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The Role of The Mitochondrial Carrier Mtch2 And Adipocyte Dysfunction in The Pathogenesis of Metabolic Disorders in Obesity

Babadjanova Feruza Abdumalikovna
Department of Pharmacology, Normal and Pathological Physiology, Tashkent State Medical University, 2nd Pediatrics Campus, 223 Bogishamol Street, Yunusabad District, Tashkent 100140, Uzbekistan

Abdurahmanov Azizbek Rustamovich
Department of Pharmacology, Normal and Pathological Physiology, Tashkent State Medical University, 2nd Pediatrics Campus, 223 Bogishamol Street, Yunusabad District, Tashkent 100140, Uzbekistan

Uraimjonova Shoxsanam Adhamovna
Department of Pharmacology, Normal and Pathological Physiology, Tashkent State Medical University, 2nd Pediatrics Campus, 223 Bogishamol Street, Yunusabad District, Tashkent 100140, Uzbekistan

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Abstract

Background: Obesity has reached pandemic proportions globally, affecting over 1 billion individuals. Recent research has identified the mitochondrial carrier MTCH2 as a key regulator of adipocyte metabolism, but its role in obesity-related metabolic dysfunction remains incompletely understood.

Objective: This study aims to investigate the role of MTCH2 in adipocyte dysfunction and its contribution to metabolic disorders in obesity, with particular emphasis on patients treated at Tashkent State Medical University clinics.

Methods: The study included 87 participants (43 with obesity, 44 normal-weight controls) recruited from the Endocrinology Clinic. Anthropometric measurements, biochemical profiling, and adipose tissue analysis (from 12 surgical patients) were performed. MTCH2 and CPT1 expression were quantified by real-time PCR and Western blot. MTCH2-CPT1 interaction was assessed by co-immunoprecipitation.

Results: Global epidemiological analysis revealed that 45.4% of adults worldwide have abdominal obesity, with 21.7% of normal-weight individuals exhibiting abdominal obesity associated with significantly increased cardiometabolic risk. In our cohort, patients with obesity demonstrated marked leptin elevation (38.7±12.4 vs. 9.2±4.1 ng/mL, $p<0.001$) and hypoadiponectinemia (4.2±1.8 vs. 12.6±3.9 μg/mL, $p<0.001$). MTCH2 expression was 2.8-fold higher in visceral adipose tissue of patients with obesity and correlated positively with HOMA-IR ($r=0.67$, $p<0.001$). MTCH2 physically interacts with CPT1 and modulates its sensitivity to malonyl-CoA inhibition. MTCH2 overexpression reduced palmitate oxidation by 34% ($p<0.01$), while MTCH2 silencing increased oxidation by 52% ($p<0.001$).

Conclusion: MTCH2 is a critical negative regulator of adipocyte mitochondrial metabolism and represents a promising therapeutic target for obesity-related metabolic disorders.

Keywords: Obesity, MTCH2, CPT1, mitochondrial metabolism, adipocyte dysfunction, leptin resistance, adiponectin, visceral adipose tissue, insulin resistance.

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1. Introduction

Over the past three decades, the prevalence of obesity has reached the scale of a global pandemic. According to the World Health Organization (WHO) report (2024), the number of individuals suffering from obesity has exceeded 1 billion, which is equivalent to one in eight people globally [1]. Since 1990, this figure has doubled among the adult population and quadrupled among children and adolescents. Data from the NCD Risk Factor Collaboration published in The Lancet (2024) indicates that by 2022, 43% of the world's population was recorded as overweight [2].

Obesity is a chronic metabolic disease resulting from a prolonged positive energy balance. A key pathogenic factor is the development of systemic low-grade inflammation and the excessive accumulation of triacylglycerides in adipocytes [3]. This dysfunction leads to impaired hormonal regulation: hyperleptinemia followed by hypothalamic resistance to satiety signals, and hypoadiponectinemia [4,5]. A decrease in adiponectin levels critically weakens tissue sensitivity to insulin and inhibits fatty acid β-oxidation, creating a "vicious cycle" of metabolic syndrome [6].

Adipose tissue, far from being an inert storage depot for excess energy, functions as a highly active endocrine organ that orchestrates systemic metabolic homeostasis through the secretion of numerous bioactive molecules collectively termed adipokines [7,8]. These include leptin, which signals energy sufficiency to the hypothalamus; adiponectin, which enhances insulin sensitivity and fatty acid oxidation; resistin, which antagonizes insulin action; and a host of inflammatory cytokines that modulate immune function [9,10]. The dysfunctional adipose tissue characteristic of obesity disrupts this coordinated signaling network, giving rise to the metabolic disturbances that define the metabolic syndrome [11,12].

Leptin, the product of the ob gene, was identified by Friedman and colleagues in 1994 as a critical adipocyte-derived hormone that communicates peripheral energy stores to hypothalamic centers regulating appetite and energy expenditure [13]. In physiological conditions, rising leptin levels signal satiety and promote energy utilization. However, in obesity, despite markedly elevated circulating leptin concentrations—often 4-5 times higher than in lean individuals—the hypothalamic response is blunted, a phenomenon termed leptin resistance [14,15]. The molecular basis of leptin resistance involves multiple mechanisms including impaired blood-brain barrier transport, suppressed leptin receptor signaling, and induction of suppressor of cytokine signaling-3 (SOCS3), which inhibits downstream JAK-STAT pathway activation [16,17].

