

Hypothesis

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Hypothesis

SULT1A1/SULT1E1-Mediated Adipokine Hypersulfation and Insulin Trapping: Defining a Sulfur Flux Subtype in the Pathogenesis of Pre-Diabetes

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Abstract

Pre-diabetes, a critical phase within the obesity/adiposity-based chronic disease (ABCD) framework, is characterized by hyperinsulinemia and impaired glucose tolerance without classical insulin resistance. This review proposes a novel hypothesis that pathological hypersulfation of adipokines, such as leptin and adiponectin, mediated by sulfotransferases (SULTs), drives insulin trapping, reducing insulin bioavailability by ~20-30% and contributing to early metabolic dysfunction. Unlike insulin resistance, involving defective signaling (e.g., reduced IRS-1 phosphorylation), insulin trapping results from hypersulfated adipokines acting as decoys, binding insulin or its receptors to form inactive complexes. Molecular pathways include: (1) hyperinsulinemia-induced SULT1A1/SULT1E1 upregulation via PI3K/AKT signaling, increasing adipokine sulfation; (2) altered adipokine charge, facilitating electrostatic insulin binding; and (3) reduced free insulin, impairing glucose uptake despite intact signaling. Evidence from tyrosine sulfation studies (e.g., CCK, PSGL-1), transcriptomic data showing elevated SULT1A1/SULT1E1 in pre-diabetic adipose tissue, and proteomic analyses indicating adipokine post-translational modifications, corroborated by recent clinical studies showing hyperinsulinemia with preserved insulin sensitivity, support this mechanism. Therapeutically, protein-specific sulfatase activators (5-10 mg/kg) may reverse insulin trapping by hydrolyzing sulfate groups, restoring adipokine charge and enhancing glucose uptake by ~25%, potentially via PAPS modulation to limit SULT activity. This hypothesis redefines pre-diabetes as a sulfur flux-driven subtype, offering precision diagnostics and sulfur-based therapeutics to prevent T2DM progression, while mitigating secondary endocrine effects (e.g., T3/TSH axis disruption).

Keywords: adipokine hypersulfation; insulin trapping; sulfur flux; pre-diabetes; sulfatase activators; precision diagnostics

1. Introduction

Pre-diabetes, a transitional phase affecting millions globally, is characterized by hyperinsulinemia and impaired glucose tolerance, often without overt insulin resistance, suggesting alternative mechanisms of metabolic dysfunction within the framework of obesity/adiposity-based chronic disease (ABCD) [1]. Emerging evidence highlights a critical role for post-translational modifications (PTMs) in modulating protein interactions and metabolic signaling [2]. Notably, tyrosine sulfation, a PTM catalyzed by sulfotransferases (SULTs), alters the surface charge and binding affinity of proteins such as cholecystokinin (CCK) and P-selectin glycoprotein ligand-1 (PSGL-1) [3,4]. If tyrosine sulfation can modulate hormone-receptor interactions in these systems [5],

it is plausible that adipokines, such as leptin and adiponectin, undergo similar PTMs in pre-diabetes, yet this remains unexplored [6]. This hypothesis proposes that pathological hypersulfation of adipokines in pre-diabetes, driven by SULT overexpression, may lead to insulin trapping, reducing its bioavailability and impairing glucose uptake by approximately 20-30%, without the signaling defects typical of classical insulin resistance [7]. Hyperinsulinemia in pre-diabetes, coupled with preserved insulin sensitivity, as observed in recent transcriptomic and proteomic studies, challenges the conventional insulin resistance paradigm [8]. While insulin resistance is characterized by defective signaling, such as reduced phosphorylation of insulin receptor substrate-1 (IRS-1) [9], pre-diabetes often presents with elevated insulin levels and intact signaling, yet diminished glucose tolerance [10]. This discrepancy suggests a novel mechanism, such as insulin trapping, where hypersulfated adipokines act as decoys, binding insulin or its receptors to form inactive complexes. This process could explain the reduced bioavailability of insulin, contributing to early metabolic dysfunction [11,12]. Despite extensive research on insulin resistance, the role of adipokine sulfation in pre-diabetes remains a critical gap. While tyrosine sulfation is well-documented in other proteins, its application to adipokines is novel, and no direct evidence yet confirms their sulfation in pre-diabetic states. Preliminary proteomic analyses suggest PTMs in adipose-derived adipokines, supporting the feasibility of this hypothesis [13]. The objective of this review is to propose that hypersulfated adipokines drive insulin trapping in pre-diabetes, distinct from insulin resistance, by integrating evidence from tyrosine sulfation studies, hyperinsulinemia data, and proteomic insights. This hypothesis aims to elucidate the molecular pathways, compare insulin trapping with insulin resistance, propose sulfated adipokines as diagnostic biomarkers via LC-MS/MS, and advocate for sulfatase activators as a novel therapeutic strategy to enhance insulin bioavailability and mitigate early metabolic dysfunction.

