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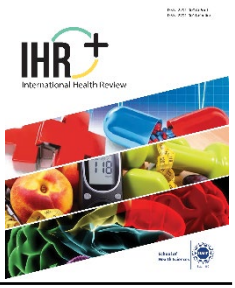

Title:	**Unravelling the Impact of Hypoxia, Reactive Oxygen Species, and Necrosis in Skeletal Muscles**
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Unravelling the Impact of Hypoxia, Reactive Oxygen Species, and Necrosis in Skeletal Muscles

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ABSTRACT

Skeletal muscle mass is strongly linked to stressors like ischemia and reactive oxygen species (ROS), both of which are regulated by oxygen availability and redox homeostasis. Intermittent ischemia and reperfusion cause a burst of reactive oxygen species, destruction of mitochondrial integrity, and inflammatory/necrotic pathways The objective of this review is to summarise existing data on the mechanistic interaction between hypoxia, ROS generation, and necrosis in skeletal muscle, as well as the role of these mechanisms in contributing to ischemia-reperfusion injury, metabolic disruption and dysfunction of skeletal muscle in the long term. The keywords examined in the literature search were skeletal muscle, hypoxia, reactive oxygen species, ischemia-reperfusion, mitochondria, and necrosis using PubMed, Scopus, and Web of Science. Articles published in English between 1990 and 2023 were peer reviewed and included, while conference abstracts, non-scientific reports, and duplicate records were excluded. The evidence suggests that hypoxia changes the use of substrates in the mitochondrion, stabilises the hypoxia-inducible factors and preconditions the muscle fibres to oxidative damage. The overproduction of ROS during reperfusion further increases the activity of inflammatory signalling, like NF-kB, calcium overload, and apoptotic and necrotic cell death. These teamed disruptions are what cause structural disintegration, dysfunctional contractional performance and retarded recuperation. An improved insight into these interrelated processes identifies prospects in therapeutic approaches such as antioxidants, enzymatic inhibition, gene-

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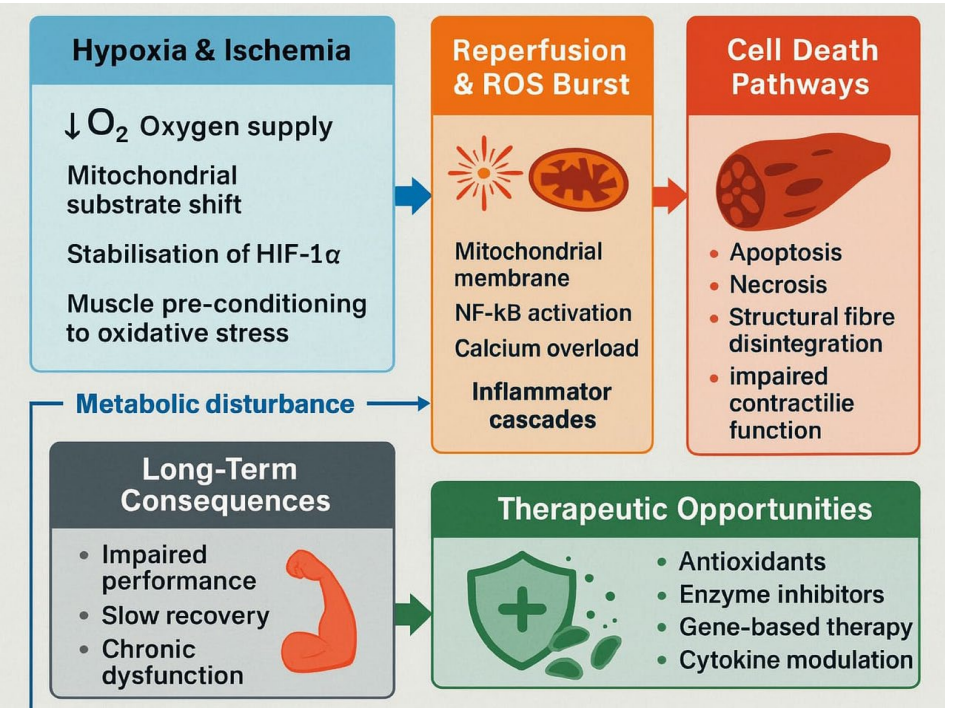
based treatment, cytokine therapy, and cell-derived exosomes- to alleviate ROS-related damage and promote muscle recovery.

