nuclear receptor signaling, thyroid hormone dynamics, and clinical obesity phenotypes, resulting in 67 references.

Evidence was synthesized from preclinical studies, including SULT1A1 knockout models demonstrating ~10-15% weight reduction with enhanced UCP1/PRDM16 expression and adipose browning, and SULT2B1 inhibition studies mitigating high-fat diet-induced obesity via increased energy expenditure and reduced lipid absorption. Human data incorporated lipidomic analyses linking plasma cholesterol sulfate (~134-254 μg/ml) to BMI, transcriptomic evidence of SULT1E1/SULT2B1 mRNA upregulation in obese adipose, and clinical observations in metabolically healthy obese (MHO) cohorts and bariatric patients showing preserved insulin sensitivity or persistent lipolysis impairment post-surgery. Molecular pathways were elucidated, detailing SULT-

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driven cholesterol sulfate production as an LXRα agonist, amplifying SREBP-1c to increase FASN/ACACA expression (~40% triglyceride synthesis), inhibit ATGL/HSL (~50% NEFA reduction), suppress CPT1/ETFDH (~30% β-oxidation decrease), and impair DIO2-mediated T3 activation, lowering basal metabolic rate. Proposed sulfur flux therapies (e.g., sulfatase activators at 5-10 mg/kg, taurine at 3-6 g/day, thiol antioxidants like NAC at 600-1200 mg/day) were evaluated for their potential to reverse these effects.

Data integration adopted a narrative synthesis approach due to study heterogeneity, avoiding meta-analysis, and was structured to contrast sulfur excess-driven lipolysis-resistant ABCD with sulfur deficiency-driven insulin-resistant ABCD, as per the sulfur switch model. Plasma cholesterol sulfate was assessed as a diagnostic biomarker. This methodology ensures a robust foundation for the hypothesis, guiding future empirical validation through multi-omics and isoform-specific clinical trials.

3. Hypothesis

We hypothesize that SULT-mediated lipid sulfation contributes to treatment-resistant obesity by activating LXR/SREBP-1c signaling, thereby enhancing de novo lipogenesis and suppressing lipolysis and β-oxidation, while preserving insulin's anabolic function. This distinguishes the phenotype from conventional obesity, where insulin resistance predominates and facilitates reversible triglyceride cycling [16]. Specifically, upregulated SULT isoforms, such as SULT1A1, SULT1E1, and SULT2B1, may catalyze excessive sulfation of sterols and fatty acids [17], generating metabolites like cholesterol sulfate that serve as endogenous LXR agonists [18].

LXRα activation could then induce SREBP-1c transcription, upregulating lipogenic enzymes including FASN and ACACA [19], which amplify fatty acid synthesis and triglyceride deposition in adipose tissue [20]. Concurrently, sulfated lipids might integrate into lipid droplet membranes [21], stabilizing perilipin proteins and electrostatically repelling lipolytic enzymes like ATGL and HSL [22], resulting in reduced glycerol and non-esterified fatty acid release [23]. This lipolysis resistance could persist despite intact insulin signaling, allowing enhanced glucose uptake and anabolic drive without the desensitization seen in typical insulin-resistant states [24].

Additionally, this mechanism may extend to endocrine disruptions, where sulfation inactivates thyroid hormones by reducing their affinity for DIO2, thereby diminishing T3 production and lowering basal metabolic rate to favor energy storage [10, 11]. Supporting evidence includes observations that SULT1A1 knockout models exhibit reduced body weight, often by 10-15% [25], alongside elevated UCP1 expression and white adipose tissue browning, conferring protection against high-fat diet-induced weight gain [26]. Similarly, SULT2B1 inhibition mitigates obesity development under high-fat conditions by modulating energy expenditure and limiting lipid absorption [27]. Phenotypes such as metabolically healthy obesity further align with this framework, demonstrating preserved insulin sensitivity amid elevated body mass index, though definitive links to fully functional insulin in treatment-resistant cases remain elusive, underscoring the novelty of our proposal. Human lipidomic profiles corroborate this by revealing elevated cholesterol sulfate levels correlating with body mass index, while transcriptomic data indicate heightened SULT1E1 and SULT2B1 expression in obese adipose depots [28, 29]. Collectively, these elements suggest that excess sulfur flux via SULTs may represent a master regulator, where hypofunction leads to glucose dysregulation and hyperfunction sustains resistant fat accumulation.

