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MOTS-C

Scientific Evidence

Human relevance, potential benefits and translational research

An expanded, reader-friendly review of what researchers know today - with the focus kept on possible human relevance.



RESEARCH FOCUS

- Exercise response
- Muscle function
- Metabolic health
- Vascular biology
- Healthy aging

Evidence reviewed through September 2026

FOR RESEARCH PURPOSES ONLY

OVERVIEW

MOTS-C in one minute

MOTS-c is a 16-amino-acid peptide encoded inside mitochondrial DNA. Mitochondria are best known for producing cellular energy, but they also send signals that help cells adapt to stress. MOTS-c appears to be one of those signals, linking mitochondrial activity with whole-body metabolism, muscle biology and stress-response pathways. [1,2]

The simplest way to think about MOTS-c: it is a naturally occurring human mitochondrial signal that becomes especially interesting when the body is under metabolic or physical stress.

WHY HUMAN RESEARCHERS CARE

MOTS-c is measurable in human blood and skeletal muscle. Its levels change with exercise, age and metabolic state, which means the biology is directly relevant to people - even though direct therapeutic use of native MOTS-c has not yet been established in published human efficacy trials.

WHERE THE BENEFIT INTEREST COMES FROM

The main areas of interest are exercise adaptation, muscle quality, glucose and insulin signaling, vascular function, and age-related metabolic resilience. Each area has a different level of human evidence.

16

amino acids in the peptide

11.9x

muscle increase after acute exercise in one human study

40

patients in an endothelial-function study

What this report does

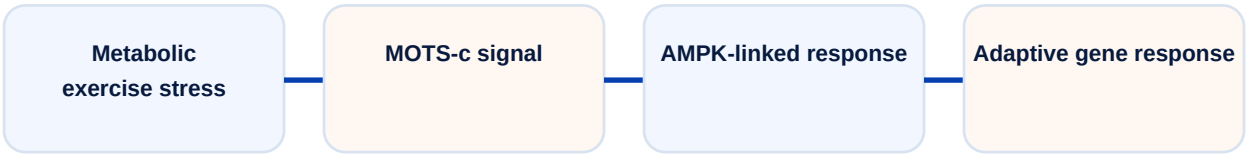
Rather than treating every laboratory result as a proven human benefit, this review separates three things: **what has been directly measured in people**, **what has been seen in animals or cells**, and **what could become a future human application if clinical trials confirm it**. That distinction makes the research easier to understand and more useful.

SIMPLE BIOLOGY

How MOTS-C may work - without the jargon

MOTS-c is part of a newer class of molecules called **mitochondrial-derived peptides**. Instead of acting only inside mitochondria, these peptides can behave like signals. MOTS-c has been shown in experimental models to interact with pathways involved in energy sensing, including AMPK, and under metabolic stress it can move into the cell nucleus and influence stress-responsive gene expression. [1,2]

A simple way to think about the pathway



This is a simplified research model; MOTS-c biology also involves nuclear translocation and broader stress-response pathways.

Why AMPK keeps appearing in the research

AMPK is often described as a cellular fuel gauge. When available energy is low - for example during exercise or other metabolic stress - AMPK helps cells shift toward energy-producing and energy-conserving processes. MOTS-c research overlaps with this pathway, which helps explain why the peptide is studied in relation to glucose handling, exercise adaptation and metabolic resilience. [1,2]

IN PLAIN ENGLISH

Researchers are interested in whether MOTS-c helps the body recognize an energy challenge and adjust how cells use fuel. That is a biological concept - not proof that taking MOTS-c recreates exercise or treats metabolic disease.

WHY THIS MATTERS FOR PEOPLE

If future trials show that the same pathways can be safely influenced in humans, the potential applications could include metabolic health, muscle function and age-related loss of physical capacity.

