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Review Paper

# Investigating the Relationship between Performing Exercise and MOTS-c in Type 2 Diabetes: A Review Study

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**Key words:**
Exercise training, Mitochondria, MOTS-c, Type 2 diabetes

## ABSTRACT

**Aims** Type 2 diabetes is a chronic disease that decreases the life expectancy of affected individuals due to several problems. Mitochondrial dysfunction is a prominent feature in type 2 diabetes. MOTS-C is a mitochondria-derived peptide with sports-like activity that has beneficial effects on metabolism and physical performance. The aim of this article is to review the performance of MOTS-c peptide and the mechanism of action of exercise training on the improvement of type 2 diabetes.

**Materials & Methods** This review study was conducted by searching the articles in Scapus, Google scholar, Pubmed and Farsi databases, including Magira and using the keywords MOTS-c, type 2 diabetes, exercise training in relation to the years 1991 to 2022. The search was limited to articles in English and Farsi whose full text was available. In general, of the 52 articles found, 45 articles whose full text was available were examined.

**Findings** Exercise training increases the MOTS-C levels, and MOTS-C activates AMPK in skeletal muscles and improves whole body energy metabolism.

**Conclusion** Exercise training improves insulin sensitivity, reducing the risk of concomitant diseases.

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طب داخلی روز
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## مقاله مروری

# بررسی رابطه‌ی تمرینات ورزشی با MOTS-c در دیابت نوع ۲؛ یک مطالعه‌ی مروری

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## چکیده

**هدف** دیابت نوع ۲ بیماری مزمنی است که امید به زندگی در مبتلایان به آن به‌دلیل برخی مشکلات پایین می‌آید. اختلال عملکرد میتوکندری ویژگی برجسته‌ای در دیابت نوع ۲ است. MOTS-C پپتیدی مشتق از میتوکندری با فعالیت تقلیدی ورزشی است که اثرهای مفیدی بر متابولیسم و ظرفیت ورزش دارد. هدف از این مقاله مروری بر عملکرد پپتید MOTS-c و مکانیسم عمل تمرینات ورزشی بر بهبود بیماری دیابت نوع ۲ است.

**مواد و روش ها** این مطالعه‌ی مروری با جست‌وجو در مقاله‌های موجود در پایگاه‌های اطلاعاتی Pubmed، Google و Scapus و پایگاه اطلاعاتی فارسی Magira، با کلیدواژه‌های MOTS-c، دیابت نوع ۲، تمرینات ورزشی، مربوط به سال‌های ۱۹۹۱ تا ۲۰۲۲ انجام شد. جست‌وجو به مقالات با زبان انگلیسی و فارسی که متن کامل آن ها موجود بود، محدود شد. به‌طور کلی، از بین ۵۲ مقاله‌ی به‌دست‌آمده، ۴۱ مقاله که متن کامل آن‌ها موجود بود، بررسی شد.

**یافته‌ها** تمرینات ورزشی سطح MOTS-C را افزایش می دهد و MOTS-C AMPK را در عضلات اسکلتی فعال می کند و متابولیسم انرژی کل بدن را بهبود می بخشد.

**نتیجه گیری** تمرین ورزشی حساسیت به انسولین را بهبود می بخشد و خطر ابتلا به بیماری های همزمان را کاهش می دهد.

کلیدواژه‌ها:
تمرینات ورزشی
دیابت نوع ۲
میتوکندری
MOTS-c

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## Introduction

Diabetes mellitus (DM) is a disease caused by an increase in blood glucose and is associated with disturbances in carbohydrate, lipid, and protein metabolism [1]. This disease is identified by high blood glucose in conditions of insulin resistance [2]. Type 2 diabetes mellitus (T2DM) poses a major challenge to public health worldwide that reduces both the quality of life and life expectancy of affected individuals. The number of adults afflicted with T2DM is expected to increase from 463 million in 2019 to 700 million by 2045 [3]. Type 2 diabetes and associated diseases and complications are global health problems, especially in developing countries [4]. The World Health Organization estimates that the number of adults (20 years and older) with diabetes will have reached 300 million people by 2025 [5]. Diabetes, as a health problem that threatens the quality of life of patients, can lead to severe and chronic complications and is considered one of the important causes of disability and mortality in several countries [6]. T2DM is one of the most common metabolic syndrome diseases [7]. The risk of early death, blindness, and developing heart, kidney, and nerve diseases in people with T2DM is equal to non-diabetic individuals [8].