GRAPHICAL ABSTRACT



Keywords: Ischemia–reperfusion injury, hypoxia, mitochondrial dysfunction, necrosis, oxidative stress, reactive oxygen species, skeletal muscle

1. INTRODUCTION

Skeletal muscle is a metabolically active tissue, which depends on the perpetual oxygen supply to maintain the contractile work, the functioning of the mitochondrion and cellular homeostasis. Oxygen deprivation, as occurs during arterial occlusion, trauma, tourniquet application or during some surgery, causes the muscle fibres to quickly shift to anaerobic metabolism, lactate builds up, intracellular acidosis ensues, and ionic stability is lost. This group of ischemic perturbations triggers premature cellular damage and primes the muscle to additional damage during reperfusion [1].

Although reperfusion is essential and often life-saving, it may cause a second wave of injury, namely excessive production of reactive oxygen species (ROS), inflammatory pathway activation, endothelial dysfunction, and mitochondrial bioenergetic failure, thereby causing limb dysfunction, delayed wound healing, compartment syndromes, and organ systemic problems [2, 3].

Skeletal muscle ischemia-reperfusion (I/R) injury is clinically experienced in a variety of conditions, such as myocardial infarction, stroke, vascular trauma, limb revascularisation, organ transplantation, and chronic diseases, including diabetes and peripheral artery disease [4]. Its great metabolic rate and high concentration of mitochondria make skeletal muscle a special target for fluctuating oxygen. The disruption of the mitochondrial electron transport chain during ischemia and sudden re-oxygenation causes a large amount of ROS that oxidises proteins, lipids and nucleic acids, which increases muscle damage [5].

Acute or chronic hypoxia triggers a series of complex adaptive responses against hypoxia-inducible factors (HIFs), which control angiogenesis, glycolysis, mitochondrial remodelling and cell survival genes [6]. Although such reactions help to adapt to particular physiological conditions (e.g., exercise training, high-altitude exposure), prolonged or extreme hypoxia may lead to the dysfunction of mitochondria, changes in muscle fibre structure, and predispose tissue to the injury caused by ROS [7].

ROS, although necessary at physiological levels for signalling and adaptation, become pathogenic when produced in excess. High ROS concentrations activate redox-sensitive transcription factors such as nuclear factor-κB (NF-κB), promote inflammatory cytokine release, disrupt calcium homeostasis, and induce mitochondrial permeability transition pore (mPTP) opening—ultimately leading to apoptosis or necrosis [8].

Necrosis has been considered a passive and uncontrolled form of cell death, but this process is now considered a regulated process that occurs in response to mitochondrial failure, protease activation, the loss of ATP, and inflammatory signalling.

The review integrates the existing data on interactions between hypoxia, ROS production, and necrotic processes to initiate skeletal muscle pathology, especially in relation to the I/R injury. The combination of

mechanistic understanding with novel therapeutic approaches, such as antioxidants, enzyme inhibitors, gene-based therapeutics, cytokines, and physical modalities, stem cell-derived exosomes, and new pharmacologic drugs are potential target as highlighted in this review of preventing or alleviating skeletal muscle injury and enhancing recovery.

1.1. Objective

To summarise existing data on the mechanistic interaction between hypoxia, ROS generation, and necrosis in skeletal muscle and the role of these mechanisms in contributing to ischemia-reperfusion injury, metabolic disruption and dysfunction of skeletal muscle in the long term.

2. MECHANISMS OF REPERFUSION INJURY

Ischemia-reperfusion (I/R) injury may occur when blood flow is reinstated in skeletal muscle that has been subjected to ischemia, and results in a cascade of metabolic and inflammatory events that alone in most cases, are more severe than the ischemic condition. Ischemia causes oxygen deprivation to disrupt oxidative phosphorylation and cause ATP depletion, intracellular acidosis, reduced activities of Na +/K + -ATPase and Ca2 + -ATPase pumps, and cytosolic calcium buildup.[1] These ionic imbalances favour cellular swelling, changes in membrane permeability and premature mitochondrial dysfunction [9].

Upon reperfusion, the sudden reintroduction of oxygen triggers excessive production of reactive oxygen species (ROS) in a series of enzymatic reactions, such as xanthine oxidase activation, dysfunctional mitochondrial electron transport, and reactions involving the NADPH oxidase, ensues.[2] Excessive levels of ROS oxidise membrane lipids, denature structural and enzymatic proteins, damage DNA and exacerbate the opening of mitochondrial permeability transition pore (mPTP).[3] mPTP opening disrupts the potential of the mitochondrial membranes, decreases ATP production, and hastens cell death [10].