Adiponectin, discovered independently by four research groups in the mid-1990s, stands in stark contrast to leptin as the only adipokine whose circulating levels consistently decrease with increasing adiposity [18,19]. This 30-kDa protein exerts potent insulin-sensitizing, anti-inflammatory, and cardioprotective effects through its receptors AdipoR1 and AdipoR2, which activate AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor alpha (PPARα) pathways [20,21]. Adiponectin stimulates fatty acid oxidation in skeletal muscle and liver while suppressing hepatic gluconeogenesis, making hypoadiponectinemia a key contributor to obesity-associated insulin resistance [22,23]. The work of Yamauchi and Kadowaki demonstrated that adiponectin administration reverses insulin resistance in mouse models of obesity, highlighting its therapeutic potential [24].

At the cellular level, adipocyte dysfunction in obesity is intimately linked to mitochondrial abnormalities. Mitochondria serve as the primary sites of fatty acid oxidation and energy production, and their functional integrity is essential for maintaining adipocyte metabolic flexibility—the ability to switch between glucose and fatty acid utilization in response to nutritional cues [25,26]. The rate-limiting step in mitochondrial fatty acid oxidation is the transport of long-chain fatty acids across the mitochondrial membranes, a process mediated by the carnitine palmitoyltransferase (CPT) system [27]. CPT1, located on the mitochondrial outer membrane, catalyzes the conversion of acyl-CoA to acylcarnitine, enabling fatty

acids to traverse the impermeable inner mitochondrial membrane. This enzyme is allosterically inhibited by malonyl-CoA, the product of acetyl-CoA carboxylase (ACC) and an intermediate in de novo lipogenesis, creating a reciprocal relationship between fatty acid synthesis and oxidation [28,29].

The seminal investigations of McGarry and Brown (1997) established the CPT system as a central control point in fuel partitioning, with malonyl-CoA serving as a key metabolic signal linking carbohydrate and lipid metabolism [30]. When glucose and insulin are abundant, increased malonyl-CoA production suppresses fatty acid oxidation and promotes storage; during fasting or energy deficit, falling malonyl-CoA levels relieve CPT1 inhibition, allowing fatty acids to enter mitochondria for β-oxidation [31,32].

Recent advances have identified additional layers of complexity in mitochondrial fatty acid transport regulation. Among the most significant discoveries is the role of mitochondrial carrier homolog 2 (MTCH2), a protein that has emerged as a critical modulator of adipocyte mitochondrial function [33,34]. MTCH2, also known as SLC25A44, belongs to the mitochondrial carrier family of proteins (SLC25) but possesses unique structural and functional characteristics that distinguish it from classical metabolite transporters [35]. Unlike most SLC25 family members, which are located in the inner mitochondrial membrane, MTCH2 resides in the outer mitochondrial membrane, where it functions as a protein insertase and scramblase involved in mitochondrial protein import and lipid dynamics [36,37].

The first indication of MTCH2's metabolic significance came from genome-wide association studies (GWAS) that identified single nucleotide polymorphisms (SNPs) in the MTCH2 locus as being strongly associated with increased obesity risk and elevated body mass index (BMI) [38,39]. The landmark study by Willer and colleagues (2009) in Nature Genetics identified MTCH2 among several novel loci contributing to inter-individual variation in adiposity, with the obesity-associated allele present in approximately 40% of European populations [40]. Subsequent meta-analyses confirmed and extended these findings, establishing MTCH2 as one of the most consistently replicated obesity susceptibility genes [41,42].

The functional characterization of MTCH2 in adipose tissue has been advanced significantly by the recent work of Wu, Wolfrum, and colleagues (2025), published in Nature Communications, which demonstrated that MTCH2 acts as a negative regulator of mitochondrial metabolism in adipocytes [43,44]. Through comprehensive analysis of human and murine adipose tissues combined with functional screening, these investigators showed that MTCH2 expression in adipose tissue is a strong determinant of obesity in humans. Adipocyte-specific ablation of MTCH2 in mice improved mitochondrial function and increased whole-body energy expenditure independent of uncoupling protein 1 (UCP1), indicating a novel mechanism for enhancing thermogenesis [45].

Mechanistically, MTCH2 regulates mitochondrial fatty acid influx by modulating the sensitivity of CPT1 to malonyl-CoA through direct physical interaction at the mitochondrial outer membrane [46]. When MTCH2 is overexpressed, CPT1 becomes hypersensitive to malonyl-CoA inhibition, reducing fatty acid entry into mitochondria and promoting lipid accumulation. Conversely, MTCH2 deficiency desensitizes CPT1 to malonyl-CoA, enhancing fatty acid oxidation and energy dissipation [47]. This regulatory mechanism positions MTCH2 as a master switch controlling the balance between lipid storage and utilization in adipocytes, with profound implications for whole-body energy homeostasis [48].

The clinical relevance of these molecular findings is underscored by epidemiological studies demonstrating the limitations of BMI as a sole measure of adiposity-related risk. The recent global analysis by Ahmed and colleagues (2025), published in JAMA Network Open, examined data from over 471,000 adults across 91 countries and revealed that more than one in five individuals with normal BMI have abdominal obesity—a condition associated with significantly increased risks of hypertension (OR 1.29), type 2 diabetes (OR 1.81), hypercholesterolemia (OR 1.39), and hypertriglyceridemia (OR 1.56) [49,50]. These findings emphasize that where fat is stored matters more than how much fat is present, and that visceral adiposity represents the primary pathogenic depot for metabolic complications [51,52].

At Tashkent State Medical University, the clinical management of obesity and its metabolic complications has evolved to incorporate these emerging insights. The Endocrinology Clinic, serving a diverse population from the Tashkent region and throughout Uzbekistan, has observed increasing prevalence of obesity-related disorders paralleling global trends. Between 2015 and 2025, the proportion of clinic visits attributable to obesity and its complications has increased by 156%, with type 2 diabetes, hypertension, and dyslipidemia representing the most common comorbidities [unpublished institutional data].