Diabetes is considered the sixth leading cause of disability in 2015. Diabetes imposes significant social and economic burdens on the individual and incurs heavy costs to the global health economies, which are estimated at 825 billion US dollars [9]. Mitochondria are essential semi-autonomous organelles that play a vital role in numerous physiological and biochemical processes. Mitochondria conduct complex physiological tasks, such as metabolism, oxidative phosphorylation through interaction with encoded nuclear factors, and free radicals and cytochrome C [10]. Mitochondria serve as the primary cellular energy source. To uphold metabolic health and ensure homeostasis, it is necessary to maintain a balanced state within the body's metabolic processes. The malfunctioning of mitochondria has the potential to interfere with the proper functioning of both the electron transport chain and beta-oxidation. The emergence of insulin resistance has resulted in significant advancements [11].

Mitochondrial dysfunction has been reported to be associated with T2DM as well as diabetes-related complications [12]. Mitochondrial communication is mediated by several encoded nuclear proteins, transient molecules, and mitochondrial metabolites [13]. Mitochondrial dysfunction has been suggested to be related to T2DM as well as diabetes-related complications [12]. Studies show that mitochondrial dysfunction is a prominent feature of T2DM. Decreased mtDNA content is highly associated with insulin resistance and strongly related to reduced glucose-stimulated insulin secretion capacity in diabetic and pre-diabetic individuals [14]. Mitochondria may actively regulate metabolic homeostasis at the cellular and organismal levels through peptides encoded in their genome [15]. Apart from metabolism and energy production, mitochondria also transmit information through mitochondria-derived peptides (MDPs) [16]. These MDPs have shown a larger mitochondrial gene pool and have changed the perception of mitochondria from "end-function" organelles to versatile retrograde signaling organelles [10]. Among the currently known MDPs, the mitochondrial open reading frame of the 12S rRNA type-c (MOTS-c) seems to mediate several physiological functions [16]. The suggested way MOTS-c works as a mitochondrial signaling peptide found in mtDNA to control metabolic balance is by targeting the skeletal muscle and influencing the folate cycle, a carbon storage system. This is achieved by regulating the genetic expression of key enzymes that rely on folate as a coenzyme, particularly its active form 5-methyltetrahydrofolate (Me-THF). Me-THF functions as a crucial coenzyme in various pathways, including the catabolism of amino acids and the biosynthesis of purines. Therefore, it partially mediates the metabolic effects of MOTS-c [17].

Physical activity has several health benefits, such as increasing life span and protecting against cardiovascular diseases, diabetes, and cancer [17]. Performing exercise can link MOTS-c adaptations and mitochondria, which aim to supply the cell's energy source and converge with important metabolic adaptations [18]. Studies have shown that exercise increases the level of MOTS-c, which in turn boosts AMPK and insulin sensitivity in muscles, thereby reducing the risk of associated diseases [19]. In addition, exercise increases the expression of MOTS-c in skeletal muscles and blood circulation [20]. The association between MOTS-c and cardiovascular risk factors, including aging, blood lipids, insulin resistance, and atherosclerosis, suggests that MOTS-c could potentially contribute to the prevention of age-related diseases, such as T2DM and cardiovascular diseases. This could be achieved through its influence on glycolipid metabolism, promotion of glucose utilization and insulin sensitivity, and preservation of endothelial function [14]. However, any protective and risk-reducing effects of exercise need to be further emphasized. In addition, understanding the basic molecular mechanisms in the adaptation of skeletal muscles with exercise and regular physical activity is of great importance. Therefore, this study aimed to review the function of MOTS-c peptide

in the body and its mechanism of action in improving type 2 diabetes and the effect of exercise training on the mitochondrial cycle of MOTS-c-AMPK.