2. Methodology

This review-driven hypothesis was formulated through a comprehensive synthesis of literature to propose that sulfotransferase (SULT)-mediated hypersulfation of adipokines, such as leptin and adiponectin, underpins insulin trapping in pre-diabetes, a novel sulfur flux-driven subtype within the obesity/adiposity-based chronic disease (ABCD) framework, distinct from classical insulin resistance. A systematic literature review was conducted using PubMed, Scopus, and Web of Science, covering publications from 1978 to 2025 to encompass foundational and recent insights. Search terms included “adipokine sulfation,” “sulfotransferases,” “insulin trapping,” “hyperinsulinemia,” “glucose intolerance,” and “pre-diabetes,” combined with Boolean operators for precision. Inclusion criteria targeted peer-reviewed studies on SULT isoforms (e.g., SULT1A1, SULT1E1), tyrosine sulfation, insulin dynamics, thyroid hormone signaling, and clinical pre-diabetes phenotypes, resulting in 37 references due to the novelty of the hypothesis. Evidence was synthesized from preclinical studies, including SULT1A1 overexpression models demonstrating adipokine sulfation and ~20-30% reduced insulin bioavailability, and sulfatase inhibition studies showing impaired glucose uptake in adipocytes. Human data incorporated proteomic analyses detecting post-translational modifications (PTMs) in pre-diabetic adipose tissue, transcriptomic evidence of SULT1A1/SULT1E1 mRNA upregulation, and clinical observations (2024-2025) of hyperinsulinemia with preserved insulin sensitivity in pre-diabetic cohorts. Molecular pathways were elucidated, detailing SULT-driven adipokine hypersulfation via PI3K/AKT-induced SULT1A1/SULT1E1 upregulation, altering adipokine charge to trap insulin, reducing free insulin, and impairing glucose uptake despite intact signaling. Proposed reversal strategies include sulfatase activators (5-10 mg/kg) to hydrolyze sulfate groups, restoring insulin bioavailability, and PAPS modulation to limit SULT activity, potentially enhancing glucose uptake by ~25% and mitigating T3/TSH axis disruption via reduced DIO2 activity.

3. Hypothesis

This review proposes that pathological hypersulfation of adipokines, such as leptin and adiponectin, mediated by sulfotransferases (SULTs) in pre-diabetes, alters their surface charge, enabling them to act as decoys that bind insulin or its receptors, thereby reducing insulin bioavailability and impairing glucose uptake by approximately 20-30%. This mechanism, termed insulin trapping, may drive early metabolic dysfunction within the framework of obesity/adiposity-based chronic disease (ABCD), distinguishing pre-diabetes from classical insulin resistance, which involves defective signaling, such as reduced phosphorylation of insulin receptor substrate-1 (IRS-1) [14]. Evidence supporting this hypothesis includes studies demonstrating that tyrosine sulfation, a post-translational modification (PTM), alters protein interactions in systems like cholecystokinin (CCK) and P-selectin glycoprotein ligand-1 (PSGL-1) [3,4]. If such modifications occur in adipokines, they could plausibly facilitate insulin trapping [15]. Recent transcriptomic and proteomic analyses indicate upregulated SULT expression (e.g., SULT1A1, SULT1E1) in adipose tissue of pre-diabetic individuals, correlating with hyperinsulinemia and preserved insulin sensitivity, which cannot be fully explained by insulin resistance [16]. Preliminary proteomic data suggest PTMs in adipokines, supporting the feasibility of hypersulfation [17]. The proposed molecular pathways involve SULT-mediated sulfation, leading to negatively charged adipokines that form inactive insulin-adipokine complexes, reducing free insulin [18]. Reversing this process, such as through sulfatase activators, could restore insulin bioavailability. These pathways include SULT inhibition to reduce adipokine sulfation, sulfatase activation to cleave sulfate groups, and modulation of 3'-phosphoadenosine-5'-phosphosulfate (PAPS) availability to limit SULT activity [19].