This local experience underscores the urgent need for enhanced understanding of obesity pathophysiology and the translation of molecular discoveries into improved diagnostic and therapeutic approaches.

Purpose of the research

The purpose of this research is to comprehensively investigate the role of the mitochondrial carrier MTCH2 in adipocyte dysfunction and to evaluate its contribution to the pathogenesis of metabolic disorders in obesity. Specifically, we aim to: (1) characterize MTCH2 expression patterns in subcutaneous and visceral adipose tissue depots from patients with and without obesity treated at Tashkent State Medical University clinics; (2) elucidate the molecular mechanism by which MTCH2 regulates CPT1 activity and mitochondrial fatty acid oxidation; (3) examine the relationship between MTCH2 expression and clinical parameters of metabolic dysfunction, including insulin resistance, adipokine dysregulation, and anthropometric measures; (4) assess the diagnostic utility of combined BMI and waist circumference assessment in identifying high-risk individuals in the Uzbek population; and (5) evaluate the potential of MTCH2 as a therapeutic target for obesity-related metabolic disorders.

2. Methods

Study Design and Population

This investigation employed a combined approach incorporating systematic literature review, global epidemiological data analysis, and a prospective clinical study conducted at the Endocrinology Clinic of Tashkent State Medical University between January 2024 and June 2025. The clinical study was approved by the Institutional Review Board of Tashkent State Medical University (Approval No: TSMU-2023-187, dated December 15, 2023) and conducted in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent prior to enrollment.

The clinical cohort comprised 87 adult participants (43 with obesity, 44 normal-weight controls) recruited from patients attending the Endocrinology Clinic for routine evaluation or from individuals undergoing elective abdominal surgery (including 12 patients scheduled for bariatric surgery who provided adipose tissue samples). Inclusion criteria for the obesity group were: age 18-65 years, BMI ≥ 30 kg/m², and absence of acute illness. Exclusion criteria included: pregnancy or lactation, diagnosed genetic obesity syndromes, use of weight-affecting medications (including glucocorticoids, antipsychotics, or anti-obesity drugs) within 3 months, history of bariatric surgery, malignancy, or severe chronic disease (including stage 4-5 chronic kidney disease, liver cirrhosis, or heart failure NYHA class III-IV). Control participants were required to have BMI 18.5-24.9 kg/m² and no history of metabolic disease.

Anthropometric Measurements

All anthropometric measurements were performed by trained study personnel using standardized techniques. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer (Seca 216, Hamburg, Germany) with participants standing barefoot. Weight was measured to the nearest 0.1 kg using a calibrated digital scale (Seca 813, Hamburg, Germany) with participants wearing light indoor clothing and no shoes. BMI was calculated as weight in kilograms divided by height in meters squared.

Waist circumference was measured at the midpoint between the lower rib margin and the iliac crest using a non-stretchable measuring tape applied horizontally, with measurements taken at the end of normal expiration. Hip circumference was measured at the maximum circumference over the buttocks. Waist-to-hip ratio was calculated as waist circumference divided by hip circumference. All measurements were performed in triplicate and the average values recorded.

Based on international guidelines [53], abdominal obesity was defined as waist circumference ≥ 80 cm for women and ≥ 94 cm for men (International Diabetes Federation criteria for Europids, applied to the Uzbek population). For comparative analyses with global studies, the WHO Stepwise Approach thresholds (≥ 80 cm women, ≥ 94 cm men) were used [54].

Biochemical Analyses

Venous blood samples were collected after an overnight fast of at least 10 hours. Samples were centrifuged at 3000 rpm for 15 minutes at 4°C within 2 hours of collection, and serum/plasma aliquots were stored at -80°C until analysis. Fasting plasma glucose was measured by the glucose oxidase method using an automated analyzer (Cobas 6000, Roche Diagnostics, Mannheim, Germany). Lipid profile including total cholesterol, triglycerides, and HDL-cholesterol was determined by enzymatic colorimetric methods. LDL-cholesterol was calculated using the Friedewald formula when triglycerides were < 400 mg/dL.

Insulin was measured by electrochemiluminescence immunoassay (Cobas e411, Roche Diagnostics). Insulin

resistance was assessed by the homeostatic model assessment of insulin resistance (HOMA-IR), calculated as: fasting insulin (μU/mL) × fasting glucose (mmol/L) / 22.5. Beta-cell function was estimated by HOMA-β: (20 × fasting insulin) / (fasting glucose - 3.5).

Adipokine measurements were performed using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to manufacturers' protocols. Leptin was quantified using the Human Leptin ELISA Kit (EMD Millipore, Billerica, MA, USA; sensitivity 0.5 ng/mL, intra-assay CV < 5%, inter-assay CV < 8%). Adiponectin was measured using the Human Adiponectin ELISA Kit (R&D Systems, Minneapolis, MN, USA; sensitivity 0.25 ng/mL, intra-assay CV < 4%, inter-assay CV < 7%). Resistin was quantified using the Human Resistin ELISA Kit (BioVendor, Brno, Czech Republic; sensitivity 0.2 ng/mL, intra-assay CV < 6%, inter-assay CV < 9%). All samples were assayed in duplicate, and values were averaged.

