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Mitochondrial bioenergetics and sarcopenic obesity: Exploring mitochondrial quality control (Mitophagy) and ros production in skeletal muscle biopsies of aging individuals with metabolic syndrome

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Abstract
Sarcopenic obesity (SO)-the co-occurrence of age-related skeletal muscle wasting and adipose accumulation-presents a severe clinical phenotype in elderly populations, particularly when exacerbated by metabolic syndrome (MetS). While impaired energy metabolism is recognized in muscle senescence, the precise molecular interplay between mitochondrial bioenergetics, excessive reactive oxygen species (ROS) generation, and compromised mitochondrial quality control (mitophagy) remains incompletely understood. The present investigation examined vastus lateralis muscle biopsies from elderly cohorts categorized into healthy lean controls (HC, n=20), sarcopenic non-obese (S, n=20), obese non-sarcopenic (O, n=20), and sarcopenic obese with metabolic syndrome (SO+MetS, n=20). High-resolution respirometry, fluorometric mitochondrial ROS quantification, and immunoblotting of key mitophagy markers (PINK1, Parkin, LC3-II/I ratio, p62) were conducted. Subjects with SO+MetS exhibited a marked 48.6% reduction in state-3 mitochondrial respiration ($P < 0.001$) and a 2.4-fold increase in mitochondrial H_2O_2 production relative to healthy controls. Concurrently, accumulation of p62/SQSTM1 alongside suppressed Parkin recruitment indicated a stalled mitophagic flux. These findings demonstrate that unresolved mitochondrial oxidative stress coupled with an arrest in mitophagy drives the accelerated muscle catabolism characteristic of sarcopenic obesity, offering targeted bioenergetic and autophagic checkpoints for clinical intervention.

Keywords: Sarcopenic obesity, metabolic syndrome, mitochondrial bioenergetics, ROS production, mitophagy, skeletal muscle, PINK1/Parkin

Introduction

Aging is universally characterized by progressive physiological decline across multiple organ systems, with skeletal muscle displaying profound structural and functional vulnerabilities. Sarcopenia entails the age-associated loss of skeletal muscle mass, quality, and contractile strength, elevating frailty, physical disability, and mortality in the elderly. Concurrently, modern sedentary lifestyles and nutritional transitions have accelerated the global prevalence of obesity and metabolic syndrome (MetS) among older demographics. The convergence of these two entities yields sarcopenic obesity (SO), an adverse metabolic state where intramyocellular and intermuscular adiposity directly exacerbates muscle protein breakdown and blunts anabolic signaling.

Skeletal muscle is an energetically demanding tissue that relies heavily on functional mitochondrial networks for ATP generation through oxidative phosphorylation (OXPHOS). In healthy myocytes, dynamic mitochondrial fission, fusion, and selective degradation-termed mitophagy-maintain energetic homeostasis and eliminate damaged, hyper-oxidized organelles. Under physiological conditions, damaged mitochondria lose their inner mitochondrial membrane potential ($\Delta\psi_m$), facilitating the stabilization of PTEN-induced kinase 1 (PINK1) on the outer mitochondrial membrane, which subsequently recruits and phosphorylates the E3 ubiquitin ligase Parkin to prime the organelle for autophagosomal engulfment.

In the milieu of metabolic syndrome, excessive circulating free fatty acids (FFAs) and chronic low-grade systemic inflammation generate systemic lipotoxicity. When lipid overload supersaturates beta-oxidation, electron transport chain (ETC) complexes become decoupled, leading to electron leakage and heightened generation of reactive oxygen species (ROS). Persistent oxidative stress damages mitochondrial DNA (mtDNA), lipid membranes, and structural proteins. If the endogenous mitophagy machinery fails to clear these dysfunctional organelles, a feed-forward cycle of bioenergetic failure, oxidative stress, and caspase activation ensues, triggering myocyte apoptosis and muscle atrophy.

Although metabolic dysfunction and muscle loss are known correlates of advanced age, few studies have directly assessed the bioenergetic profile alongside dynamic mitophagic marker expression in fresh human skeletal muscle biopsies from sarcopenic individuals with confirmed metabolic syndrome. This study evaluates mitochondrial oxygen consumption rates, ROS generation, and molecular markers of mitochondrial quality control in skeletal muscle biopsies of elderly individuals diagnosed with sarcopenic obesity and metabolic syndrome.

Materials and Methods

Study Cohort and Ethical Approval

Eighty elderly individuals aged 60-78 years were recruited from clinical outpatient centers in central Odisha, India, and classified into four cohorts (n=20 per group):

1. **Healthy Controls (HC):** Normal BMI, normal appendicular skeletal muscle mass index (ASMI), no MetS.

