MOTS-c

PATIENT EDUCATION GUIDE — MITOCHONDRIAL METABOLIC PEPTIDE THERAPY

Harriman Precision Health
Physician-Supervised Telemedicine Wellness
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What Is MOTS-c?

MOTS-c (Mitochondrial Open Reading Frame of the 12S rRNA-c) is one of the most scientifically unique peptides in regenerative medicine — because unlike virtually every other therapeutic peptide, it is encoded directly within the mitochondrial genome rather than the nuclear genome.[1] This makes MOTS-c a mitochondria-derived peptide (MDP), a small signaling molecule produced by the cell's own energy-generating organelles in response to stress, metabolic challenge, and — critically — exercise.[2]

When cellular stress occurs (during intense exercise, metabolic demand, or age-related decline), mitochondria release MOTS-c. It travels from the mitochondria into the cytoplasm and then into the cell nucleus, where it regulates the expression of genes governing energy metabolism, insulin sensitivity, cellular stress adaptation, and inflammation.[3] MOTS-c levels naturally decline with age — a decline that correlates directly with the reduced metabolic efficiency, increasing insulin resistance, and diminishing physical capacity that characterize aging.[4] Research published in *Nature Communications* demonstrated that intermittent MOTS-c treatment in late-life mice increased physical capacity and healthspan, while in humans, exercise was shown to induce MOTS-c expression in skeletal muscle by nearly 12-fold.[5]

How It Works

MOTS-c's primary mechanism involves activation of AMPK (AMP-activated protein kinase) — the master regulator of cellular energy balance in the body.[6] When AMPK is activated, it promotes glucose uptake into cells without requiring insulin, stimulates fatty acid oxidation (fat burning), drives mitochondrial biogenesis (creation of new mitochondria), and

inhibits energy-consuming processes that are not immediately necessary. This mechanism explains why MOTS-c is frequently described as an "exercise mimetic" — it activates many of the same molecular signaling pathways that vigorous physical activity engages, making it particularly valuable for patients whose exercise capacity is limited by injury, age, or metabolic disease.[7] MOTS-c also translocates to the cell nucleus under stress conditions, where it directly regulates gene expression through antioxidant response elements — providing a second layer of metabolic and stress-adaptation benefit beyond AMPK activation.[3]

What MOTS-c Is Used For

Metabolic health and insulin sensitivity: MOTS-c has demonstrated significant improvements in insulin sensitivity and glucose metabolism in preclinical studies, including reversal of age-related skeletal muscle insulin resistance.[1] It is increasingly used in metabolic health and diabetes risk reduction protocols. **Weight management and fat loss:** Through AMPK activation and enhanced fatty acid oxidation, MOTS-c improves metabolic flexibility — the body's ability to efficiently shift between burning carbohydrates and fat for fuel. Patients with metabolic resistance to fat loss, including those on GLP-1 programs, may benefit from MOTS-c as a complementary metabolic activator. **Exercise performance and recovery:** Animal studies have demonstrated substantial improvements in endurance and treadmill performance across all age groups treated with MOTS-c, with the mechanism involving improved glucose utilization and metabolic efficiency in muscle tissue.[7] **Longevity and healthspan:** MOTS-c is gaining significant attention in longevity medicine as a peptide that addresses aging at the mitochondrial level — the origin point of cellular energy decline.[4] **Cardiovascular health:** MOTS-c plays a role in vascular endothelial function and has been studied for its potential protective effects on cardiac metabolic health.[8]

What to Expect: Timeline of Results

Metabolic improvements — improved energy, reduced fatigue with exertion, and better post-meal glucose stability — are often among the first changes patients notice, typically within two to four weeks of consistent use. Exercise recovery and endurance improvements develop progressively through weeks four to eight. Meaningful improvements in body

composition and insulin sensitivity, particularly in patients with metabolic resistance, typically develop over eight to twelve weeks of consistent use combined with appropriate exercise and nutrition. MOTS-c's effects are most pronounced when paired with physical activity — the two appear to amplify each other through the shared AMPK-PGC-1α pathway.[6]

Standard Protocol

Parameter	Details
Dose	5–10 mg per injection (individualized; lower doses used initially)
Frequency	3x weekly (research-supported protocol for metabolic and longevity goals)
Route	Subcutaneous injection; rotate sites
Cycle Length	8–12 weeks; 4-week rest period before repeating
Timing	Pre-exercise timing may amplify metabolic and performance benefits
Medication Source	Compounded by Empower Pharmacy (Houston, TX)

Safety Profile

MOTS-c is a naturally occurring peptide produced by the body's own mitochondria, giving it an inherent physiological familiarity that contributes to its favorable safety profile. Side effects are minimal in available research — injection site reactions are the most commonly reported finding, and are typically brief and mild.[4] MOTS-c does not affect the HPG axis, is not a hormone, and does not require post-cycle therapy. As with all compounded peptides, it is used off-label and large-scale human clinical trials are ongoing. Patients with active malignancy should discuss use with their physician given MOTS-c's cell growth and metabolic signaling properties.

> ### How to Maximize Your Results
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> - **Exercise — Especially Around Injection Timing**[5] — MOTS-c and exercise activate the same AMPK-PGC-1α pathway — they are

synergistic. Injecting before or after a training session appears to amplify both the peptide's and the exercise's metabolic effects. MOTS-c is one of the few peptides where training frequency and intensity directly enhance the therapeutic outcome.

- **Low-Glycemic, High-Fiber Diet**[8] — MOTS-c improves insulin sensitivity and glucose metabolism — dietary choices that maintain stable blood glucose amplify these effects. Reduce refined carbohydrates and sugar; emphasize fiber, lean protein, and healthy fats for the best metabolic synergy.
- **Stack with NAD+**[9] — MOTS-c activates AMPK; NAD+ powers the sirtuins. Both target complementary mitochondrial pathways. The combination addresses metabolic aging from two distinct but reinforcing angles and is increasingly used in comprehensive longevity protocols.
- **Consistent Sleep Schedule**[10] — Circadian disruption impairs mitochondrial function and AMPK signaling. A consistent sleep schedule — same bedtime and wake time — supports the circadian metabolic rhythms MOTS-c works within.
- **Adequate Protein and Leucine**[11] — MOTS-c supports muscle metabolic efficiency. Adequate protein (0.7–1.0 g/lb) ensures the muscle tissue benefiting from improved insulin sensitivity has the substrate for maintenance and growth.

Is MOTS-c an "exercise pill"?

It activates several key pathways that exercise engages — but it does not replicate all the benefits of exercise. Think of MOTS-c as amplifying and complementing the metabolic adaptations of physical activity, not replacing them. Patients who exercise during their MOTS-c cycle consistently see better outcomes than those who don't.[7]

Can MOTS-c help with GLP-1 weight loss?

Yes — MOTS-c's metabolic activation through AMPK is complementary to GLP-1's appetite and glucose mechanisms. For patients on semaglutide who have plateaued or want to improve metabolic flexibility during weight loss, MOTS-c is a clinically rational addition. Discuss with your physician.

Harriman Precision Health are physician-supervised and individualized. MOTS-c is an off-label compounded therapy; the majority of research is preclinical. Questions? Contact us through your patient portal.

References

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Research cited includes peer-reviewed published studies and preclinical models. MOTS-c is an emerging area of clinical research; large-scale human trials are ongoing. All therapies at Harriman Precision Health are physician-supervised and individualized. This document does not constitute a guarantee of clinical outcomes.