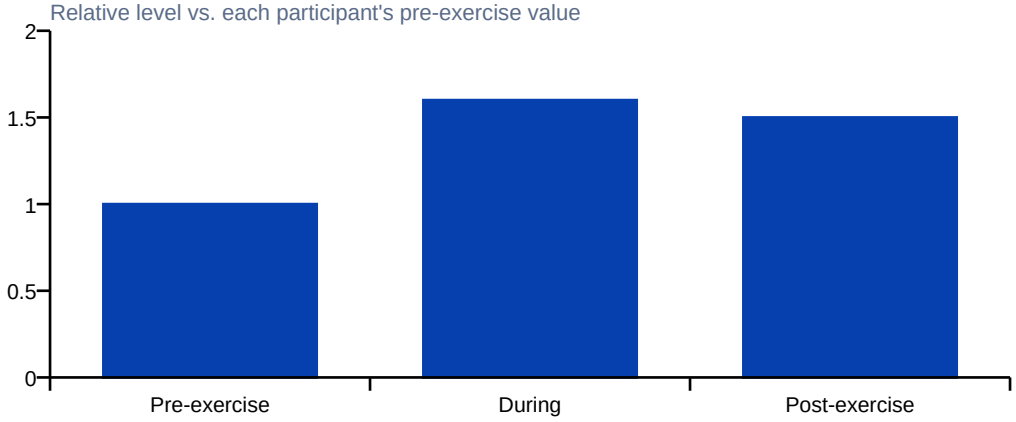
HUMAN PHYSIOLOGY

Exercise: the strongest direct human signal

One of the clearest findings in the field is that the human body changes its own MOTS-c levels during exercise. In a 2021 study, ten sedentary healthy young men completed high-intensity cycling. Skeletal-muscle MOTS-c increased approximately **11.9-fold after exercise**. Circulating levels rose about **1.6-fold during exercise** and **1.5-fold immediately after**, then moved back toward baseline during recovery. [3]

Circulating endogenous MOTS-c during acute cycling

Relative level vs. each participant's pre-exercise value



Source: Reynolds et al., Nature Communications (2021), n=10 healthy young men.

Why this is important: MOTS-c is not only a molecule that produces interesting effects in mice. The peptide is part of the normal human physiological response to a real-world stressor - exercise.

A second human exercise study adds nuance

A separate study compared endurance exercise, resistance exercise and a control condition. Circulating MOTS-c showed a similar upward pattern after endurance exercise, although the MOTS-c change itself did not reach statistical significance in that experiment. The result suggests that exercise intensity, exercise type and measurement method may influence what researchers observe. [4]

Potential human benefit area

The practical research question is whether the same signaling system that naturally responds to strenuous exercise could eventually be used to support **exercise adaptation, metabolic flexibility or physical resilience**. That possibility is scientifically plausible, but administered native MOTS-c has not yet been shown in published human trials to improve endurance, strength or recovery.

HUMAN MUSCLE BIOLOGY

Muscle strength, quality and physical function

Muscle is one of the most interesting tissues in MOTS-c research because it is both a major consumer of glucose and one of the tissues most affected by aging. Human studies suggest that endogenous MOTS-c may track with aspects of muscle quality and force production. [5,6]

HEALTHY AGING MEN

In a study comparing young, middle-aged and older men, circulating MOTS-c decreased with age, yet skeletal-muscle MOTS-c was about 1.5 times higher in the middle-aged and older groups. In older men, higher muscle MOTS-c was associated with better muscle quality - more leg-press strength relative to thigh size. [5]

PHYSICALLY ACTIVE ADULTS

A 2023 preliminary study of 20 healthy active adults found resting serum MOTS-c was positively correlated with jump power, force, total muscle mass and leg muscle mass. It was not related to maximal oxygen uptake. [6]

What does that mean in practical terms?

These findings do **not** prove that higher MOTS-c causes stronger muscles. They do show that MOTS-c is linked to measurable human muscle characteristics. That is why researchers are exploring whether the peptide is part of the signaling network that helps muscle adapt to workload, maintain metabolic efficiency and preserve function with age.

Potential human benefit area: preserving muscle quality and supporting physical-function biology. Current evidence is encouraging at the association level, but direct improvement from administered MOTS-c remains unproven.

A useful distinction

Strength, **muscle mass**, **muscle quality** and **endurance** are not the same outcome. Current MOTS-c data are more suggestive for muscle quality and force-related measures than for aerobic capacity. [5,6]

HUMAN METABOLIC RELEVANCE

Metabolic health: glucose, insulin and fuel use

MOTS-c was originally discovered through work on metabolic homeostasis. In preclinical studies, administered MOTS-c improved insulin sensitivity and protected mice from diet- and age-related metabolic dysfunction. [1] Human researchers then began asking a different question: **do naturally occurring MOTS-c levels change with insulin resistance and obesity?**

The answer so far is yes - but not in a simple direction.