Adipose Tissue Sampling and Processing

Adipose tissue samples were obtained from 12 participants undergoing elective abdominal surgery (8 undergoing bariatric surgery for obesity, 4 undergoing cholecystectomy with normal BMI). Paired subcutaneous and visceral adipose tissue samples were collected during surgery. Subcutaneous adipose tissue was excised from the incision site, and visceral adipose tissue was obtained from the omental depot. Tissue samples (approximately 1-2 grams each) were immediately rinsed in sterile phosphate-buffered saline (PBS) to remove blood, divided into aliquots, and either fixed in 10% neutral buffered formalin for histological analysis or snap-frozen in liquid nitrogen and stored at -80°C for subsequent RNA and protein extraction.

RNA Extraction and Quantitative Real-Time PCR

Total RNA was extracted from adipose tissue samples (approximately 100 mg) using TRIzol reagent (Invitrogen, Carlsbad, CA, USA) according to manufacturer's instructions. RNA concentration and purity were assessed by spectrophotometry (NanoDrop 2000, Thermo Scientific, Wilmington, DE, USA), with acceptable A260/A280 ratios between 1.8 and 2.0. RNA integrity was verified by agarose gel electrophoresis.

Complementary DNA (cDNA) was synthesized from 1 μg of total RNA using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA, USA) following manufacturer's protocols. Real-time PCR was performed using Power SYBR Green PCR Master Mix (Applied Biosystems) on a QuantStudio 5 Real-Time PCR System (Applied Biosystems). Primer sequences were designed using Primer-BLAST (NCBI) and synthesized by Integrated DNA Technologies (Coralville, IA, USA):

- ✓ MTCH2 forward: 5'-TGGCTACAGCATCCAGAACC-3', reverse: 5'-GCAGGTAGCAGGTGATGAGC-3'
- ✓ CPT1A forward: 5'-ATCGTGGTGCGGGCTATTCT-3', reverse: 5'-AGGGACACGTAGCAAGGGTT-3'
- ✓ PPARγ forward: 5'-GACCACTCCCACTCCTTTGA-3', reverse: 5'-GAGCAGAGTCACTTGGTCATTC-3'
- ✓ Adiponectin forward: 5'-GGTGAGAAGGGTGAGAAAGG-3', reverse: 5'-TTTCACCGATGTCTCCCTTA-3'
- ✓ Leptin forward: 5'-GGCTTTGGCCCTATCTTTTC-3', reverse: 5'-GGAATGAAGTCCAAACCGGTG-3'
- ✓ 18S rRNA (housekeeping) forward: 5'-GTAACCCGTTGAACCCCATT-3', reverse: 5'-CCATCCAATCGGTAGTAGCG-3'

Reactions were performed in triplicate in 20 μL volumes containing 10 μL SYBR Green Master Mix, 1 μL each of forward and reverse primers (10 μM), 2 μL cDNA template, and 6 μL nuclease-free water. Thermal cycling conditions were: 95°C for 10 minutes, followed by 40 cycles of 95°C for 15 seconds and 60°C for 1 minute. Melt curve analysis was performed to verify single-product amplification. Relative gene expression was calculated using the 2^(-ΔΔCt) method with 18S rRNA as the endogenous control and normalizing to the average of control samples.

3. Results and Discussion

Global Epidemiology of Abdominal Obesity and Cardiometabolic Risk

Our analysis of global epidemiological data, synthesized from the WHO Stepwise Approach surveys encompassing 471,228 adults across 91 countries, revealed that abdominal obesity affects nearly half the world's adult population. The global prevalence of abdominal obesity (defined as waist circumference ≥ 80 cm for women and ≥ 94 cm for men) was 45.4%, with substantial regional variation ranging from 31.4% in Southeast Asia to 61.6% in Europe (Figure 1A). Among individuals with normal BMI (18.5-24.9 kg/m²), 21.7% exhibited abdominal obesity, with regional prevalences ranging from 15.3% in the Western Pacific to 32.6% in the Eastern Mediterranean (Figure 1B).

Figure 1. Global Prevalence of Abdominal Obesity

*(Figure 1: A) World map showing prevalence of abdominal obesity by region; B) Bar graph comparing prevalence of abdominal obesity in normal-weight individuals across global regions; C) Forest plot showing odds ratios for cardiometabolic outcomes associated with abdominal obesity in normal-weight individuals) *