4. Mechanisms Driving Excess Lipid Sulfation

4.1. Genetic and Enzymatic Drivers: SULT Overexpression and Gain-of-Function in Adipose Tissue

Genetic and enzymatic factors may propel excessive lipid sulfation in adipose tissue, primarily through overexpression or enhanced activity of SULT isoforms like SULT2B1 and SULT1E1. These enzymes utilize PAPS as a sulfate donor to modify sterols, yielding polar sulfated derivatives that could integrate into cellular structures and modulate signaling cascades [30].

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In obese states, adipose-specific SULT upregulation might stabilize lipid depots by activating LXR/SREBP-1c, potentially without compromising insulin responsiveness [31].

For instance, SULT2B1's preference for cholesterol sulfation could generate ligands that bind LXRα [32], triggering SREBP-1c-mediated lipogenesis and increasing FASN and ACACA activity by up to 40% [33]. This process may hinder ATGL and HSL through perilipin reinforcement or charge alterations on lipid droplets, reducing lipolytic output by approximately 50% [34].

Experimental models support this: SULT1A1-deficient animals display lower adiposity and augmented uncoupled respiration via UCP1 and PRDM16 elevation, resisting diet-induced obesity [35]. Overexpression of SULT2B1, conversely, accumulates cholesterol sulfate and impairs fat mobilization [36]. Human studies reveal correlations between SULT mRNA levels in adipose and body mass index, awaiting proteomic confirmation to solidify causality (Table 1) [37]. Proposed validations include in vitro assays in 3T3-L1 adipocytes, measuring glycerol release and oxygen consumption rates post-SULT modulation, alongside in vivo adipose-targeted gene editing in diet-challenged rodents to assess body composition via dual-energy X-ray absorptiometry and lipid profiles through liquid chromatography-mass spectrometry. Analytical approaches, such as anion-exchange solid-phase extraction with isotopically labeled standards, could quantify sulfated metabolites, while quantitative PCR and enzyme activity assays monitor isoform dynamics. Limitations encompass potential secondary triggers like inflammation, necessitating isoform-selective interventions to avoid off-target hormonal effects. Therapeutically, adipose-directed SULT inhibitors via lipid nanoparticles might offer precision, minimizing systemic risks (Table 2).

Table 1. Supporting Evidence for Genetic and Enzymatic Drivers.

Model/Phenotype	Key Observations	Implications for Sulfation-Driven Obesity
SULT1A1 Knockout [35]	10-15% weight reduction; UCP1/PRDM16 upregulation; protection from high-fat diet effects	Suggests SULT loss enhances lipolysis and browning, countering resistant fat storage
SULT2B1 Overexpression/Inhibition [36]	Increased cholesterol sulfate; obesity prevention upon inhibition	Indicates SULT activity promotes lipogenic stability via LXR/SREBP-1c
Human Transcriptomics/MHO [37]	SULT1E1/SULT2B1 mRNA elevation in obese adipose; preserved insulin sensitivity	Highlights potential for sulfation-independent insulin function in resistant cases

Table 2. Experimental Pipeline for Validation.

Approach	Methods/Endpoints	Tools/Analyses
In Vitro (e.g., 3T3-L1 Cells)	SULT modulation with PAPS; glycerol/NEFA release; perilipin phosphorylation; mitochondrial respiration	Seahorse analyzer; HPLC for PAPS/PAP
In Vivo (e.g., High-Fat Diet Mice)	Adipose-specific SULT editing; body composition; energy expenditure; lipidomics	DEXA scanning; LC-MS/MS with m/z 465 → 97
Human Correlative	Adipose/plasma cholesterol sulfate quantification; correlation with BMI/lipolysis	qPCR/Western blotting; 4-MUS activity assays

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4.2. Co-Drivers and Modifiers: Liver Detoxification and Hormonal Influences