Human study	What was measured	Reader-friendly interpretation
Cataldo et al. 2018	Lean vs. adults with obesity; insulin-sensitivity markers	Average MOTS-c was similar between groups, but its relationship with insulin sensitivity changed with metabolic status. [7]
Yoon et al. 2025	22 lean and 32 adults with obesity	MOTS-c was higher in obesity and was independently associated with BMI and HOMA-IR, suggesting a possible compensatory stress response. [8]
Other metabolic cohorts	Diabetes, obesity and related conditions	Results vary by population, age, disease state and assay; MOTS-c is not a simple "higher is better" biomarker. [9]

Potential human benefit area: improving metabolic flexibility - the ability to shift between fuels and respond appropriately to changing energy demand. This remains a research hypothesis for administered native MOTS-c, not an established clinical effect.

Why inconsistent blood levels are not necessarily bad science

A signaling molecule can rise because the body is doing well, because it is compensating for stress, or because production and clearance have changed. This is common in metabolic biology. For MOTS-c, the most reasonable interpretation today is that circulating levels reflect **context-dependent metabolic signaling**, not a single ideal number.

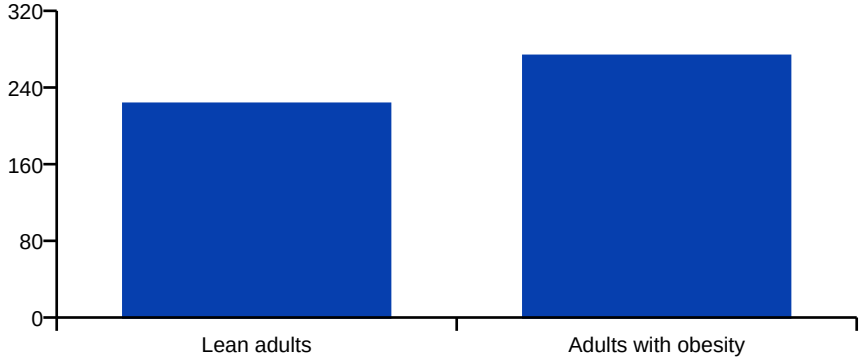
METABOLISM IN CONTEXT

Body weight and obesity: promising biology, complex human signals

Animal studies made MOTS-c famous in part because treated mice showed improved metabolic health and resistance to diet-induced obesity. [1] Human data are more complicated because most studies measure the MOTS-c people naturally produce rather than administer the peptide as a therapy.

One 2025 adult cohort found higher circulating MOTS-c with obesity

Mean plasma concentration (pg/mL); results differ across cohorts and assays.



Source: Yoon et al., Journal of Clinical & Translational Endocrinology (2025).

In the 2025 Mayo Clinic-linked cohort shown above, adults with obesity had higher circulating MOTS-c than lean adults. BMI and insulin resistance independently predicted higher levels, and the researchers suggested that the rise may represent a compensatory response to metabolic stress. In a small follow-up group, major weight loss after bariatric surgery did not significantly change circulating MOTS-c over six months. [8]

WHAT LOOKS INTERESTING

MOTS-c consistently intersects with glucose handling, skeletal-muscle metabolism and energy-sensing pathways. That keeps weight-related and metabolic applications scientifically interesting.

WHAT IS NOT YET PROVEN

There is no published human efficacy trial showing that native MOTS-c administration produces clinically meaningful weight loss. Animal effects should not be presented as established human results.

How to read the weight-loss discussion

The strongest current case for MOTS-c is not that it is a proven weight-loss drug. It is that the peptide sits inside biological pathways that influence how muscle and other tissues respond to energy demand. If future human intervention studies are positive, the more meaningful benefit may be **metabolic function** rather than weight alone.

ENDOTHELIAL BIOLOGY

Vascular health: a human signal worth watching

Healthy blood vessels depend on the endothelium - the thin cellular lining that controls vessel tone, blood flow and many aspects of vascular signaling. A 2018 Mayo Clinic-led study measured circulating MOTS-c in 40 patients undergoing coronary angiography and direct endothelial-function testing. Twenty had normal endothelial function and twenty had endothelial dysfunction. [10]

Patients with coronary endothelial dysfunction had lower circulating MOTS-c, and MOTS-c levels were positively associated with both microvascular and epicardial coronary endothelial function. [10]

Why this finding is meaningful

Unlike a general survey or questionnaire, this study used a clinically relevant physiological test of coronary blood-vessel function. The sample was small, so it cannot establish cause and effect, but it connects MOTS-c with a human vascular phenotype that matters.

POSSIBLE FUTURE APPLICATION

Supporting endothelial resilience or vascular metabolic signaling is a plausible area for future human trials, particularly because mitochondrial stress and endothelial dysfunction often occur together.

EVIDENCE LIMIT

Lower MOTS-c may be a marker of vascular dysfunction rather than its cause. A trial that administers a MOTS-c-based therapy and directly measures vascular outcomes would be needed to show benefit.