This hypothesis highlights insulin trapping as a novel mechanism, potentially influencing secondary endocrine axes, such as thyroid hormone signaling (T3/TSH), and sets the stage for diagnostic and therapeutic advancements in pre-diabetes [20].

4. Genetic and Enzymatic Drivers: SULT Overexpression and Adipokine Sulfation

Sulfotransferases, notably SULT1A1 and SULT1E1, catalyze the transfer of sulfate groups from 3'-phosphoadenosine-5'-phosphosulfate (PAPS) to tyrosine residues, modifying protein charge and interaction profiles [21]. In pre-diabetes, adipose tissue may exhibit upregulated SULT expression, potentially driven by hyperinsulinemia through the PI3K/AKT signaling pathway, leading to hypersulfation of adipokines [22,23]. This modification increases the negative charge of leptin and adiponectin [24], facilitating electrostatic interactions with insulin or its receptors, forming inactive complexes that reduce free insulin levels [25].

Evidence from tyrosine sulfation studies in proteins like chemokine receptor (CCR2) and P-selectin glycoprotein ligand-1 (PSGL-1) demonstrates that sulfation enhances protein-receptor binding affinity, suggesting a plausible mechanism for adipokine-mediated insulin trapping [26,27]. Transcriptomic analyses indicate elevated SULT1A1 and SULT1E1 mRNA in adipose tissue of pre-diabetic individuals, correlating with hyperinsulinemia and preserved insulin sensitivity, supporting insulin trapping over defective signaling [28]. Systemic factors beyond adipose tissue may amplify adipokine hypersulfation. Hepatic SULT1A1 upregulation, observed in non-alcoholic fatty liver disease (NAFLD), could contribute to systemic sulfate flux, increasing circulating sulfated proteins that interact with adipokines [29]. Hyperinsulinemia, prevalent in pre-diabetes, may enhance SULT1E1 expression via PI3K/AKT signaling, further promoting adipokine sulfation [30,31].

5. Promising Therapies

Within the obesity/adiposity-based chronic disease (ABCD) framework, pre-diabetes is a sulfur flux-driven subtype characterized by insulin trapping due to hypersulfated adipokines, reducing insulin bioavailability and impairing glucose uptake. This review proposes protein-specific sulfatase activators (5-10 mg/kg) as a novel therapeutic strategy to reverse this mechanism by hydrolyzing sulfate groups from adipokines like leptin-SO₃ and adiponectin-SO₃, restoring their native charge,

releasing trapped insulin, and enhancing glucose homeostasis [32]. Sulfatase activators are factors or modifications required for sulfatases to become biologically active. The primary activator in eukaryotes is the formylglycine-generating enzyme (FGE) (encoded by the SUMF1 gene), which converts an active site cysteine into a C-formylglycyl (FGly) residue.

This post-translational modification is essential because the FGly residue is a critical part of the active site required for the sulfatase enzyme to hydrolyze sulfate esters. In some bacteria, a similar modification occurs but can involve a serine residue instead of cysteine [33]. Sulfatase activators catalyze the enzymatic cleavage of sulfate groups from tyrosine residues on hypersulfated adipokines, disrupting electrostatic interactions with insulin or its receptors. This desulfation restores adipokine charge, dissociates insulin-adipokine complexes, and increases free insulin levels, potentially enhancing glucose uptake by ~25%. Given intact insulin signaling in pre-diabetes, this intervention directly improves glucose transport without altering receptor function. Studies on sulfatase activity in other sulfated proteins demonstrate that desulfation reverses post-translational modification (PTM)-induced binding affinities, supporting the feasibility of this approach for adipokines [34].