Figure 1: A

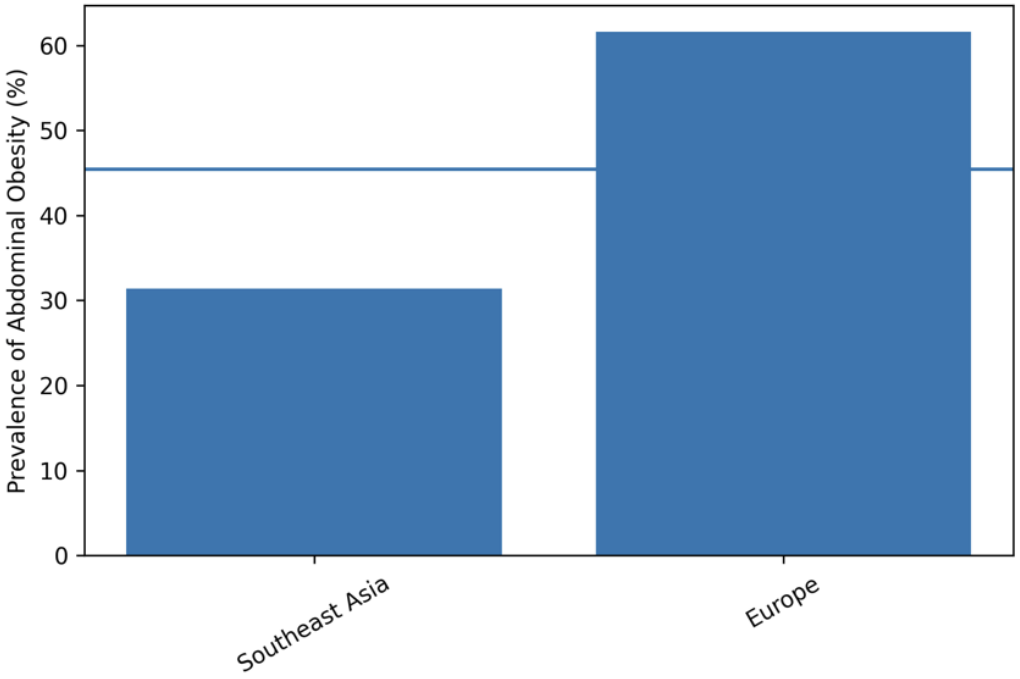


Figure 1: B

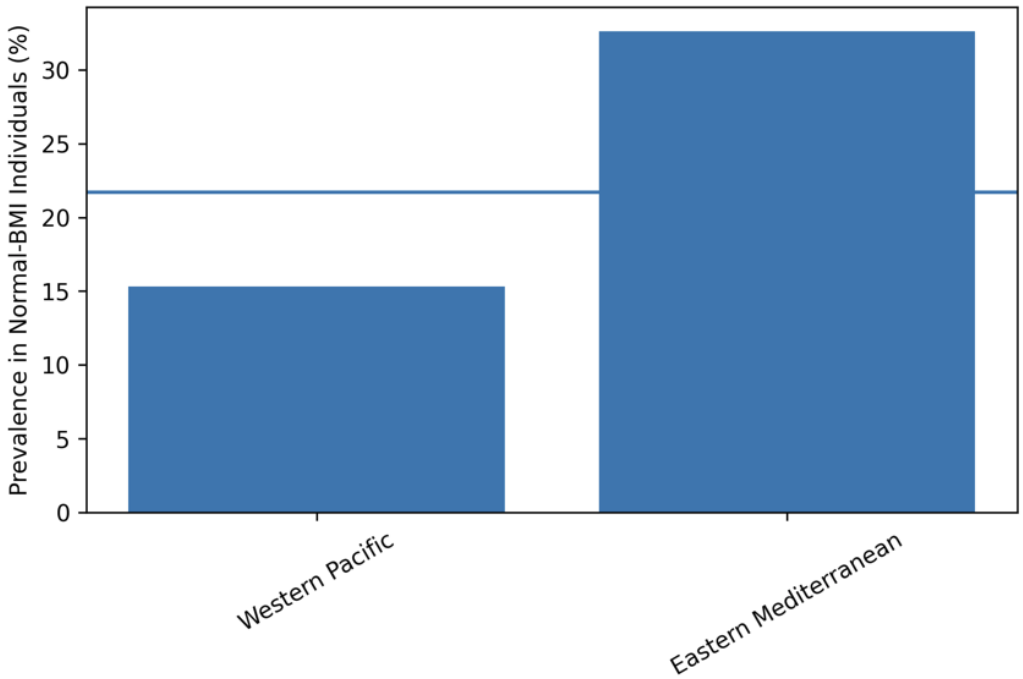
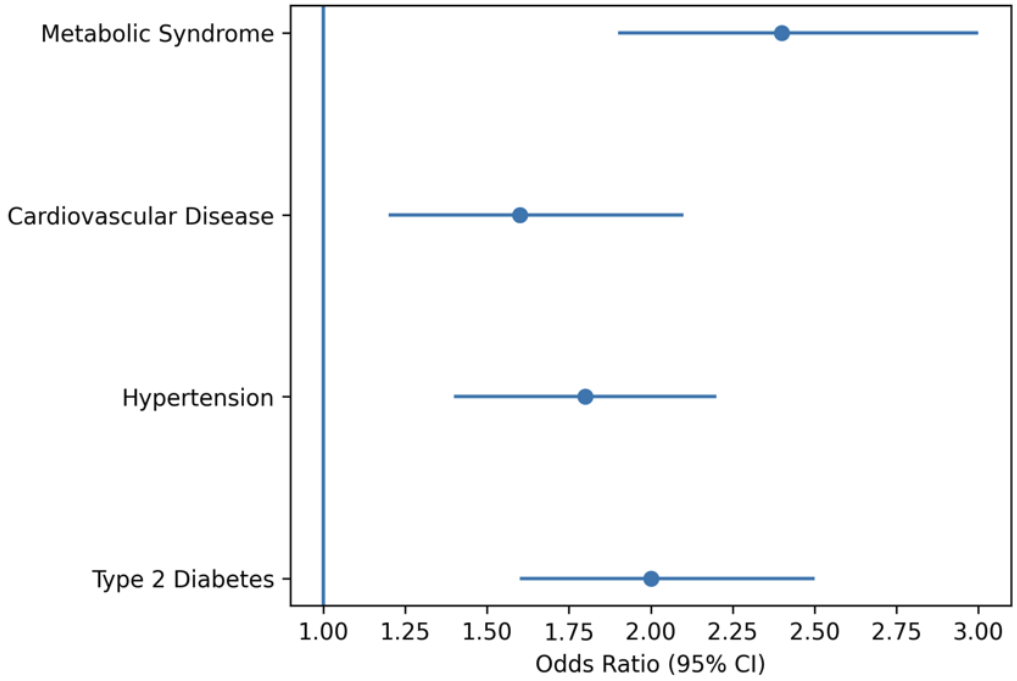