## Materials and Methods

This review study was conducted by searching the articles available in the Scopus, Google Scholar, and Pubmed databases, as well as in Persian databases, including Magiran, which were published from 1991 to 2022. The search process was conducted using the following English keywords: "T2DM", "Exercise training", "Mitochondria", "MOTS-c MDPs", "PGC-1α" and their combination with AND and OR functions, as well as the following Persian keywords: "Type 2 diabetes", "Exercise training", "Mitochondria", and "Mitochondria-derived peptides". The inclusion criteria were original research articles, and the study population included type 2 diabetic patients, while the exclusion criteria involved reports, lectures, conferences, non-compliance of the article with the subject under study, and lack of access to the full text of the articles. Based on the initial search, 98 articles were examined, of which 46 articles were removed due to being repetitive and unrelated. Finally, 52 articles were left, and after investigating the full text of the articles, 46 articles were included in the study (Figure 1).

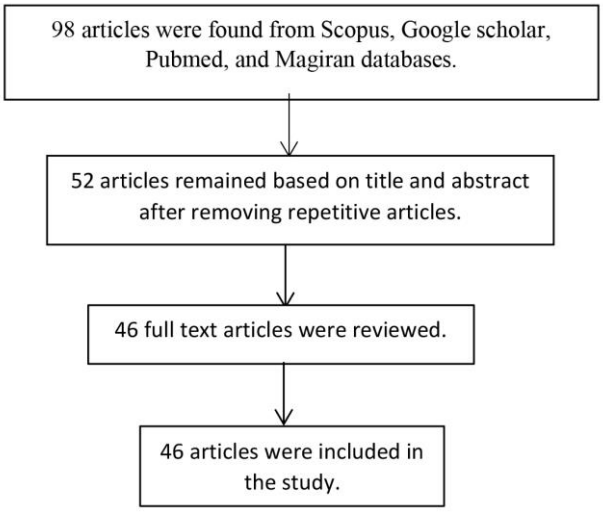


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**Figure 1.** Process of inclusion of articles in the study

## Results

In this section, the obtained articles whose full text was available were examined. The results of the present study showed that performing exercise could elevate MOTS-c levels, which in turn triggers AMPK in skeletal muscles, leading to enhanced overall energy metabolism in the body. This process improves insulin sensitivity and thus reduces the risk of associated diseases. In research consistent with our findings, Dieli-Conwright et al. (2021) investigated the effect of aerobic and resistance exercise on the mitochondrial peptide MOTS-c in Hispanic and non-Hispanic white breast cancer survivors. They suggested that the enhancement of MOTS-c through exercise could potentially lead to improved insulin sensitivity and body composition [20]. In another study conducted by Zempo et al. (2021), titled "A pro-diabetogenic mtDNA polymorphism in the mitochondrial-derived peptide", it was stated that polymorphism m.1382A>C was associated with sensitivity to T2DM in men, possibly by doing exercise, and contributed to the risk of T2DM in sedentary men by decreasing MOTS-c activity. The C allele of the m.1382A>C polymorphism alters body composition and raises the risk of T2DM in Japanese men, especially in sedentary individuals. The m.1382A>C polymorphism leads to a substitution of Lys (K) with Gln (Q) at amino acid 14 in the MOTS-C peptide, resulting in reduced responsiveness to insulin when compared to the wild-type MOTS-C [21]. In a distinct investigation, David Ruiz et al. (2022) conducted a study to investigate the evolution of peptides derived from mitochondria and their association with changes in insulin resistance during the early stages of pregnancy in 28 pregnant women. They found that the levels of MOTSc, especially, decreased sharply from the first to the second trimester of pregnancy and may play a role in increasing insulin resistance in early pregnancy [22].