It is also the endothelium that is activated by reperfusion, as it stimulates the expression of adhesion molecules like ICAM-1 and VCAM-1 that attract neutrophils and macrophages to the injury site [4]. These inflammatory cells produce proteins: proteases, elastases, myeloperoxidase, and other ROS, which increase oxidative and proteolytic injury in muscle fibres [5]. An important controller of this inflammatory process is the nuclear factor-kB (NF-kB), which is stimulated through oxidative stress and

cytokines. NF-kB signalling augments inducible nitric oxide synthase (iNOS), pro-inflammatory and chemokines, which deepens inflammation and aggravates tissue damage [6].

The interplay between oxidative stress and inflammation, with changes in calcium homeostasis, switches the muscle to regulated necrosis, apoptosis, or a combination of the two, depending on the extent of injury, which leads to the severe functional impairment and tissue damage seen following delayed limb ischemia, trauma, and vascular reconstruction.

3. HYPOXIA IN SKELETAL MUSCLE

Hypoxia is a major determinant of skeletal muscle physiology and pathology. Acute or chronic oxygen tension impairment impairs mitochondrial generation of ATP, causing the need to rely on anaerobic glycolysis and increasing lactate accumulation and intracellular acidosis [9]. Prolonged hypoxia disturbs the tricarboxylic acid cycle, lowers oxidative enzyme activity and changes mitochondrial morphology and efficiency [11].

Central to hypoxic adaptation is the activation of hypoxia-inducible factors (HIF-1α and HIF-2α)**.** Under normoxia, prolyl hydroxylase–mediated hydroxylation targets HIF-α for rapid proteasomal degradation. Hypoxia inhibits this process, stabilising HIF-α, allowing it to translocate to the nucleus, dimerise with HIF-β, and activate transcription of genes involved in glycolysis, angiogenesis (including VEGF), erythropoiesis, and cell survival [11]. In skeletal muscle, HIF-mediated angiogenesis enhances local capillary density, increasing oxygen delivery to meet metabolic demands [12].

However, hypoxia also alters redox homeostasis. The production of ROS by mitochondrial complexes I and III and cytosolic oxidases under low oxygen tension is paradoxical, as it leads to electron accumulation and inhibits oxygen elimination, thereby triggering the onset of oxidative stress, causing damage to mitochondrial membranes, stimulating apoptotic pathways, and predisposing skeletal muscle to further damage, in particular, during reperfusion [13].

Chronic hypoxia initiates muscle fibre structural and metabolic rearrangements, including increases in the ratio between the prevalence of more oxidative fibre types, reduced cross-sectional area of fibres, and ratios of capillaries to fibres [14]. These compensations can reduce the strength

and endurance of muscles. In addition, hypoxia influences the increase in the growth of satellite cells, protein turnover and the process of mitochondrial biogenesis that, respectively, influence muscle repair and regeneration following injury [15].

Limited physical activity can also result in skeletal muscle hypoxia, and there are a number of factors that reduce activity among youngsters. A recent systematic review in young adults shows that heavy traffic, unsafe road design, and lack of walking/cycling facilities consistently discourage active transport, while well-connected, mixed-use neighbourhoods and supportive social norms make walking and cycling much more likely [16, 17].

The interplay between hypoxia and ROS is especially pertinent when it comes to physiological stressors, including exercise, exposure at high altitude, and pathological ischemia. Hypoxia and reoxygenation cycles increase the production of ROS and inflammatory signatures, which are connected to the hypoxic stress that leads to muscle atrophy, slowing down the recovery, and making the muscle vulnerable to necrosis.

4. REACTIVE OXYGEN SPECIES (ROS) AND SKELETAL MUSCLE

Reactive oxygen species (ROS) are chemically reactive molecules that play dual roles in skeletal muscle physiology. At low concentrations, ROS participate in redox signalling, regulate vascular tone, mediate contraction, and support adaptive responses to exercise [18]. However, excessive ROS, particularly during ischemia–reperfusion, chronic inflammation, or metabolic dysfunction, can overwhelm antioxidant defences and induce oxidative stress, leading to cellular injury.

4.1. Sources of ROS in Skeletal Muscle

Mitochondria represent the primary source of ROS in skeletal muscle, especially under conditions of disrupted electron transport. Leakage of electrons from complexes I and III results in the reduction of oxygen to superoxide, which is subsequently converted to hydrogen peroxide and hydroxyl radicals [19]. Non-mitochondrial sources include NADPH oxidases (NOX enzymes), xanthine oxidase, uncoupled nitric oxide synthase, and inflammatory cell–derived oxidases. These enzymatic systems amplify ROS production during reperfusion and inflammatory activation.