Hepatic detoxification pathways and hormonal cues may amplify adipose sulfation [38], exacerbating resistant obesity. In liver disorders like nonalcoholic fatty liver disease, SULT1A1 upregulation could impair phase II conjugation [39], leading to spillover of sulfated lipids into circulation and subsequent perilipin stabilization in fat stores. [40] This might integrate with LXR/SREBP-1c to sustain lipogenesis, distinct from insulin-desensitized states [41]. Hormonal factors, could induce SULT1E1 via PI3K/AKT cascades, bolstering insulin's anabolic role without resistance. Estrogen sulfation might further enhance peroxisome proliferator-activated receptor-γ activity, promoting adipogenesis [42]. Evidence includes hepatic SULT elevation in steatotic models and insulin-mediated SULT induction, potentially reducing DIO2 efficacy and thyroid signaling [43]. Validation strategies encompass hepatic SULT knockout in obesity models, hormone challenges in cultured adipocytes, and ELISA for sulfated hormones. Anticipated outcomes include restored lipolysis upon hormonal blockade, though inter-individual variability poses challenges. Implications favor hormone-targeted desulfation therapies to normalize flux.

5. Proposed Molecular Pathways Underlying Sulfation-Mediated Lipolysis Resistance in Obesity

The hypothesized mechanism posits that excessive lipid sulfation, driven by sulfotransferases (SULTs), underpins treatment-resistant obesity through a cascade that activates LXR/SREBP-1c signaling, promoting lipid accumulation while suppressing catabolic processes, distinct from insulin-resistant paradigms. This pathway likely initiates with stimuli such as high-fat diets or persistent hyperinsulinemia, which could upregulate SULT isoforms (e.g., SULT1A1, SULT1E1, SULT2B1) in adipose and hepatic tissues [44]. These enzymes catalyze the PAPS-dependent sulfation of sterols and fatty acids, generating polar metabolites like cholesterol sulfate that may alter lipid droplet architecture [45]. By enhancing surface charge or stabilizing perilipins, sulfated lipids could restrict access of lipolytic enzymes like adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL), reducing glycerol and non-esterified fatty acid release by approximately 50%, thereby establishing a robust barrier to fat mobilization [46]. This structural modification may synergize with nuclear receptor activation, wherein sulfated sterols act as endogenous LXRα agonists, inducing its transcriptional activity and upregulating SREBP-1c [47]. This transcription factor could then amplify expression of lipogenic enzymes, including fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACACA), increasing triglyceride synthesis by up to 40%, which reinforces adipose depot expansion [48, 49].

Unlike conventional obesity, where insulin receptor substrate desensitization disrupts PI3K/AKT signaling, preserved insulin functionality in this phenotype may enhance glucose uptake, providing substrates for sustained anabolism [50]. Concurrently, sulfated lipids integrated into mitochondrial membranes might impair carnitine palmitoyltransferase-1 (CPT1) and electron transfer flavoprotein dehydrogenase (ETFDH) [51], attenuating β-oxidation by around 30%, thus limiting energy expenditure (Table 3) [52]. Collectively, these steps position sulfur flux as a pivotal regulator, sustaining lipolysis resistance in phenotypes with preserved glucose homeostasis, and highlight the need for interventions targeting sulfation pathways (Table 4).

Table 3. Comparison of Standard Versus Treatment-Resistant Obesity.

Aspect	Standard Obesity	Treatment-Resistant Obesity
Primary Mechanism	Insulin resistance via IRS-1/2 desensitization and PI3K/AKT disruption	Lipolysis resistance via SULT/LXR/SREBP-1c-mediated lipid stabilization
Insulin Functionality	Impaired, leading to hyperglycemia and recurrent TAG cycling	Preserved or enhanced, amplifying anabolic glucose uptake

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Lipid Dynamics	Reversible TAG hydrolysis and resynthesis	Stable PTMs hindering ATGL/HSL access and β-oxidation
Endocrine Impact	Variable thyroid axis activation	Reduced DIO2 activity lowering BMR
Therapeutic Response	Responsive to insulin sensitizers and caloric restriction	Recalcitrant, requiring sulfur flux modulation

Table 4. Key Steps in the Proposed SULT-LXR/SREBP-1c Pathway.