MOTS-c has also been investigated in animal studies. Reynolds et al. (2021), in a study titled" MOTS-c is an exercise-induced mitochondrial-encoded regulator of age-dependent physical decline and muscle homeostasis" reported that aging was regulated by genes encoded in both our mitochondrial and nuclear genomes. They also suggested that MOTS-c could improve physical performance in young mice, increase physical capacity in old mice, and improve mouse lifespan [23]. Furthermore, the study conducted by Yang et al. (2021) provided evidence supporting the notion that the AMPK/PGC-1α pathway had the ability to enhance the release and/or synthesis of MOTS-c in skeletal muscle. This finding implies that the exercise intervention and the application of recombinant MOTS-c could hold promise in addressing the challenges posed by obesity and diabetes [24]. The findings of a study by Guo et al. (2020) showed that the APPL1-SIRT1-PGC-1α pathway regulated the production and/or secretion of skeletal muscle MOTS-c by mediating adiponectin signaling. This study provides insight into the basic cellular and molecular pathways in the pathogenesis of diabetes and suggests that MOTS-c is a potential

new therapeutic target in the treatment of diabetes [25]. Kim et al. (2019) also stated that MOTS-c improved insulin sensitivity and increased β-oxidation to prevent fat accumulation in DIO mice through these pathways [16].

**Table 1**. Summary of the research conducted in the human field

| Authors | Year | Country | Title of the study | Study method | Type of study | Sample size | Results |
|---|---|---|---|---|---|---|---|
| Dieli-Conwright et al. | 2021 | USA | Effect of aerobic and resistance exercise on the mitochondrial peptide MOTS-c in Hispanic and Non-Hispanic White breast cancer survivors | Random | Trial | 49 women | Following exercise-induced improvement in MOTS-c, insulin sensitivity and body composition may also improve. |
| Zempo et al. | 2021 | Japan | A pro-diabetogenic mtDNA polymorphism in the mitochondrial-derived peptide, MOTS-c | Random | Trial | 12,068 individuals | The C allele of the m.1382A>C polymorphism alters body composition and increases the risk of T2DM in Japanese men, especially in sedentary individuals. |
| David Roayez et al. | 2022 | Spain | Evolution of humanin and MOTS c mitochondria-derived peptides and changes in insulin sensitivity during early pregnancy in women with and without gestational diabetes. | Random | Trial | 73 pregnant women | MOTSc levels, especially, have a sharp decrease from the first to the second trimester of pregnancy and may contribute to the increase in insulin resistance in early pregnancy. |
| Zhang et al. | 2018 | China | Circulating MOTS-c levels are decreased in obese male children and adolescents and associated with insulin resistance | Random | Experimental | 40 obese children and adolescents | MOTS-c levels in the obese group were significantly decreased compared to the control group, and MOTS-c is associated with markers of insulin resistance and obesity. |
| Walden et al. | 2021 | USA | Acute endurance exercise stimulates circulating levels of mitochondrial-derived peptides in humans | Random | Experimental | 30 individuals | Circulating levels of mitochondrial-derived peptides are regulated by endurance exercise in healthy subjects. Furthermore, circulating MDP levels were not associated with fitness level, however skeletal muscle MOTS-c levels were inversely related to skeletal muscle mtDNA copy number. |
| Ramanjaneya et al. | 2019 | Qatar | Mitochondrial-derived peptides are down regulated in diabetes subjects. Frontiers in endocrinology | Random | Experimental | 255 individuals | MDPs HN and MOT-c, similar to ADP, are decreased in T2DM and correlated with HbA1c. Mitochondrial dysfunction contributes to |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | glycemic dysregulation and metabolic defects in T2DM. |
| Gianotti et al. | 2008 | Argentina | A decreased mitochondrial DNA content is related to insulin resistance in adolescents | Random | Experimental | 175 individuals | Decreased mtDNA content in peripheral leukocytes is associated with insulin resistance. It seems that this result is not related to the previously mentioned species in the genes involved in the regulation of mitochondrial biogenesis. |
| Komar et al. | 2005 | India | Prevalence of insulin resistance in first degree relatives of type 2 diabetes patients | Random | Experimental | 172 individuals | A strong positive correlation was observed between HOMAIR and FPI insulin resistance indices in these patients. |
| Boden et al. | 1991 | Philadelphia | Effects of fat on insulin-stimulated carbohydrate metabolism in normal men | Random | Experimental | 18 individuals | During hyperinsulinemia, lipid rapidly replaced carbohydrate as a fuel for oxidation in muscle, preventing glucose uptake hours later, possibly by interfering with muscle glycogen formation. |