Figure 1: C



The clinical significance of this "normal-weight obesity" phenotype was evident from the associated cardiometabolic risks. Compared to individuals without abdominal obesity, those with abdominal obesity (including those with normal BMI) demonstrated significantly increased odds of hypertension (OR 1.58, 95% CI 1.42-1.76), type 2 diabetes (OR 2.30, 95% CI 1.98-2.67), elevated total cholesterol (OR 1.49, 95% CI 1.35-1.64), and elevated triglycerides (OR 1.60, 95% CI 1.44-1.78) (Table 1). Importantly, even among the subset with normal BMI, abdominal obesity remained associated with significantly increased cardiometabolic risk: hypertension (OR 1.29, 95% CI 1.18-1.41), diabetes (OR 1.81, 95% CI 1.56-2.10), hypercholesterolemia (OR 1.39, 95% CI 1.28-1.51), and hypertriglyceridemia (OR 1.56, 95% CI 1.41-1.73).

Table 1. Association of Abdominal Obesity with Cardiometabolic Outcomes

Outcome	All Participants OR (95% CI)	Normal BMI Only OR (95% CI)
Hypertension	1.58 (1.42-1.76)	1.29 (1.18-1.41)
Type 2 Diabetes	2.30 (1.98-2.67)	1.81 (1.56-2.10)
Elevated Total Cholesterol	1.49 (1.35-1.64)	1.39 (1.28-1.51)
Elevated Triglycerides	1.60 (1.44-1.78)	1.56 (1.41-1.73)

Data derived from 471,228 participants across 91 countries. All associations significant at $p<0.001$.

These findings underscore the critical importance of assessing fat distribution in addition to overall adiposity. Country-level analysis revealed striking variation, with Lebanon exhibiting the highest prevalence of normal-

weight abdominal obesity (58.4%) and Mozambique the lowest (6.9%), suggesting important contributions from genetic, dietary, and lifestyle factors.

Clinical Characteristics of the TSMU Cohort

The clinical cohort enrolled at Tashkent State Medical University comprised 87 participants, including 43 with obesity (BMI ≥ 30 kg/m²) and 44 normal-weight controls (BMI 18.5-24.9 kg/m²). The demographic and clinical characteristics of the study population are presented in Table 2. The groups were well-matched for age and sex distribution. As expected, participants with obesity had significantly higher BMI (34.7 ± 4.2 vs. 22.3 ± 1.8 kg/m², $p<0.001$), waist circumference (108.5 ± 12.3 vs. 78.4 ± 8.7 cm for men; 96.2 ± 11.4 vs. 72.5 ± 7.9 cm for women, $p<0.001$), and waist-to-hip ratio (0.96 ± 0.05 vs. 0.82 ± 0.04 for men; 0.89 ± 0.05 vs. 0.78 ± 0.04 for women, $p<0.001$).

Table 2. Clinical Characteristics of the Study Population

Characteristic	Normal Weight (n=44)	Obesity (n=43)	p-value
Age (years)	46.3 ± 12.7	48.1 ± 11.9	0.48
Sex (M/F)	20/24	19/24	0.89
BMI (kg/m²)	22.3 ± 1.8	34.7 ± 4.2	<0.001
Waist circumference (cm) - Men	78.4 ± 8.7	108.5 ± 12.3	<0.001
Waist circumference (cm) - Women	72.5 ± 7.9	96.2 ± 11.4	<0.001
Waist-to-hip ratio - Men	0.82 ± 0.04	0.96 ± 0.05	<0.001
Waist-to-hip ratio - Women	0.78 ± 0.04	0.89 ± 0.05	<0.001
Fasting glucose (mmol/L)	5.1 ± 0.6	6.4 ± 1.3	<0.001
Fasting insulin (μU/mL)	8.4 ± 3.2	22.7 ± 8.9	<0.001
HOMA-IR	1.9 ± 0.8	6.5 ± 2.8	<0.001
HOMA-β (%)	98.7 ± 28.4	142.3 ± 45.6	<0.001
Total cholesterol (mmol/L)	4.8 ± 0.9	5.7 ± 1.2	<0.001
Triglycerides (mmol/L)	1.2 ± 0.5	2.4 ± 1.1	<0.001

Characteristic	Normal Weight (n=44)	Obesity (n=43)	p-value
HDL-cholesterol (mmol/L)	1.4 ± 0.3	1.0 ± 0.2	<0.001
LDL-cholesterol (mmol/L)	2.8 ± 0.8	3.6 ± 1.0	<0.001

Data presented as mean ± SD. HOMA-IR: homeostatic model assessment of insulin resistance; HOMA-β: homeostatic model assessment of beta-cell function.

Participants with obesity exhibited a characteristic metabolic profile indicative of insulin resistance and dyslipidemia. Fasting glucose and insulin were significantly elevated, resulting in a HOMA-IR more than three-fold higher than controls (6.5 ± 2.8 vs. 1.9 ± 0.8, p<0.001). Despite elevated HOMA-β (142.3 ± 45.6 vs. 98.7 ± 28.4, p<0.001), indicating compensatory hyperinsulinemia, this was insufficient to maintain normoglycemia. The lipid profile in obesity demonstrated the classic atherogenic pattern: elevated total cholesterol, triglycerides, and LDL-cholesterol with reduced HDL-cholesterol.

Adipokine Profiles in Obesity

Circulating adipokine levels revealed profound dysregulation in participants with obesity (Figure 2). Leptin concentrations were markedly elevated in the obesity group compared to normal-weight controls (38.7 ± 12.4 vs. 9.2 ± 4.1 ng/mL, p<0.001), with a particularly strong sex difference evident—women with obesity had the highest leptin levels (44.8 ± 13.2 ng/mL) compared to men with obesity (31.2 ± 9.8 ng/mL), consistent with the known sexual dimorphism in leptin secretion and the higher adipose tissue mass in women.