4.2. ROS as Mediators of Oxidative Injury

The skeletal muscle oxidative stress is a type of stress that harms the cellular structure by oxidising proteins, peroxidising lipids, and breaking DNA strands. The loss of membrane integrity due to lipid peroxidation and the decrease in force production by oxidation of contractile proteins are the effects. Unregulated ROS also stimulate redox-regulated signalling pathways such as NF-kB, MAPKs and p53 that mediate the effect on apoptosis, autophagy, cytokines, and repair [20].

Reperfusion in opening the mitochondrial permeability transition pore (mPTP) leads to the loss of membrane potential, cessation of ATP production, and release of pro-apoptotic factors, including cytochrome c [21]. These events prime the muscle for programmed cell death or necrosis depending on the severity of mitochondrial damage.

4.3. ROS, Fatigue, and Muscle Dysfunction

The experimental results indicate that ROS build-up is one of the factors that cause decreased myofibrillar calcium sensitivity, deficiency of excitation-contraction coupling, and premature muscle fatigue.[7] Increased levels of ROS during recurrent contractions or ischemia disrupt the activity of the ryanodine receptors, calcium regulation, and contractile strength [22]. The presence of chronic oxidative stress has been suggested to be the cause of sarcopenia, cachexia, diabetes-associated myopathy, and muscle atrophy in chronic pathology.

5. NECROSIS AND TISSUE DAMAGE IN SKELETAL MUSCLES

Necrosis was historically considered an uncontrolled form of cell death, but recent evidence demonstrates that specific biochemical pathways modulate necrotic injury, particularly during ischemia-reperfusion [23].

5.1. Mechanisms Leading to Muscle Necrosis

Severe ATP depletion during ischemia impairs ion pumps, causing cytosolic accumulation of sodium, calcium, and hydrogen ions. This ionic imbalance stimulates activation of proteases such as calpains and cathepsins, phospholipases, and endonucleases, all of which degrade cellular structures and the cytoskeleton [24]. Mitochondrial failure is central to necrosis: permeability transition, ROS overload, and calcium dysregulation create a self-amplifying cycle resulting in irreversible myocyte injury [25].

However, the neutrophil and macrophage infiltrations during reperfusion also enhance the necrosis through the release of ROS, nitric oxide, cytokines, and proteolytic enzymes. Peroxynitrite, which is formed as a result of a reaction between nitric oxide and superoxide, causes lipid peroxidation and nitration of proteins, which increases the destruction of tissues [26].

5.2. Inflammation and Necrotic Progression

Tumour necrosis factor-a (TNF-a), IL-1b, and IL-6 are inflammatory cytokines which affect necrotic progression. In experimental models, TNF-α has been reported to suppress microvascular perfusion, encourage the expression of endothelial adhesion molecules and generate secondary muscle injury, which is central in the continuation of tissue injury [27]. Figure 1 presents the graphical description of the linkage between inflammatory markers and muscle injury.

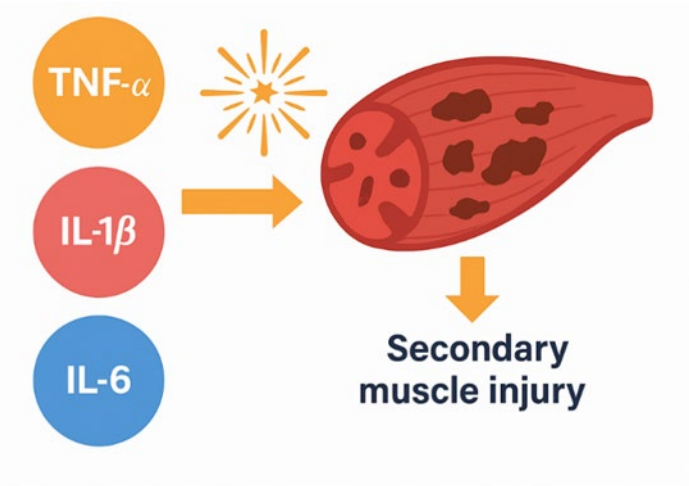


Figure 1. The Effect of Inflammatory Markers on Skeletal Muscles

5.3. Clinical Consequences of Necrosis

Muscle necrosis can manifest clinically as:

- Compartment syndrome due to oedema and increased hydrostatic pressure
- Limb dysfunction or loss
- Reperfusion-associated systemic inflammation

- Release of myoglobin, causing renal injury
- Increased susceptibility to infection and delayed healing

The extent of necrosis is linked to the period of ischemia, the perfusion level that remained, temperature, and the type of muscle fibre [15]. The deep muscles that have a small collateral circulation are more prone to irreversible damage.