## Structure of MOTS-c

Mitochondria produce numerous small polypeptides from Student Org Resource Fee regions of mtDNA that have significant biological activity [17]. Apart from metabolism and energy production, mitochondria also transmit information through peptides derived from mitochondria, such as MOTS-c [26]. MOTS-c contains 16 amino acids encoded by the mitochondrial RsrRNA gene region and is mainly expressed in skeletal muscle tissues; however, it is detected in other tissues as well as in blood plasma in both rodents and humans [15].

## Mechanism of action of MOTS-c in type 2 diabetes

This peptide performs various functions and acts as an important cellular protector in helping to maintain mitochondrial function and cell viability under stressful conditions, regulating metabolic homeostasis [15]. MOTS-c stimulates glucose utilization and oxidation of lipids, reduces inflammation, and protects against experimental models of metabolic disease [19]. MOTS-c enhances mitochondrial metabolism and regulates critical processes, such as aging, inflammation, and insulin resistance [27]. Research on rodents indicates that MOTS-c is involved in ameliorating insulin resistance resulting from T2DM [19]. PGC-1a is a transcription factor that plays an important role in regulating mitochondrial function by enhancing the expression of proteins responsible for the transcription of mitochondrial genes and it also applies to mitochondrial DNA [19]. Suppression of skeletal muscle PGC-1a is associated with obesity, diabetes, and metabolic diseases. The findings show that the APPL-PGC-1α pathway regulates the production and/or the secretion of skeletal muscle MOTS-c by mediating adiponectin signaling [25]. The suggested way MOTS-c works as a mitochondrial signaling peptide found in mtDNA to control metabolic balance is by targeting the skeletal muscle and influencing the folate cycle, a carbon storage system. This is achieved by regulating the genetic expression of key enzymes that rely on folate as a coenzyme, particularly its active form 5-methyltetrahydrofolate (Me-THF). Me-THF functions as a crucial coenzyme in various pathways, including amino acid breakdown and purine synthesis. Therefore, it partially mediates the metabolic effects of MOTS-c [17] (Figure 2). In a study, Manjunath et al. showed that the expression of MOTS-c was lower in type 2 diabetes, providing further evidence that mitochondrial dysfunction contributes to the dysregulation of blood

sugar and metabolic effects in T2DM [29]. MOTS-c controls the methionine folate cycle and leads to an increase in AICAR levels and finally activates AMPK and causes the expression of GLUT4 in skeletal muscles, thereby increasing glucose uptake.