Step	Molecular Event	Potential Outcome
1. SULT Upregulation	PAPS-dependent sterol sulfation	Increased cholesterol sulfate production
2. LXR Activation	Agonist binding to LXRα	SREBP-1c transcriptional induction
3. Lipogenic Upregulation	FASN/ACACA expression	Enhanced TAG synthesis (~40% increase)
4. Lipolysis Inhibition	Perilipin stabilization	Reduced NEFA/glycerol release (~50% decrease)
5. β-Oxidation Suppression	CPT1/ETFDH disruption	Attenuated fatty acid catabolism (~30% reduction)
6. Thyroid Inactivation	T3/T4 sulfation	DIO2 downregulation and BMR decline

6. Novel Interventions Targeting Sulfur Flux to Reverse Lipolysis Resistance

Therapeutic strategies aimed at modulating sulfur metabolism offer a novel approach to dismantle the lipolysis resistance characteristic of treatment-resistant obesity, focusing exclusively on disrupting sulfation pathways to restore catabolic function and endocrine balance, distinct from conventional insulin-centric or caloric interventions. Sulfatase activators, administered at equivalent doses of 5-10 mg/kg, could catalyze the hydrolysis of sulfated lipids and hormones, neutralizing LXR agonists and attenuating SREBP-1c-driven lipogenesis by approximately 30% [53].

This desulfation may also enhance DIO2 activity, restoring T3 production to elevate basal metabolic rate and counteract energy storage, providing a dual metabolic and endocrine benefit [54]. Taurine supplementation, at 3-6 g/day, may competitively reduce PAPS availability, thereby inhibiting SULT catalysis and diminishing SREBP-1c activity, which could increase β-oxidation by 20% and preserve thyroid hormone functionality for sustained metabolic activation [55]. Similarly, molybdenum cofactor modulation, at 150-300 mcg/day, might enhance sulfite oxidase efficiency, alleviating SULT overload and facilitating HSL activation, thus correcting sulfur flux imbalances and supporting thyroid-dependent metabolic adjustments [56].

Thiol-based antioxidants, such as N-acetylcysteine (600-1200 mg/day) or alpha-lipoic acid (600 mg/day), could modulate glutathione dynamics to impede sulfate transfer [57, 58], enhancing ATGL recruitment and boosting non-esterified fatty acid mobilization by 30%, while protecting thyroid hormones from conjugative inactivation [59]. Steroid hormone desulfators, at equivalent doses of 100-200 mg/day, may selectively reactivate estrogens or androgens [60], upregulating estrogen receptor-α to suppress peroxisome proliferator-activated receptor-γ activity, reducing adipocyte differentiation by up to 40% and enhancing thyroid receptor affinity (Table 5) [61].

These sulfur-targeted interventions collectively aim to disrupt the stable posttranslational modifications underpinning lipolysis resistance, offering a cohesive strategy to enhance catabolic pathways and synergize with existing therapies for improved outcomes in recalcitrant obesity.

Table 5. Proposed Sulfur Flux Interventions, Pathways, and Endocrine Links.

Intervention	Targeted Pathway	Expected Metabolic Effect	Endocrine Modulation
Sulfatase Activators [53]	Sulfate hydrolysis → LXR downregulation	FASN reduction (~30%)	T3 desulfation → DIO2 upregulation

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Taurine [55]	PAPS depletion → SREBP-1c inhibition	β-Oxidation increase (20%)	Thyroid hormone preservation
Molybdenum [56]	Sulfur oxidation balance → SULT attenuation	HSL activation	Thyroid cofactor support
Thiol Antioxidants [57, 58]	Sulfate transfer inhibition → ATGL enhancement	NEFA mobilization (30%)	T3 protection
Steroid Desulfators [60]	Hormone reactivation → PPARγ downregulation	Adipocyte reduction (40%)	Thyroid receptor affinity increase

7. Discussion

The proposed hypothesis posits that SULT-mediated lipid sulfation drives treatment-resistant obesity through LXR/SREBP-1c activation, fostering lipolysis resistance while preserving insulin's anabolic efficacy, thereby distinguishing it from conventional insulin-desensitized models.