5.4. Necroptosis and Regulated Necrosis

Recent studies indicate that necrosis may occur through regulated pathways such as necroptosis, mediated by receptor-interacting protein kinases (RIPK1, RIPK3) and mixed lineage kinase domain-like (MLKL) proteins [16]. Necroptosis is triggered by cytokines, ROS, and mitochondrial dysfunction, providing a potential therapeutic target for intervention in I/R injury.

6. THERAPEUTIC STRATEGIES FOR SKELETAL MUSCLE INJURY

Skeletal muscle injury led by hypoxia, oxidative stress and necrosis needs a multifaceted approach to its management. Therapy can focus on the inflammation, oxidative injury, dysfunction in the metabolic processes, or on the regenerative ability. Other emerging techniques are biologics, gene modulation and cell-based therapies. The section sums up the existing evidence on pharmacologic, enzymatic, genetic, cytokine-driven and physical modalities in the reduction of muscle injury and recovery improvement.

6.1. Drug-Based Therapies

Pharmacologic interventions aim to reduce oxidative stress, modulate inflammation, improve metabolic efficiency, or enhance muscle regeneration.

6.1.1. Antioxidants. Antioxidants are a common research topic due to their therapeutic potential in skeletal muscle injury, which is mainly central to ROS. The free radical scavengers like vitamin E, N-acetylcysteine (NAC), coenzyme Q10, resveratrol, melatonin, and pyrroloquinoline quinone have been shown to scavenge free radicals, prevent mitochondrial membrane damage, and preserve contractile proteins [1]. Antioxidants can inhibit redox-sensitive signal transduction, including NF-kB and MAPK

cascades, and inflammatory amplification [2].

6.1.2. Metabolic and Anti-inflammatory Agents. Metformin promotes the maintenance of redox through the activation of AMP-activated protein kinase (AMPK), aggravates glycolysis, and maintains mitochondrial activity [3]. Lithium chloride drugs and malotilates have anti-inflammatory and anabolic action through the GSK3 and IGF-1 pathways [4]. Cytokine-mediated muscle catabolism is inhibited by selective inhibitors of the inflammatory signalling by Janus kinase inhibitors such as tocilizumab and ruxolitinib [5].

6.1.3. Traditional Medicines. Bioactive compounds from traditional medicinal systems (e.g., *Morus alba*, *Salvia miltiorrhiza*, ginsenosides) possess antioxidant and anti-inflammatory properties that may ameliorate hypoxia- and ROS-induced muscle injury [6]. While promising, these agents require rigorous clinical validation. A summary of drug-based therapy is presented in Table 1.

Table 1. Drug-based Therapy to Reduce Oxidative Stress, Inflammation and Muscle Injury

Category	Therapies	Key Mechanisms	Main Effects
Drug-Based	Antioxidants (Vit E, NAC, CoQ10, Resveratrol, Melatonin, PQQ)	Scavenge ROS; protect mitochondria; block NF-κB/MAPK	↓Oxidative stress; ↓Inflammation
	Metabolic Agents (Metformin)	Activate AMPK; support mitochondrial function	Improved redox balance; metabolic stability
	Anti-inflammatory/Anabolic Agents (Lithium chloride, Malotilate)	Modulate GSK3 & IGF-1 pathways	↓Inflammation; ↑Muscle repair
	Cytokine Inhibitors (Tocilizumab, Ruxolitinib)	Block JAK-mediated cytokine signalling	↓Cytokine-driven catabolism
	Traditional Medicines (Morus alba, Salvia miltiorrhiza, Ginsenosides)	Antioxidant & anti-inflammatory phytochemicals	Reduced ROS-induced injury (preclinical)

6.2. Enzymatic Modulators

Enzymatic therapies target proteases, inflammatory enzymes, and immune mediators implicated in muscle injury.

6.2.1. Cyclooxygenase-2 (COX-2) Inhibitors. COX-2 inhibitors such as celecoxib and meloxicam reduce inflammation, prevent excessive proteolysis, and attenuate denervation-induced muscle atrophy [7]. By limiting prostaglandin synthesis, these drugs decrease oxidative injury and stabilise fibre structure.

6.2.2. Histone Deacetylase (HDAC) Inhibitors. Compounds such as trichostatin A and suberoylanilide hydroxamic acid (SAHA) enhance muscle regeneration by promoting chromatin relaxation, increasing transcription of growth-related genes, and improving microvascular perfusion [8]. In neuromuscular disease models, HDAC inhibition increases SMN protein levels and reduces muscle damage.

6.2.3. Phosphodiesterase (PDE) Inhibitors. Agents such as pentoxifylline, rolipram, and roflumilast inhibit PDE-mediated degradation of cyclic nucleotides, thereby enhancing protein synthesis, reducing inflammatory signalling, and preventing muscle proteolysis [9]. These compounds activate pathways such as cAMP/EPAC/Akt, which promote muscle integrity in metabolic disorders.