How this connects to metabolism

Blood-vessel health, insulin sensitivity and mitochondrial function are biologically connected. Endothelial cells constantly respond to energy demand and oxidative stress. MOTS-c is interesting because the same peptide appears in research on both metabolic homeostasis and vascular function, creating a logical bridge between the two fields. [2,10]

AGING BIOLOGY

Healthy aging: resilience rather than a simple "anti-aging" claim

Aging research is one of the reasons MOTS-c receives so much attention. Mitochondrial function, muscle quality, glucose regulation and stress adaptation all change with age. MOTS-c touches each of these systems experimentally, which makes it a useful molecule for studying **metabolic resilience** - the ability to respond to physiological stress and return toward balance. [2,3,5,11]

What has actually been shown in humans?

Human studies show that MOTS-c biology changes with age. Circulating MOTS-c has been reported to decline across age groups in healthy men, while skeletal-muscle expression can increase and relate to muscle quality. [5] Exercise also stimulates endogenous MOTS-c in human muscle and blood. [3] Together, these results support a role in age-sensitive physiology, even though they do not prove an anti-aging treatment effect.

What animal studies add

In mice, MOTS-c administration has improved physical performance across age groups and late-life treatment has increased physical capacity and healthspan-related measures. [3] These experiments provide a reason to study human translation, but mouse outcomes should be viewed as **proof of biological possibility**, not proof of a human therapeutic benefit.

> **Potential human benefit area: maintaining metabolic and physical resilience as people age. This is one of the most compelling research themes, but it is still an emerging field rather than a proven human anti-aging therapy.**

A better way to describe the concept

Instead of saying MOTS-c "reverses aging," the evidence supports a more precise idea: **MOTS-c is involved in pathways that influence how muscle and metabolism respond to stress, and those pathways are highly relevant to healthy aging.**

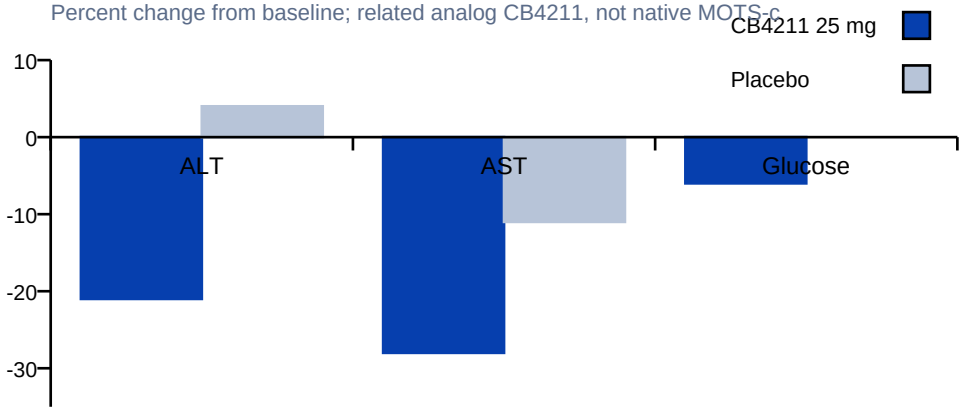
HUMAN INTERVENTION

Clinical translation: what the CB4211 analog tells us

CB4211 is a modified analog derived from mitochondrial peptide biology; it is not native MOTS-c. A randomized Phase 1a/1b development program enrolled 88 participants overall. In the small Phase 1b exploratory group involving adults with fatty liver disease and obesity, sponsor-reported results compared CB4211 25 mg (n=11) with placebo (n=9) for four weeks. [12,13]

Sponsor-reported Phase 1b changes after 4 weeks

Percent change from baseline; related analog CB4211, not native MOTS-c



Exploratory subgroup: CB4211 n=11; placebo n=9. Source: CohBar SEC filing (2021).

The sponsor reported statistically significant placebo-adjusted reductions in ALT, AST and fasting glucose at four weeks, along with a trend toward lower body weight. Liver-fat content decreased substantially in both groups, so that imaging outcome did not demonstrate a clear treatment advantage. [13]

Why include an analog in a MOTS-c report? Because it shows that this biological family has reached controlled human intervention research. But the results cannot simply be transferred to native MOTS-c.

What this adds to the human story

Most native MOTS-c human research is observational or physiological - researchers measure what the body already produces. CB4211 provides a small translational bridge showing that a drug candidate inspired by mitochondrial-derived peptide biology can be administered to humans and produce measurable metabolic biomarker changes. Larger efficacy studies would be needed to determine clinical value.