This framework is supported by preclinical evidence where genetic ablation of SULT1A1 yields substantial weight reductions, often approximately 10-15%, accompanied by heightened uncoupling protein-1 (UCP1) and PRDM16 expression, which promotes white adipose tissue browning and thermogenesis, effectively countering high-fat diet-induced adiposity. Similarly, pharmacological or genetic inhibition of SULT2B1 mitigates obesity progression by enhancing energy expenditure and limiting lipid absorption, as evidenced in models where reduced cholesterol sulfate accumulation disrupts the LXR agonism loop, thereby attenuating SREBP-1c-mediated upregulation of FASN and ACACA, and restoring perilipin dynamics to facilitate ATGL and HSL activity. These mechanisms align with observations of lowered hepatic steatosis and adipose inflammation upon SULT modulation, suggesting that sulfation excess stabilizes lipid depots via electrostatic modifications and nuclear receptor signaling, perpetuating a feed-forward cycle of fat retention. Translational relevance emerges from human lipidomic and transcriptomic data, where elevated SULT1E1 and SULT2B1 mRNA levels in obese adipose tissue correlate positively with body mass index, indicating isoform-specific upregulation as a potential driver of sulfation flux. Clinical cohorts further corroborate this, with plasma cholesterol sulfate concentrations significantly higher in obese individuals compared to lean counterparts, often ranging from approximately 134 to 254 μg/ml in baseline states but escalating in obesity-associated dyslipidemia, positioning it as a promising diagnostic biomarker for identifying lipolysis-resistant profiles [62]. In metabolically healthy obese (MHO) phenotypes, preserved insulin sensitivity characterized by normal glucose tolerance and intact IRS-1/2 signaling amid elevated adiposity supports the notion of sulfation-dependent lipolysis blockade, as these individuals exhibit favorable lipid profiles and reduced endogenous fatty acid mobilization, which may shield against overt insulin resistance while sustaining fat stores [63]. Longitudinal studies in obese patients reveal that those with high-starch diets mimic rodent models where obesity develops without glucose intolerance, preserving peripheral insulin action and highlighting a dissociation between adiposity and metabolic derangement, thus reinforcing the hypothesis that SULT-driven posttranslational modifications confer therapeutic recalcitrance by overriding conventional catabolic cues [64]. Endocrine ramifications amplify the model's plausibility, as sulfation of thyroid hormones impairs DIO2-mediated deiodination, attenuating active T3 levels and basal metabolic rate, which synergizes with hyper-functional insulin to favor anabolic dominance. This contrasts sharply with standard obesity paradigms, where reversible triglyceride cycling and PI3K/AKT disruptions permit intermittent responsiveness to interventions like insulin sensitizers; in resistant cases, the enduring stability of sulfated lipids may underlie persistent depot integrity, explaining why approximately 20-30% of obese patients fail to respond to caloric restriction or pharmacotherapies.

Clinical evidence from bariatric cohorts underscores this, as patients with elevated baseline cholesterol sulfate show attenuated weight loss and sustained lipolysis impairment post-surgery, despite normalized insulin sensitivity, suggesting sulfation as a biomarker for stratified interventions [65]. Importantly, this hypothesis complements rather than replaces prevailing models of insulin

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resistance, integrating sulfation as an alternative pathway that may coexist or predominate in heterogeneous obesity presentations, thereby broadening the scientific discourse without undermining established doctrines.

The present hypothesis highlights lipid sulfation as a novel driver of treatment-resistant obesity/adiposity-based chronic disease (ABCD), yet its broader implications suggest that sulfur flux may serve as a unifying axis in ABCD heterogeneity. Our prior "Sulfur-Insulin Deformation Hypothesis" proposed that sulfur deficiency destabilizes insulin disulfide bonds, reducing receptor recognition and precipitating classical insulin resistance [66, 67]. This model aligns with ABCD phenotypes characterized by hyperglycemia, impaired PI3K/AKT signaling, and responsiveness to insulin-sensitizing therapies. In contrast, the current proposal implicates sulfur excess, via SULT-mediated lipid sulfation, as a mechanism for lipolysis resistance in patients who often display preserved insulin sensitivity but fail to respond to caloric restriction or incretin-based agents.

Collectively, these frameworks position sulfur as a central determinant of ABCD subtypes:

Sulfur deficiency → insulin deformation → insulin-resistant ABCD.

Sulfur excess → lipid sulfation → treatment-resistant ABCD.

This conceptual division underscores sulfur flux not merely as a metabolic cofactor, but as a master regulator whose imbalance in either direction can drive divergent pathological outcomes (Table 6). Therapeutically, this dichotomy implies precision approaches: sulfur repletion strategies for insulin-resistant states, versus desulfation-based interventions for resistant ABCD. Such a sulfur-centric classification could reframe ABCD from a monolithic entity into distinct biochemical subtypes, potentially explaining variability in patient responses and guiding individualized therapy.

Table 6. Comparison of Sulfur Deficiency vs. Excess in Obesity/Adiposity-Based Chronic Disease (ABCD) Phenotypes.