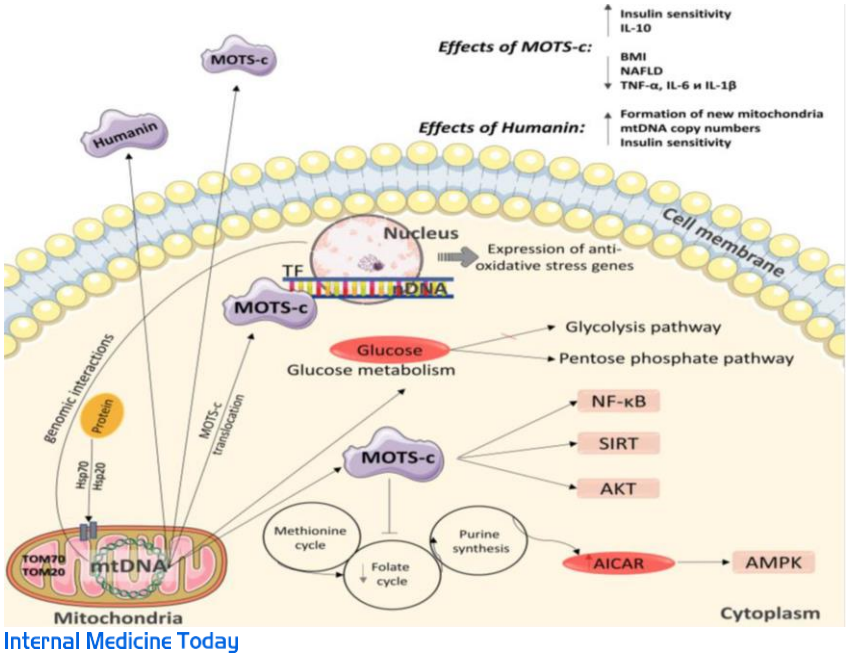


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**Figure 2.** Effects of MOTS-c mitochondrial peptides [30]

In addition, MOTS-c can prevent insulin resistance and obesity in CD-1 mice fed a high-fat diet (HFD) and prevent HFD-induced obesity in C57BL/6 J mice [19]. Clinical findings in humans also relate lower MOTS-c plasma levels to insulin resistance. A thorough analysis of how MOTS-c moves in insulin uptake may be related to mitochondrial retrograde signaling and glucose transporter type 4 (GLUT4). GLUT4 in its active phase in fat cells and muscles stimulates glucose transport in response to insulin stimulation [31]. Increased expression of mitochondrial fusion through the modulation of MFN2 and microRNA-106b causes GLUT4 signal transduction and glucose homeostasis in the body [32].

**Table 2.** Summary of the research conducted in the animal field

| Authors | Year | Country | The title of the study | Study method | Type of study | Sample size | Results |
|---|---|---|---|---|---|---|---|
| Reynolds et al. | 2021 | USA | MOTS-c is an exercise-induced mitochondrial-encoded regulator of age-dependent physical decline and muscle homeostasis. | Random | Experimental | 12 | MOTS-c improves physical performance in young mice, increases physical capacity in old mice, improves mouse lifespan. |
| Bhullar et al. | 2021 | Canada | Mitofusion is required for MOTS-c induced GLUT4 translocation | Random | Experimental | - | Inhibition of the two GTPases by TNFα abolished the ability of MOTS-c to stimulate GLUT4 translocation and glucose uptake. Linking mitofusion to MOTS-c-induced GLUT4 translocation. |
| Young et al. | 2021 | China | MOTS-c synergistically interacts with exercise intervention to regulate PGC-1α expression, reduce insulin resistance, and increase glucose metabolism in mice through the AMPK signaling pathway | Random | Experimental | - | AMPK/PGC-1α pathway can induce the secretion and/or production of MOTS-c in skeletal muscle, implying the possible role of exercise intervention and recombinant MOTS-c in the treatment of obesity and diabetes. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Guo et al. | 2020 | China | Adiponectin treatment improves insulin resistance in mice by regulating the expression of the mitochondrial-derived peptide MOTS-c and its response to exercise via APPL1–SIRT1–PGC-1α | Random | Experimental | 20 | The APPL1-SIRT1-PGC-1α pathway regulates skeletal muscle MOTS-c production and/or secretion by mediating adiponectin signaling. MOTS-c is a potential new therapeutic target in the treatment of diabetes. |
| Kim et al. | 2019 | USA | The mitochondrial-derived peptide MOTS-c is a regulator of plasma metabolites and enhances insulin sensitivity | Random | Experimental | 12 | MOTS-c improves insulin sensitivity and increases β-oxidation to prevent fat accumulation in DIO mice through these pathways. |
| Lu et al. | 2019 | China | Mitochondrial-derived peptide MOTS-c enhances adipose thermogenic activation to promote cold adaptation | Random | Experimental | 32 rats | MOTS-c activated the AMPK pathway to improve energy expenditure and insulin sensitivity. In conclusion, MOTS-c is a high potential candidate for the chronic treatment of menopausal metabolic disorder. |

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It has been reported that there is a correlation between GLUT4 translocation induced by MOTS-c [33]. MOTS-c increases glucose utilization and restores metabolic homeostasis through the activation of AMPK-dependent mechanisms in skeletal muscle and protected rodents [34].