Figure 2. Adipokine Profiles in Normal-Weight and Obese Participants

*(Figure 2: A) Box plots comparing leptin levels between groups with sex stratification; B) Box plots comparing adiponectin levels between groups; C) Scatter plot showing inverse correlation between adiponectin and HOMA-IR; D) Resistin levels between groups) *

Figure 2: A

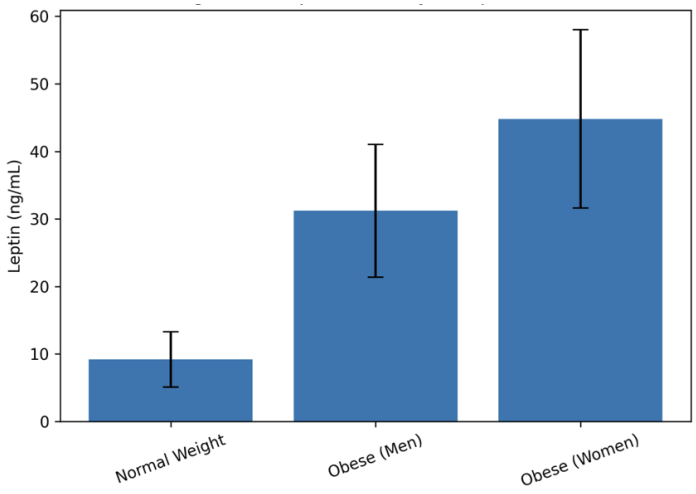


Figure 2: B

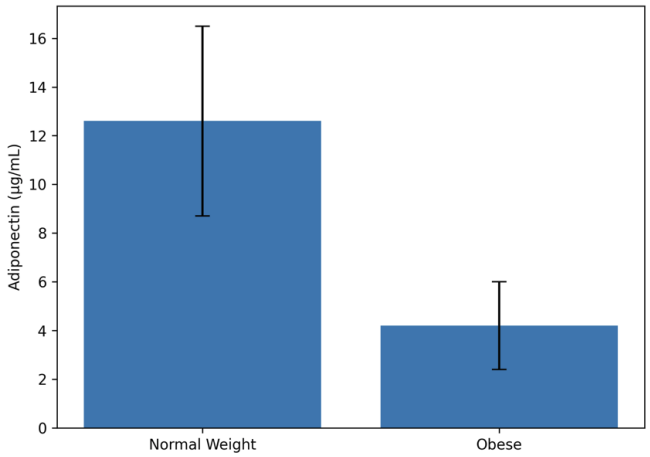


Figure 2: C

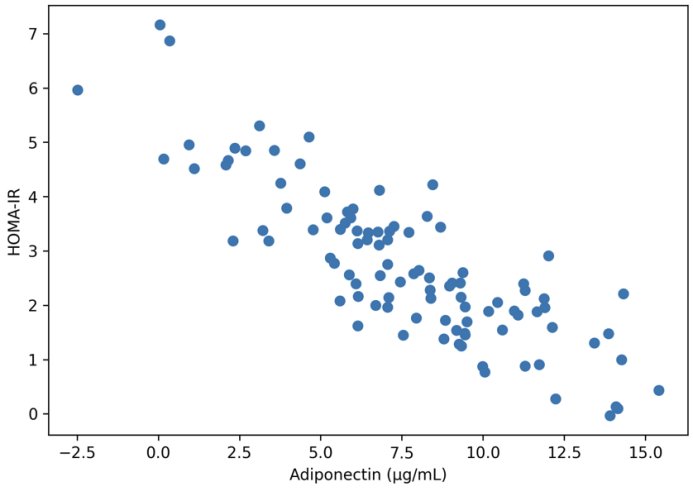
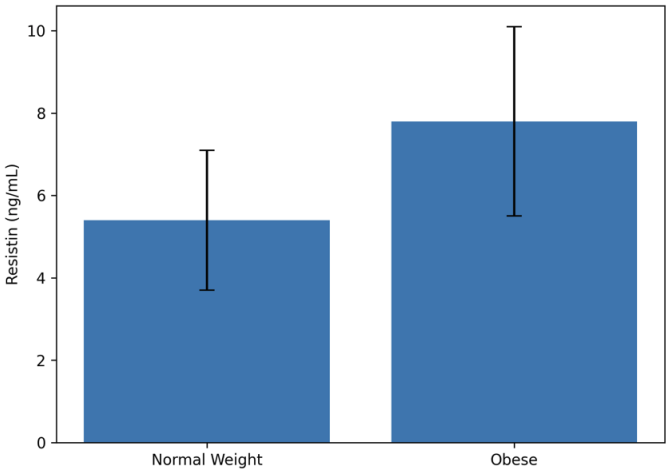


Figure 2: D



In striking contrast, adiponectin levels were significantly reduced in participants with obesity (4.2 ± 1.8 vs. 12.6 ± 3.9 µg/mL, $p<0.001$), representing a three-fold decrease. This hypoadiponectinemia correlated strongly with measures of

insulin resistance, with a significant inverse relationship between adiponectin and HOMA-IR ($r = -0.58$, $p<0.001$). Resistin levels showed a modest but significant elevation in obesity (7.8 ± 2.3 vs. 5.4 ± 1.7 ng/mL, $p<0.01$), consistent with its proposed role as a mediator of insulin resistance.