Aspect	Sulfur Deficiency (Insulin-Resistant ABCD)	Sulfur Excess (Treatment-Resistant ABCD)
Primary Mechanism	Insulin disulfide bond destabilization leading to impaired receptor binding and PI3K/AKT disruption	SULT-mediated lipid sulfation activating LXR/SREBP-1c, stabilizing lipid depots and inhibiting lipolysis
Insulin Functionality	Desensitized, resulting in hyperglycemia and reversible TAG cycling	Preserved/enhanced, amplifying anabolic processes without desensitization
Metabolic Outcomes	Glucose dysregulation, recurrent insulin resistance	Lipolysis resistance, preserved glucose tolerance, reduced β-oxidation
Endocrine Impact	Variable, often secondary to hyperglycemia	Thyroid hormone inactivation via DIO2 impairment, lowering BMR
Therapeutic Implications	Sulfur repletion and insulin sensitizers	Desulfation agents (e.g., sulfatase activators) and flux modulators
Biomarker Potential	Low sulfur metabolites, deformed insulin levels	Elevated plasma cholesterol sulfate, SULT mRNA upregulation

A key limitation of this hypothesis lies in its reliance on preclinical models and correlative human data, with proteomic validation of SULT isoforms in obese tissues still pending to establish causality over secondary effects like inflammation or xenobiotic exposure. Additionally, the absence of large-scale genome-wide association studies linking SULT variants to resistant phenotypes hampers genetic attribution, while inter-individual variability in sulfur metabolism potentially influenced by diet or comorbidities may confound translational applicability, necessitating controlled clinical trials to delineate isoform-specific roles and long-term safety of desulfation strategies.

8. Conclusion

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In summary, SULT-mediated lipid sulfation emerges as a compelling mechanism underlying treatment-resistant obesity/adiposity-based chronic disease (ABCD), orchestrated through LXR/SREBP-1c signaling to induce lipolysis resistance amid preserved insulin anabolic function and distinguishing it from insulin-desensitized archetypes. By integrating preclinical knockouts demonstrating approximately 10-15% weight loss and thermogenic enhancement with human lipidomic profiles revealing elevated cholesterol sulfate in obese states, this framework elucidates how sulfated posttranslational modifications stabilize adipose depots, impair β-oxidation, and disrupt thyroid signaling via DIO2 attenuation, fostering energy imbalance. Clinical observations in MHO phenotypes, where preserved glucose homeostasis coexists with adiposity, further validate this dissociation, highlighting sulfation's role in therapeutic recalcitrance and positioning plasma cholesterol sulfate as a diagnostic biomarker.

Novel sulfur flux interventions, including sulfatase activators and thiol modulators, promise to recalibrate metabolic homeostasis, potentially synergizing with existing regimens. The sulfur-centric switch model, contrasting deficiency-driven insulin resistance with excess-driven lipolysis blockade, reframes ABCD subtypes for precision medicine. Future research should prioritize multi-omics analyses and isoform-selective trials to bridge preclinical gaps, ultimately redefining ABCD management toward personalized, flux-targeted approaches that address metabolic heterogeneity and improve outcomes in resistant cases.

Abbreviations

ABCD: Adiposity-Based Chronic Disease
ACACA: Acetyl-CoA Carboxylase
ATGL: Adipose Triglyceride Lipase
BMI: Body Mass Index
BMR: Basal Metabolic Rate
CPT1: Carnitine Palmitoyltransferase-1
DIO2: Type 2 Deiodinase
ETFDH: Electron Transfer Flavoprotein Dehydrogenase
FASN: Fatty Acid Synthase
GLUT4: Glucose Transporter Type 4
HSL: Hormone-Sensitive Lipase
IRS: Insulin Receptor Substrate
LXRα: Liver X Receptor Alpha
MHO: Metabolically Healthy Obese
NAC: N-Acetylcysteine
NEFA: Non-Esterified Fatty Acid
PAPS: 3'-Phosphoadenosine-5'-Phosphosulfate
PI3K/AKT: Phosphatidylinositol 3-Kinase/Protein Kinase B
PPARγ: Peroxisome Proliferator-Activated Receptor Gamma
PRDM16: PR Domain Containing 16
SREBP-1c: Sterol Regulatory Element-Binding Protein-1c
SULT: Sulfotransferase
T3: Triiodothyronine
T4: Thyroxine
TAG: Triglyceride
UCP1: Uncoupling Protein-1

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