### MOTS-c and exercise

Physical activity has numerous health benefits, such as increasing life span and protecting against cardiovascular diseases, diabetes, and cancer [18]. Mitochondria are the main sources of biological energy. During sports activities, they play an important role in signaling physical activity to other organs [35]. The activation of PGC-1a is a crucial element in the process of skeletal muscle adaptations, as it holds a pivotal position in both muscle adaptations and the activation of signaling pathways [36]. Intermittent training seems to be a strong activating factor for mitochondrial biogenesis [37]. Exercise stimulates the production and secretion of MOTS-c in skeletal muscles and can increase insulin sensitivity [16]. Exercise regulates MOTS-c expression and leads to elevated levels of GLUT4 and AMPK protein expression [35]. During intense exercise, MOTS-c levels rise in both human plasma and skeletal muscles, and administering MOTS-c externally enhances aerobic capacity [23]. Regular physical activity triggers the PGC-1α pathway, leading to heightened mitochondrial biogenesis and augmented mitochondrial content. From this point of view, exercise may improve the endocrine and paracrine function of MOTS-c in skeletal muscle [27].

Studies show that exercise increased the plasma and skeletal muscle expression of MOTS-c along with the skeletal muscle expression of APPL1, SIRT1, and PGC-1α in normal rats [25]. In addition, performing exercise can create a link between MOTS-c adaptations and mitochondria, which aim to provide the cell's energy source and converge with important metabolic adaptations [19]. Research results show that exercise boosts MOTS-c expression in both skeletal muscles and blood circulation. Furthermore, it elevates MOTS-c levels, and MOTS-c activation of AMPK in skeletal muscles enhances overall body energy metabolism [17]. In addition, it improves insulin sensitivity and thus reduces the risk of associated diseases [20]. Studies have reported that exercise elevates and stimulates MOTS-c in plasma. Research has demonstrated that exercise intervention increases the production of MOTS-c and improves glucose metabolism in rats [23].

## Discussion

During the last century, human life expectancy in technologically advanced societies has been significantly extended due to extensive knowledge about the underlying mechanisms of sustainable health and disease. As a result, a high percentage of people in these societies reach the age of 100 years. However, certain lifestyle-related diseases remain a problem. The question arises whether the aging process is happening more healthily than in the past. Major barriers to sustainable health are metabolic diseases, such as obesity and T2DM. These diseases develop

easily and can be challenging to address, ultimately exerting a devastating effect on the long-term well-being of individuals. T2DM presents a growing concern for public health in Asia, as the discovery of ethnic-specific mtDNA polymorphisms has a substantial impact on the vulnerability to T2DM [21]. Mitochondrial dysfunction has been suggested to be related to T2DM as well as to the development of complications associated with diabetes. Blake et al. showed that mitochondrial dysfunction is involved in diabetes-related complications that affect the kidneys, nervous system, heart, and retina [12]. Aerobic exercise has been shown to stimulate the synthesis and release of MOTS-c within the skeletal muscles and increase insulin sensitivity [16].

MOTS-c is a recently identified mitochondrial-derived peptide consisting of 16 amino acids [19]. MOTS-c can be secreted in the blood circulation and act as an independent and hormonal cell [15]. MOTS-c targets skeletal muscle to promote insulin sensitivity and prevent diet-induced obesity and insulin resistance in mice. Research shows that the circulating level of MOTS-c is significantly lower in young obese men [38]. This index has a negative relationship with insulin resistance in thin people, and it has been observed to be diminished in patients with T2DM and T1D diabetes [29, 39]. In a study, researchers showed that MOTS-c could be induced by exercise and increase physical performance in mice of different ages through the regulation of muscle homeostasis [23]. Recently, Joseph et al. (2021) reported that MOTS-c could prevent pancreatic islet destruction and suppress autoimmune diabetes [40]. All these reports indicate that MOTS-c acts as an endocrine agent to regulate metabolism within or between cells [41].