2. **Sarcopenic (S):** Low ASMI and handgrip strength, normal BMI, no MetS.
3. **Obese (O):** Elevated BMI/adiposity, normal muscle mass/strength, no MetS.
4. **Sarcopenic Obese + MetS (SO+MetS):** Low ASMI, high adiposity, and satisfying ≥ 3 NCEP-ATP III diagnostic criteria for Metabolic Syndrome.

All procedures were approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants in adherence to the Declaration of Helsinki.

Muscle Biopsy Sampling

Percutaneous needle biopsies (~80-120 mg) were obtained from the *vastus lateralis* muscle under local anesthesia (2% lidocaine) using a Bergstrom needle with manual suction. Samples were immediately partitioned: one portion was placed into ice-cold preservation solution (BIOPS) for immediate respirometric assays, while the remainder was snap-frozen in liquid nitrogen and stored at -80Â°C for biochemical and molecular assays.

High-Resolution Mitochondrial Respirometry

Mitochondrial bioenergetics were quantified using an Oxygraph-2k high-resolution respirometer in permeabilized muscle fiber bundles. Muscle fibers were mechanically separated and permeabilized using saponin (50\, \mu\text{g/mL}). Substrate-uncoupler-inhibitor titration (SUIT) protocols were applied:

- **LEAK State (L_N):** Supported by Complex I substrates (malate 2mM, pyruvate 5mM, glutamate 10mM).
- **OXPHOS Capacity (P_{CI}):** Initiated via saturating ADP (5mM).
- **Maximal Electron Transport System (ETS_{CI+CII}):** Succinate (10mM) addition followed by stepwise uncoupling with FCCP (0.5µM steps).

Mitochondrial ROS Quantification

Mitochondrial hydrogen peroxide (H_2O_2) emission rates were measured fluorometrically in isolated mitochondria using the Amplex Red reagent (50µM) in the presence of horseradish peroxidase (1U/mL) and superoxide dismutase (30U/mL) at 37°C (Ex/Em = 563/587nm).

Protein Extraction and Western Blotting

Muscle tissue was homogenized in RIPA lysis buffer containing protease and phosphatase inhibitor cocktails. Equal protein aliquots (30µg) were resolved via SDS-PAGE (10-12%) and electrotransferred onto PVDF membranes. Membranes were probed with primary antibodies against PINK1, Parkin, p62/SQSTM1, LC3B, and GAPDH (loading control), followed by HRP-conjugated secondary antibodies. Blots were imaged via enhanced chemiluminescence (ECL) and quantified densitometrically.

Statistical Analysis

Data are presented as Mean±Standard Deviation (SD). Normality was verified via the Shapiro-Wilk test. Group comparisons were conducted using one-way ANOVA followed by Tukey's post-hoc test in SPSS version 26.0. Differences were considered statistically significant at $P < 0.05$.

Results

Baseline Anthropometric and Clinical Characteristics

The metabolic and body composition parameters of the study cohorts are summarized in Table 1. The SO+MetS cohort exhibited significantly elevated fasting blood glucose, homeostatic model assessment of insulin resistance (HOMA-IR), triglycerides, and waist circumference alongside markedly lower handgrip strength ($P < 0.001$) relative to control cohorts.

Table 1: Baseline Clinical, Anthropometric, and Biochemical Parameters

Parameter	Healthy Control (HC)	Sarcopenic (S)	Obese (O)	Sarcopenic Obese + MetS
Age (years)	66.4 ± 4.2	68.1± 3.9	65.8 ± 4.5	67.9 ± 4.1
BMI (kg/m^2)	22.4 ± 1.6	20.1± 1.4	31.8 ± 2.1*	32.4 ± 2.5*
ASMI (\text{kg/m} ^2)	7.8±0.6	5.4 ± 0.4*	7.6 ± 0.5	5.2 ± 0.4*
Handgrip Strength (kg)	34.2 ± 3.8	20.4 ±2.7*	31.5 ± 3.4	17.6 ± 2.1*
Fasting Glucose (mg/dL)	88.6 ± 7.4	92.1± 8.2	104.3 ± 9.6*	142.8±14.5*
HOMA-IR	1.4 ± 0.3	1.6 ± 0.4	3.2 ± 0.6^*	5.8 ±0.9*
Triglycerides (mg/dL)	112.5±14.2	120.3± 16.5	168.4 ±18.7*	224.6 ± 26.3*

* $P < 0.05$ vs. HC; # $P < 0.05$ vs. S and O groups

Mitochondrial Respirometry and ROS Emission

Mitochondrial bioenergetic capacity in permeabilized skeletal muscle fibers was markedly depressed in individuals with SO+MetS. State-3 OXPHOS respiration supported by Complex I+II substrates decreased by 48.6% in the SO+MetS group compared to HC ($P < 0.001$), with a corresponding drop in the Respiratory Control Ratio (RCR) indicating severe uncoupling (Table 2).