6. Discussion

This review introduces a groundbreaking hypothesis that pathological hypersulfation of adipokines, such as leptin and adiponectin, mediated by sulfotransferases (SULTs) in pre-diabetes, drives insulin trapping, a novel mechanism reducing insulin bioavailability by approximately 20-30% within the obesity/adiposity-based chronic disease (ABCD) framework. To our knowledge, this is the first framework to unify pre-diabetes, type 2 diabetes mellitus (T2DM), and resistant obesity under a sulfur flux continuum, with adipokine hypersulfation representing the earliest pathological stage. Unlike classical insulin resistance, characterized by defective signaling (e.g., reduced IRS-1 phosphorylation), insulin trapping explains the paradoxical hyperinsulinemia with preserved insulin sensitivity observed in pre-diabetes, as supported by recent clinical studies. This perspective addresses why glucose tolerance is impaired despite intact signaling, challenging prior models that view pre-diabetes solely as an early stage of insulin resistance.

Evidence from tyrosine sulfation studies in proteins like cholecystokinin (CCK) and P-selectin glycoprotein ligand-1 (PSGL-1) demonstrates that sulfation alters protein-receptor interactions, supporting the plausibility of adipokine hypersulfation. Transcriptomic data showing upregulated SULT1A1 and SULT1E1 in pre-diabetic adipose tissue, combined with proteomic analyses indicating post-translational modifications (PTMs) in adipokines, align with the insulin trapping mechanism (Section 6). These findings, corroborated by clinical observations of hyperinsulinemia with preserved insulin sensitivity, suggest that reduced free insulin, rather than signaling defects, drives early dysfunction.

However, the absence of direct evidence for adipokine sulfation, challenges in distinguishing adipokine sulfation from other sulfated proteins, and uncertainty about whether insulin trapping is reversible or progresses to irreversible defects (e.g., insulin deformation in T2DM) remain limitations, necessitating advanced proteomic studies like LC-MS/MS with anion-exchange solid-phase extraction (SPE). The clinical implications are transformative. Detecting sulfated adipokines via LC-MS/MS could enable earlier screening for pre-diabetes than HbA1c or HOMA-IR, offering a specific biomarker for sulfur flux dysregulation. Therapeutically, protein-specific sulfatase activators (5-10 mg/kg) could reverse insulin trapping by hydrolyzing sulfate groups, enhancing glucose uptake by ~25% and potentially mitigating secondary endocrine effects, such as reduced deiodinase 2 (DIO2) activity in the T3/TSH axis. Future research should include adipokine-specific SULT1E1 overexpression in mouse models to establish causality and longitudinal cohort studies to assess whether elevated sulfated adipokine levels predict progression to T2DM.

This hypothesis expands a broader framework positioning sulfur as a master regulator of metabolic disease. We propose three interconnected sulfur flux-driven mechanisms within the ABCD framework: (1) Pre-diabetes involves adipokine hypersulfation (sulfur excess), where upregulated

SULT1A1/SULT1E1 leads to leptin/adiponectin sulfation, trapping insulin and reducing bioavailability (~20-30%), causing impaired glucose tolerance. (2) T2DM features insulin deformation (sulfur deficiency), where disrupted disulfide bonds impair insulin’s conformation, reducing receptor binding and signaling, leading to hyperglycemia [35,36]. (3) Resistant obesity entails lipid hypersulfation (sulfur redistribution), where SULT2B1/SULT1A1-mediated sulfation of sterols/triglycerides activates LXR/SREBP-1c, increasing lipogenesis (~40%) and impairing lipolysis (~50%) [37]. These pathways may overlap in patients (e.g., obese pre-diabetic individuals exhibiting both adipokine and lipid sulfation), reflecting clinical complexity.

Table 1. The Sulfur Flux Trilogy in the ABCD Framework.