6.3. Gene-Based Therapeutic Approaches

Gene modulation offers targeted intervention for muscle-mass regulation, mitochondrial stability, and protein homeostasis.

6.3.1. Therapeutic Gene Editing. Gene-editing tools (e.g., antisense oligonucleotides, CRISPR-derived techniques) have been applied to genetic myopathies such as Duchenne muscular dystrophy (DMD). Agents such as ataluren, eteplirsen, golodirsen, and viltolarsen facilitate exon skipping and partially restore dystrophin production [10].

6.3.2. Modulation of Muscle-Regulating Genes. Downregulation of catabolic genes (e.g., STAT3, MSTN/myostatin) and overexpression of protective genes such as PGC-1α, TFAM, and SIRT1 have been shown to enhance muscle regeneration, improve mitochondrial function, and reduce oxidative injury [11].

6.3.3. Non-coding RNAs. MicroRNAs (miR-497-5p, miR-223-3p) and

long noncoding RNAs regulate pathways involved in muscle differentiation, metabolism, and fibrosis. Manipulation of miR-29, miR-26a, or circRNAs can modulate PI3K/Akt signalling and improve outcomes in chronic muscle injury [12]

6.4. Stem Cell and Exosome-Based Therapies

Regenerative therapies aim to restore muscle structure and function through direct cell replacement or paracrine support.

6.4.1. Muscle-Derived Stem Cells (MDSCs). Satellite cells, $CD133^{+}$ progenitors, and pericytes contribute to muscle repair by differentiating into myotubes and secreting trophic factors [13]. MDSCs have shown potential in conditions such as sarcopenia, muscular dystrophy, and diabetic myopathy.

6.4.2. Mesenchymal Stem Cells (MSCs). Adipose-, bone marrow-, and umbilical cord–derived MSCs reduce fibrosis, inhibit inflammation, and promote angiogenesis [14]. Their paracrine actions enhance mitochondrial stability and reduce ROS production.

6.4.3. Exosomes. Exosomes deliver microRNAs, proteins, and antioxidants that modulate inflammation and promote regeneration. Exosomes enriched in miR-26a, miR-29, or FOXO3a regulators improve muscle fibre size and limit atrophy in ischemic and degenerative [15].

6.5. Cytokine-Based Therapies

Cytokines regulate myogenesis, angiogenesis, and protein synthesis.

6.5.1. Growth Factors. VEGF, fibroblast growth factor (FGF), hepatocyte growth factor (HGF), and bone morphogenetic protein-7 (BMP-7) enhance cell proliferation, capillary formation, and tissue repair [16]. IGF-1 increases satellite cell activation and protein synthesis, reducing muscle degradation.

6.5.2. Chemokines and Myokines. SDF-1 promotes the recruitment of myogenic and vascular progenitor cells, while irisin and PEDF enhance mitochondrial biogenesis and reduce fibrosis. These molecules hold promise for treating muscle wasting associated with chronic disease [17].

6.6. Physical and Device-Based Therapies

6.6.1. Neuromuscular Electrical Stimulation (NMES). NMES

improves muscle strength, reduces atrophy, and enhances functional recovery in immobilised or denervated muscles [18]. It is particularly useful in spinal cord injury and chronic kidney disease patients.

6.6.2. Electroacupuncture and Low-Level Laser Therapy. Electroacupuncture reduces fibrosis and inflammation by modulating TGF-β signalling, while low-level laser therapy improves mitochondrial function and decreases ROS production [19, 20].

6.6.3. Optogenetic Stimulation. Emerging optogenetic methods use light-activated ion channels (e.g., channelrhodopsin-2) to control muscle contraction more precisely than electrical stimulation, minimising collateral nerve activation [21].

6.7. Nutritional and Social Therapy

Research indicates that even modest physical activity during periods of limited mobility can slow down muscle mass loss and preserve fibre structure, aiding the muscle in maintaining strength despite decreased use. Focus group research with district authorities from the environment, public safety, and education sectors demonstrates that tailoring communication about health inequities to different audiences helps decision-makers better recognise local disparities and plan more coordinated, equity-focused interventions [28-30].