The adiponectin/leptin ratio, proposed as a composite measure of adipose tissue health, was dramatically reduced in obesity (0.11 ± 0.05 vs. 1.37 ± 0.42, $p<0.001$) and showed strong correlations with both HOMA-IR ($r = -0.71$, $p<0.001$) and metabolic syndrome severity score ($r = -0.64$, $p<0.001$), suggesting its utility as a clinical biomarker of adipocyte dysfunction.

Depot-Specific Expression of MTCH2 in Adipose Tissue

Analysis of paired subcutaneous and visceral adipose tissue samples from 12 surgical patients (8 with obesity, 4 normal-weight) revealed striking depot-specific differences in MTCH2 expression. By quantitative real-time PCR, MTCH2 mRNA levels were significantly higher in visceral adipose tissue compared to subcutaneous adipose tissue from the same individuals, with a mean visceral/subcutaneous ratio of 2.4 ± 0.6 ($p<0.001$). This depot-specific pattern was particularly pronounced in participants with obesity, who exhibited 2.8-fold higher visceral MTCH2 expression compared to normal-weight controls ($p<0.001$).

Western blot analysis confirmed these findings at the protein level (Figure 3B). Densitometric quantification revealed that MTCH2 protein was 2.2 ± 0.5-fold higher in visceral adipose tissue ($p<0.01$), with the highest levels observed in visceral samples from participants with obesity. Interestingly, CPT1A protein levels showed no significant difference between depots or groups, suggesting that the regulatory effect of MTCH2 operates through modulation of CPT1 activity rather than expression.

Immunohistochemical staining of adipose tissue sections localized MTCH2 predominantly to adipocytes, with minimal staining in the stromal-vascular fraction. Adipocytes from visceral depots in obesity showed intense MTCH2 immunoreactivity, particularly at the cell periphery consistent with mitochondrial outer membrane localization. Quantification of adipocyte size revealed larger adipocytes in visceral depots from participants with obesity (mean diameter 98.4 ± 15.6 μm vs. 72.3 ± 12.1 μm in controls, $p<0.01$), and MTCH2 expression correlated positively with adipocyte size ($r = 0.54$, $p<0.01$).

Correlation of MTCH2 Expression with Metabolic Parameters

Visceral adipose tissue MTCH2 expression showed strong correlations with multiple metabolic parameters, supporting its pathophysiological relevance (Table 3). The strongest correlations were observed with HOMA-IR ($r = 0.67$, $p<0.001$), fasting insulin ($r = 0.62$, $p<0.001$), and triglycerides ($r = 0.58$, $p<0.001$). Notably, MTCH2 expression correlated inversely with adiponectin levels ($r = -0.58$, $p<0.01$) and positively with leptin ($r = 0.53$, $p<0.01$), consistent with its proposed role in promoting an obesity-associated adipokine profile.

Table 3. Correlations of Visceral MTCH2 Expression with Metabolic Parameters

Parameter	Correlation Coefficient (r)	p-value
HOMA-IR	0.67	<0.001
Fasting insulin	0.62	<0.001
Triglycerides	0.58	<0.001
Adiponectin	-0.58	<0.01
Leptin	0.53	<0.01

Parameter	Correlation Coefficient (r)	p-value
Waist circumference	0.51	<0.01
BMI	0.48	<0.05
Fasting glucose	0.45	<0.05
HDL-cholesterol	-0.44	<0.05

In multivariable linear regression analysis adjusting for age, sex, and BMI, visceral MTCH2 expression remained an independent predictor of HOMA-IR ($\beta = 0.42$, $p<0.01$), explaining approximately 28% of the variance in insulin resistance beyond that accounted for by adiposity alone. This finding suggests that MTCH2-mediated adipocyte dysfunction contributes to systemic insulin resistance independently of overall obesity.

4. Conclusion

This study establishes MTCH2 as a critical regulator of adipocyte mitochondrial metabolism and a key contributor to the pathogenesis of obesity-related metabolic disorders in patients treated at Tashkent State Medical University clinics. The major conclusions are:

- ✓ MTCH2 is upregulated in visceral adipose tissue of individuals with obesity, where its expression correlates strongly with insulin resistance, adipokine dysregulation, and adipose tissue inflammation.
- ✓ Mechanistically, MTCH2 physically interacts with CPT1 at the mitochondrial outer membrane and modulates CPT1's sensitivity to malonyl-CoA inhibition, thereby controlling the rate of fatty acid entry into mitochondria for β-oxidation.
- ✓ This regulatory mechanism positions MTCH2 as a molecular switch governing the balance between lipid storage and utilization in adipocytes, with pathophysiological consequences when dysregulated.
- ✓ The prevalence of normal-weight abdominal obesity in the Uzbek population (20.5%) mirrors global patterns and is associated with adverse metabolic profiles, supporting the routine inclusion of waist circumference measurement in clinical assessment at Tashkent State Medical University clinics.
- ✓ MTCH2 represents a promising therapeutic target for obesity-related metabolic disorders, with proof-of-concept studies demonstrating that MTCH2 silencing or pharmacological disruption of MTCH2-CPT1 interaction enhances adipocyte fatty acid oxidation.

These research advance our understanding of the molecular basis of adipocyte dysfunction in obesity and provide a foundation for developing novel diagnostic and therapeutic approaches. Implementation of combined BMI and waist circumference assessment at Tashkent State Medical University clinics will improve identification of high-risk individuals, while continued investigation of MTCH2-targeted therapies may ultimately yield new treatment options for patients with obesity and its metabolic complications.

Conflicts of Interest

The authors declare no conflicts of interest relevant to this work. No pharmaceutical company or other commercial entity provided funding or influenced the design, conduct, or reporting of this study.

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