EVIDENCE MAP

Potential human benefit areas - what human evidence exists

The table below separates the **type of human evidence** available in each research area from the stronger question of whether MOTS-c has been proven as a treatment.

Research area	Type of human evidence	What can reasonably be said today
Exercise response	Direct physiology studies	Endogenous MOTS-c responds to acute exercise in human muscle and circulation. [3,4]
Muscle function	Small human cohorts	Associations with muscle quality, force and power are encouraging but not yet intervention evidence. [5,6]
Metabolic health	Multiple observational cohorts	MOTS-c repeatedly tracks with insulin resistance and obesity, although the direction differs by population. [7-9]
Vascular function	Clinical association study	Lower circulating MOTS-c was associated with coronary endothelial dysfunction in a 40-patient study. [10]
Healthy aging	Age-related human associations	Human muscle and circulating levels change with age; therapeutic anti-aging effects are not established. [3,5,11]
Direct native MOTS-c therapy	No established efficacy trial	Published human therapeutic efficacy data remain insufficient. [14]

The most defensible human-focused summary

Exercise and muscle biology currently provide the clearest direct human relevance. **Metabolic health** has a larger research base but more variable biomarker findings. **Vascular and aging applications** are scientifically plausible and supported by human associations, yet need intervention trials. Direct therapeutic claims for native MOTS-c remain ahead of the published human evidence.

For a reader, the key distinction is simple: MOTS-c has meaningful human biology today, while most therapeutic benefit claims still belong to the next stage of research.

READER FAQ

Common questions - answered plainly

Is MOTS-c naturally found in people?

Yes. It is encoded by mitochondrial DNA and has been measured in human blood and skeletal muscle. [2,3,5]

Does exercise affect MOTS-c?

Yes. One controlled human study found marked increases in skeletal-muscle MOTS-c after acute cycling and smaller temporary increases in circulating MOTS-c. [3]

Does that mean MOTS-c is "exercise in a vial"?

No. Exercise changes many hormones, metabolites, mechanical signals and neural pathways. MOTS-c may be one part of the response, but no human trial has shown that native MOTS-c reproduces the full effects of exercise.

Could it help muscle function?

That is a credible research question. Human studies link endogenous MOTS-c with muscle quality, force and muscle mass, but those are associations rather than proof of a treatment effect. [5,6]

Could it help insulin sensitivity or metabolic health?

Preclinical evidence is strong, and human biomarker studies repeatedly connect MOTS-c with insulin-resistance biology. The direction of circulating levels varies by population, so the therapeutic meaning is still being defined. [1,7-9]

What about blood-vessel health?

A small human study found lower circulating MOTS-c in patients with coronary endothelial dysfunction. This supports further research but does not prove that giving MOTS-c improves vascular function. [10]

Is it proven for longevity or anti-aging?

No. Healthy-aging interest comes from mitochondrial signaling, muscle and metabolic data, plus animal studies. Human therapeutic longevity evidence is not established. [3,5,11,14]

BOTTOM LINE

What to remember after reading this report

MOTS-c is unusual among experimental peptides because the strongest story does not begin with an injected compound - it begins with **normal human physiology**. People naturally make MOTS-c, exercise changes it, aging changes it, and metabolic and vascular states appear to influence it. That gives the research a genuine human foundation. [3,5,7-10]

THE POSITIVE CASE

The peptide sits at the intersection of several high-value research areas: mitochondrial signaling, skeletal-muscle function, metabolic flexibility, endothelial biology and age-related resilience. Human observational and physiological studies support each of these areas to varying degrees.

THE SCIENTIFIC BOUNDARY

The gap is direct intervention. As of 2026, publicly available evidence remains insufficient to establish clinical effectiveness of administered native MOTS-c for proposed human uses. [14] That gap is exactly what future controlled trials would need to address.

Human-focused conclusion

The most compelling potential benefits to study in people are **exercise adaptation and physical function**, **muscle quality**, **metabolic and insulin-response biology**, **vascular function**, and **healthy-aging resilience**. The evidence is strongest when MOTS-c is discussed as a naturally occurring mitochondrial signal and weakest when preclinical findings are treated as though they already prove a therapeutic effect in humans.

MOTS-c is best described today as a high-interest human mitochondrial signaling peptide with meaningful physiological evidence and several plausible benefit areas that still require direct clinical confirmation.

Research-use note: This document is an educational scientific review. It does not provide dosing instructions, medical advice, or a recommendation for human administration.

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