7. CONCLUSION

Hypoxia, oxidative stress, and necrosis are closely related processes that interact with each other and contribute to skeletal muscle damage, especially when it comes to the context of ischemia-reperfusion. Hypoxia interferes with mitochondrial metabolism and stabilises HIF-dependent transcriptional pathways, which change angiogenesis, glycolysis, and cellular survival. In reperfusion, mitochondrial and enzymatic sources of excessive ROS accumulation start the oxidative damage, activation of inflammatory processes, and permeabilisation of the mitochondrion, leading to apoptotic or necrotic cell death. Hypoxia preconditions the muscle to ROS sensitivity, and the presence of inflammatory cytokines like TNF-α enhances necrotic outcomes, which emphasises that these pathways are connected.

Existing treatment methods, such as antioxidants, COX-2 inhibitors, HDAC inhibitors, PDE inhibitors, gene-targeted therapies, cytokine

modulation, exosomes derived from stem cells, and physical modalities, are all proving to be potential areas for reducing oxidative damage and enhancing regeneration. But most of them are experimental, and to translate the research to clinical use greater mechanistic understanding is needed.

7.1. Recommendations

Future studies should focus on clarifying the temporal relationship between hypoxia-driven metabolic changes and ROS-mediated injury. Identifying molecular checkpoints that determine whether a myocyte undergoes apoptosis, necroptosis, or necrosis, developing targeted therapies that modulate redox signalling without impairing physiological ROS functions and enhancing regenerative biology**,** particularly through exosomes, non-coding RNAs, and stem cell–based interventions. An integrated mechanistic understanding that incorporates hypoxia, oxidative stress and necrotic pathways will be important in devising effective strategies to maintain skeletal muscle function and enhance outcomes in ischemic, traumatic and degenerative pathways.

Author Contribution

Farwa Munir: conceptualization, writing-original draft, writing- review & editing. **Farooq Manzoor:** supervision, validation. **Shahzaib Naeem:** conceptualization, writing-original draft. **Emad Abdulrahman H. Alsaedi:** data curation, methodology. **Maryum Hamayoun:** data curation, writing-original draft. **Sher Wali Khan:** data curation, writing-original draft. **Atif Amin Baig:** supervision, validation

Conflict of Interest

The authors of the manuscript have no financial or non-financial conflict of interest in the subject matter or materials discussed in this manuscript.

Data Availability Statement

All data used in the development of this review article are derived from previously published studies available in public scientific databases, including PubMed, Scopus, and Web of Science. No new datasets were generated or analysed. Additional information can be obtained from the corresponding author upon reasonable request.

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REFERENCES

1. Powers SK, Morton AB, Ahn B, Smuder AJ. Redox control of skeletal muscle atrophy. *Free Rad Biol Med*. 2016;98:208-217.

https://doi.org/10.1016/j.freeradbiomed.2016.02.021

2. Granger DN, Kvietys PR. Reperfusion injury and reactive oxygen species: the evolution of a concept. *Redox Biol*. 2015;6:524-551. https://doi.org/10.1016/j.redox.2015.08.020
3. Kalogeris T, Baines CP, Krenz M, Korthuis RJ. Cell biology of ischemia–reperfusion injury. *Int Rev Cell Mol Biol*. 2012;298:229-317. https://doi.org/10.1016/B978-0-12-394309-5.00006-7
4. Blaisdell FW. The pathophysiology of skeletal muscle ischemia and the reperfusion syndrome: a review. *Cardiovasc Surg*. 2002;10(6):620-630. https://doi.org/10.1016/S0967-2109(02)00070-4
5. Zuo L, Zhou T, Pannell BK, Ziegler AC, Best TM. Biological and physiological role of reactive oxygen species—the good, the bad, and the ugly. *Acta Physiol*. 2015;214(3):329-348. https://doi.org/10.1111/apha.12515
6. Eltzschig HK, Carmeliet P. Hypoxia and inflammation. *N Engl J Med*. 2011;364(7):656-665. https://doi.org/10.1056/NEJMra0910283
7. Mason SD, Howlett RA, Kim MJ, et al. Loss of skeletal muscle HIF-1α results in altered exercise endurance. *PLoS Biol*. 2004;2(10):e288. https://doi.org/10.1371/journal.pbio.0020288
8. Jackson MJ. Reactive oxygen species and redox-regulation of skeletal muscle adaptations to exercise. *Philos Trans R Soc Lond B Biol Sci*. 2005;360(1464):2285-2291. https://doi.org/10.1098/rstb 2005.1767
9. Golstein P, Kroemer G. Cell death by necrosis: towards a molecular definition. *Trends Biochem Sci*. 2007;32(1):37-43. https://doi.org/10.1016/j.tibs.2006.11.001
10. Du J, Wang X, Miereles C, et al. Activation of caspase-3 is an initial step triggering muscle proteolysis in catabolic conditions. *J Clin Invest*. 2004;113(1):115-123. https://doi.org/10.1172/JCI18330
11. Piccirillo R. Exercise-induced skeletal muscle adaptations: Redox signalling and the role of PGC-1α. *Front Cell Dev Biol*. 2020;8:e665. https://doi.org/10.3389/fcell.2020.00665
12. Hoek TLV, Li C, Shao Z, Schumacker PT, Becker LB. Significant levels of oxidants are generated by isolated cardiomyocytes during

ischemia before reperfusion. *J Mol Cell Cardiol*. 1997;29(9):2571-2583. https://doi.org/10.1006/jmcc.1997.0464