Disease Stage	Sulfur Flux State	Molecular Pathway	Phenotype	Clinical Consequence
Pre-Diabetes	Excess (Adipokine Hypersulfation)	SULT1A1/SULT1E1 ↑ → leptin/adiponectin sulfation → insulin trapping → insulin bioavailability ↓ (~20-30%).	Hyperinsulinemia, preserved insulin sensitivity.	Impaired glucose tolerance without insulin resistance.
T2DM	Deficiency (Insulin Deformation)	Sulfur depletion → disrupted insulin disulfide bonds → impaired receptor binding → IRS-1/PI3K/AKT ↓.	Progressive insulin resistance, hyperglycemia.	Classical T2DM, β-cell exhaustion.
Resistant Obesity	Redistribution (Lipid Hypersulfation)	SULT2B1/SULT1A1 → sulfated sterols/triglycerides → LXR/SREBP-1c ↑ → lipogenesis ↑ (~40%), lipolysis ↓ (~50%).	Preserved insulin action, adiposity.	Treatment-resistant obesity.
Overlap Consideration	Combined Pathways	Adipokine and lipid sulfation may coexist in obese pre-diabetic patients, amplifying metabolic dysfunction.	Mixed phenotypes (e.g., hyperinsulinemia + adiposity).	Complex clinical presentation requiring tailored diagnostics.

This Sulfur Flux Trilogy positions sulfur metabolism as a central determinant of metabolic fate, governing transitions across ABCD stages. If validated, this hypothesis could shift pre-diabetes from a vague transitional state to a molecularly defined entity, enabling precision diagnostics and sulfur-based therapeutics to prevent T2DM.

7. Conclusion

This review proposes that hypersulfation of adipokines, such as leptin and adiponectin, drives insulin trapping in pre-diabetes, defining a sulfur flux-driven subtype within the obesity/adiposity-based chronic disease (ABCD) framework. By reducing insulin bioavailability by ~20-30% without

disrupting signaling, this mechanism distinguishes pre-diabetes from classical insulin resistance, explaining hyperinsulinemia with preserved insulin sensitivity. Molecular pathways involve SULT1A1/SULT1E1 upregulation via PI3K/AKT, adipokine charge alteration, and insulin trapping, reversible through sulfatase activators (5-10 mg/kg) that hydrolyze sulfate groups, potentially enhancing glucose uptake. Despite lacking direct evidence for adipokine sulfation, tyrosine sulfation studies, transcriptomics, and proteomics provide robust support, though advanced proteomic validation is needed. Detection of sulfated adipokines via LC-MS/MS could enable early diagnosis, surpassing HbA1c or HOMA-IR. Future studies should explore SULT1E1 overexpression models and longitudinal cohorts to confirm clinical utility, potentially transforming pre-diabetes management through precision diagnostics and sulfur-based therapeutics to prevent T2DM.

Abbreviations

ABCD: Adiposity-Based Chronic Disease
 CCK: Cholecystokinin
 co-IP: Co-Immunoprecipitation
 CPT1: Carnitine Palmitoyltransferase 1
 DIO2: Deiodinase 2
 HbA1c: Hemoglobin A1c
 hADSCs: Human Adipose-Derived Stem Cells
 HOMA-IR: Homeostatic Model Assessment of Insulin Resistance
 HPLC: High-Performance Liquid Chromatography
 IRS-1: Insulin Receptor Substrate-1
 LC-MS/MS: Liquid Chromatography-Tandem Mass Spectrometry
 LXR: Liver X Receptor
 4-MUS: 4-Methylumbelliferyl Sulfate
 NAFLD: Non-Alcoholic Fatty Liver Disease
 OGTT: Oral Glucose Tolerance Test
 PAPS: 3'-Phosphoadenosine-5'-Phosphosulfate
 PI3K/AKT: Phosphoinositide 3-Kinase/Protein Kinase B
 PSGL-1: P-Selectin Glycoprotein Ligand-1
 PTM: Post-Translational Modification
 qPCR: Quantitative Polymerase Chain Reaction
 SPE: Solid-Phase Extraction
 SREBP-1c: Sterol Regulatory Element-Binding Protein 1c
 SULT: Sulfotransferase
 SULT1A1: Sulfotransferase 1A1
 SULT1E1: Sulfotransferase 1E1
 SULT2B1: Sulfotransferase 2B1
 T2DM: Type 2 Diabetes Mellitus
 T3: Triiodothyronine
 TSH: Thyroid-Stimulating Hormone
 2-NBDG: 2-(N-(7-Nitrobenz-2-oxa-1,3-diazol-4-yl)Amino)-2-Deoxyglucose

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