MOTS-c is associated with glucose uptake and metabolism in mice and lipid metabolism in humans and is believed to work through an AMPK-mediated mechanism [19, 42]. MOTS-c has been shown to stimulate other intracellular networks in addition to the AMPK pathway as indicated by insulin-mediated AKT signaling following MOTS-c injection in mice. In vitro experiments in skeletal muscle cells differentiated with MOTS-c show that MOTS-c stimulates skeletal muscle glucose uptake and insulin sensitivity in mice, which further emphasizes the involvement of MOTS-c in metabolism [43].

MOTS-c plays a crucial role in governing the folic acid metabolic cycle and the recently discovered purine biosynthetic pathway, leading to the activation of AMPK, a well-known regulator of exercise [19]. Exercise, being a metabolic stressor, also triggers the AMPK pathway [44]. However, it remains uncertain whether exercise has the capability to regulate the secretion or production of MOTS-c [27]. It is worth emphasizing that MOTS-c might function similarly to regular exercise in protecting against the harmful effects of high-fat diets [45]. Therefore, as a potential signal from the mitochondria, MOTS-c can facilitate the response of mitohormesis induced by exercise, thereby promoting physiological adaptation and improving exercise tolerance [24].

The impact of engaging in physical activities can have contrasting effects. Recent research has shown that exercise has the ability to stimulate the paracrine and endocrine effects of MOTS-c in skeletal muscle cells [27]. The regulation of MOTS-c through exercise may involve the AMPK/PGC-1a pathway. Therefore, further investigation is necessary to fully comprehend the role of exercise in controlling MOTS-c expression. Li et al. also made a significant discovery that MOTS-c prescription can reduce insulin resistance through the AMPK pathway [19]. The combined effects of MOTS-c treatment and exercise intervention on the expression of GLUT4, MOTS-c, and PGC-1a in skeletal muscle, as well as the levels of ACC and AMPK phosphorylation, are synergistic. Consequently, these findings suggest that exercise can work in conjunction with MOTS-c to stimulate MOTS-c expression in skeletal muscle, resulting in an improvement in insulin [16].

## Conclusion

In summary, this study provides evidence that PGC-1a may play a crucial role in regulating MOTS-c in skeletal muscle, and that AMPK can facilitate the secretion and/or production of MOTS-c through the activation of PGC-1α. Furthermore, the current study sheds light on the signaling mechanisms by which exercise intervention controls MOTS-c expression, reduces insulin resistance, and enhances glucose metabolism in obese mice. As a result, modulating MOTS-c levels may present a novel approach to the treatment of insulin resistance and other metabolic disorders [24].

Knowledge about such mechanisms can be the basis for the prevention and treatment of metabolic and chronic diseases associated with physical inactivity. Researchers are looking for alternative methods for prevention or treatment with fewer complications in diabetic patients, which necessitates conducting more research in the field of aerobic exercises on diabetes. Given the significance of exercise in preventing the complications of T2DM disease, the impact it carries on the mechanism of mitochondrial peptides, the crucial part mitochondria play in glucose irregularities and T2DM, as well as the signaling pathways associated with mitochondria and their involvement in diabetes mellitus, approaches that alleviate mitochondrial

dysfunction will open up new possibilities for treating diabetes and its associated complications. Therefore, it is necessary to conduct further studies to understand the improvement of cellular mechanisms related to mitochondrial adaptation and the effect of various sports exercises on this cycle.

This peptide has positive effects on the regulation of carbohydrate metabolism and can interact with the nuclear genome.

## Ethical Considerations

### Compliance with ethical guidelines

This research is a review article with no human or animal sample.

### Funding

This study was done self-funding.

### Authors' contributions

All authors have contributed to the design, execution, and writing of all sections of the current study.

### Conflicts of interest

The authors declared no conflict of interest.

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