13. Tidball JG. Regulation of muscle growth and regeneration by the immune system. *Nat Rev Immunol*. 2017;17(3):165-178. https://doi.org/10.1038/nri.2016.150
14. Pisconti A, Dekempeneer L, Le Grand F. The emerging role of TNF-α in skeletal muscle development and regeneration. *Skeletal Muscle*. 2019;9(1):e1.
15. Chatzigeorgiou A, Halapas A, Kalafatakis K, Kamper EF. The role of cytokines in muscle damage and repair. *Front Biosci*. 2008;13:5144-5156. https://doi.org/10.2741/3083
16. Arif I, Ullah F. Impact of traffic stress, built environment, and socioecological factors on active transport among young adults. *Sustainability*. 2025;17(20):e9159. https://doi.org/10.3390/su17209159
17. Arif I, Jaweria A, Munir F. Health impacts of road traffic near school: narrative review. *Pak Armed Forc Med J*. 2025;75(1):209-216. https://doi.org/10.51253/pafmj.v75i
18. Song Y, Zhao X, Zhang J, et al. The role of VEGF in skeletal muscle regeneration. *Front Physiol*. 2021;12:e680220. https://doi.org/10.3389/fphys.2021.680220
19. Boppart MD, De Lisio M. Exercise and stem cells. *Prog Mol Biol Transl Sci*. 2015;135:423-456. https://doi.org/10.1016/bs.pmbts.2015.07.016
20. Arif I. Telehealth intervention of cardiovascular diseases patients: a quantitative study. *Glob Drug Des Develop Rev*. 2022;7(4):1-13. https://doi.org/10.31703/gdddr.2022(VII-IV).01
21. Bijlsma AY, Meskers CG, Westendorp RG, Maier AB. Chronology of muscle mass loss: Age-related muscle loss in humans. *Age (Dordr)*. 2013;35(1):249-258. https://doi.org/10.1007/s11357-011-9342-9
22. Khan Y, Yablon LM, Rios CN, et al. Low-level laser therapy improves muscle regeneration in an ischemia-reperfusion model. *Lasers Med Sci*. 2020;35(3):727-736. https://doi.org/10.1007/s10103-019-02863-2
23. Llewellyn ME, Thompson KR, Deisseroth K, Delp SL. Orderly

recruitment of motor units under optical control in vivo. *Nat Med*. 2010;16(10):1161-1165. https://doi.org/10.1038/nm.2228

24. Hurley BF, Hanson ED, Sheaff AK. Strength training as a countermeasure to ageing muscle: efects on muscle mass, strength, and function. *Sports Med*. 2011;41(4):289-306. https://doi.org/10.2165/11585920-000000000-00000
25. Yu T, Robergs RA, Yang Y. Exercise-induced mitochondrial stress: a brief review. *Sports Med Health Sci*. 2022;4(2):68-74. https://doi.org/10.1016/j.smhs.2022.03.001
26. O'Leary MF, Hood DA. Denervation-induced oxidative stress and autophagy in skeletal muscle. *Autophagy*. 2009;5(2):230-231. https://doi.org/10.4161/auto.5.2.7424
27. Liu L, Cheung WF, Li B, Chen S. Stem cell-based therapies for muscle regeneration: Current challenges and future directions. *Stem Cells Int*. 2022;2022:1-18. https://doi.org/10.1155/2022/7440039
28. Liu X, Wang D, Zhang X, Li Y, Li L. Role of microRNAs in skeletal muscle atrophy. *Front Physiol*. 2021;12:e685087. https://doi.org/10.3389/fphys.2021.685087
29. Arif I. Determinants of happiness among university students: a cross-sectional study in Pakistan. *Glob Soc Sci Rev*. 2024 ;9(1):248-256. http://dx.doi.org/10.31703/gssr.2024(IX-I).22
30. Arif I. Fundamental stratification of communication to overcome health inequities. *Glob Immunol Infect Dis Rev*. 2024;9(2):1-7. http://dx.doi.org/10.31703/giidr.2024(IX-II).01