Conversely, net mitochondrial H_2O_2 production was elevated 2.4-fold in SO+MetS muscle biopsies relative to HC (184.2 ± 19.6 vs. 76.4 ± 8.5pmol.min^{-1}.mg^{-1}, $P < 0.001$).

Table 2: Mitochondrial Respirometric Indices and ROS Production in Skeletal Muscle

Bioenergetic Variable	HC	S	O	SO + MetS
LEAK Respiration (L_N)	12.4 ± 1.8	14.1 ± 2.1	16.5 ±2.4*	19.8±2.6*
OXPHOS Capacity (P_{CI+II})	68.5 ± 6.2	49.2 ± 5.1*	54.7±5.8*	35.2 ±4.3*
ETS Capacity (E_{CI+II})	79.2 ± 7.4	56.8 ± 6.3*	61.4 ± 6.9*	41.0 ± 4.9*
RCR (P/L_N)	5.52 ±0.48	3.48 ± 0.36*	3.31 ±0.34*	1.77 ± 0.21*
H_2O_2 Emission	76.4 ±8.5	118.2 ± 12.4*	134.6 ± 14.1*	184.2 ±19.6*

Respiration expressed in pmol O_2.mg^{-1} wet weight; H_2O_2 emission in pmol.min^{-1}.mg^{-1}

Mitophagy Signaling Alterations

Immunoblotting revealed distinct dysregulation of the PINK1-Parkin autophagic pathway across groups:

- **PINK1 Expression:** Significantly upregulated by 64% in the SO+MetS group compared to HC ($P < 0.01$), indicating elevated membrane depolarization.
- **Parkin Translocation:** Cytosolic/mitochondrial fraction analysis revealed a 52% reduction in translocated Parkin in SO+MetS muscle despite high PINK1 levels ($P < 0.01$).
- **p62/SQSTM1 Accumulation:** Elevated by 2.1-fold in SO+MetS ($P < 0.001$), reflecting stalled autophagic degradation.
- **LC3B-II / LC3B-I Ratio:** Significantly reduced in SO+MetS (0.42 \pm 0.06) compared to HC (1.14 ± 0.12, $P < 0.001$).

Discussion

Sarcopenic obesity combined with metabolic syndrome represents one of the most debilitating muscle disorders in the aging population. The results of this study establish that bioenergetic decline and oxidative stress in skeletal muscle are significantly worse when sarcopenia co-occurs with systemic metabolic derangements.

Our respirometric analyses demonstrate that OXPHOS capacity and RCR are severely diminished in the SO+MetS phenotype. In skeletal muscle, lipid overload leads to excessive intramyocellular diacylglycerols and ceramides, which directly inhibit Complex I and Complex III activity. This structural impairment decouples the mitochondrial membrane potential, increasing LEAK respiration and escalating electron leakage to molecular oxygen, generating high concentrations of superoxide and H_2O_2.

Crucially, our molecular data identify an arrested mitophagic flux as a central driver of this pathology. Under physiological stress, elevated ROS triggers the stabilization of PINK1, which recruits Parkin to ubiquitinate outer mitochondrial membrane proteins, promoting autophagosomal sequestration via LC3B-II and p62 clearance. However, in our SO+MetS cohort, despite marked PINK1 stabilization, Parkin recruitment was diminished, and p62 accumulated substantially. This stagnation indicates that chronic lipotoxicity, hyperinsulinemia, and systemic low-grade inflammation impair downstream autophagosome completion and lysosomal fusion.

As a consequence of stalled mitophagy, dysfunctional, leaky mitochondria persist within the sarcoplasm, continuously releasing ROS and pro-apoptotic factors (e.g., cytochrome c) into the cytosol. This sustained cellular stress activates muscle-specific E3 ubiquitin ligases (MuRF-1, Atrogin-1) and caspase cascades, accelerating muscle fiber proteolysis, loss of contractile integrity, and rapid muscle wasting characteristic of sarcopenic obesity.

Conclusion

This study demonstrates that skeletal muscle deterioration in sarcopenic obesity with metabolic syndrome is fundamentally underpinned by severe mitochondrial bioenergetic collapse, excessive ROS generation, and a critical block in PINK1/Parkin-mediated mitophagy. Interventions aimed at restoring mitochondrial quality control-such as targeted mitophagy activators, mitochondrial-targeted antioxidants, and precision exercise-induced metabolic conditioning-represent high-priority therapeutic avenues to preserve muscle functional independence in aging populations.

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