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Review Article

Molecular Mechanism of Physical Exercise in Increasing Genetic Expression of Sirtuin 1 (SIRT1): A Systematic Review

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Abstract

Background: Obesity is associated with decreased levels of protein sirtuin 1 (SIRT1). This decrease can disrupt SIRT1 activity, leading to reduced antioxidant defenses, increased oxidative stress, impaired fatty acid oxidation, and reduced energy expenditure. These changes can contribute to a positive energy balance and long-term weight gain. Exercise is an alternative way to prevent decreased sirtuin 1 level. Sirtuin 1 plays a role in cell maintenance, stress markers, determining cell fate, maintaining energy balance, preventing DNA damage, and maintaining the stability and continuity of cell function. ***Objective***: This study aims to determine and measure how the mechanism of physical exercise can increase the expression of SIRT1. ***Methods***: Several journal databases, such as Embase, PubMed, Web of Science, ScienceDirect, and Scopus, were searched for this study. The criteria for this study included papers on oxidative stress, physical exercise, and SIRT1 published during the previous five years. The only publications rejected for inclusion in this analysis were those published in non-reputable journals. Using Embase, Web of Science, PubMed, ScienceDirect, and Scopus databases, a total of 1,891 publications were found. These systemic breakthrough criteria have been examined and discussed in about 9 studies. ***Results***: Physical exercise can increase the expression of SIRT1. ***Conclusions***: Physical exercise is proven to increase the expression of SIRT1 to influence the increase of biogenesis in mitochondria, which will have a favorable and beneficial impact on the degree of human health.

Keywords: Molecular mechanisms, Oxidative stress, Physical exercise, SIRT1.

الآلية الجزيئية للتمرينات البدنية في زيادة التعبير الجيني للسيرتوين 1 (SIRT1): مراجعة منهجية

الخلاصة

الخلفية: ترتبط السمنة بانخفاض مستويات البروتين سيرتوين 1 (SIRT1). يمكن أن يؤدي هذا الانخفاض إلى تعطيل نشاط SIRT1، مما يؤدي إلى تقليل الدفاعات المضادة للأكسدة، وزيادة الإجهاد التأكسدي، وضعف أكسدة الأحماض الدهنية، وتقليل إنفاق الطاقة. يمكن أن تساهم هذه التغييرات في توازن الطاقة الإيجابي وزيادة الوزن على المدى الطويل. التمرين هو طريقة بديلة لمنع انخفاض مستوى السيرتوين 1. يلعب Sirtuin 1 دورا في صيانة الخلايا، وعلامات الإجهاد، وتحديد مصير الخلية، والحفاظ على توازن الطاقة، ومنع تلف الحمض النووي، والحفاظ على استقرار واستمرارية وظيفة الخلية. **الهدف**: تهدف هذه الدراسة إلى تحديد وقياس كيف يمكن لآلية التمرين البدني أن تزيد من التعبير عن SIRT1. **الطرائق**: تم البحث في العديد من قواعد بيانات المجلات ، مثل Embase و PubMed و Web of Science و ScienceDirect و Scopus، لهذه الدراسة. تضمنت معايير هذه الدراسة أوراقا حول الإجهاد التأكسدي والتمارين البدنية و SIRT1 المنشورة خلال السنوات الخمس الماضية. كانت المنشورات الوحيدة التي تم رفضها لإدراجها في هذا التحليل هي تلك المنشورة في المجلات غير ذات السمعة الطيبة. باستخدام قواعد بيانات Embase و Web of Science و PubMed و ScienceDirect و Scopus ، تم العثور على ما مجموعه 1,891 منشورا. تم فحص معايير الاختراق النظامي هذه ومناقشتها في حوالي 9 دراسات. **النتائج**: يمكن أن تزيد التمارين البدنية من التعبير عن SIRT1. **الاستنتاجات**: ثبت أن التمارين البدنية تزيد من التعبير عن SIRT1 للتأثير على زيادة التكوين الحيوي في الميتوكوندريا، والتي سيكون لها تأثير إيجابي ومفيد على درجة صحة الإنسان.

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INTRODUCTION

Sirtuin has a very important role as a cell guardian and stress marker; it determines cell fate, maintains energy balance, prevents DNA damage, and maintains the stability and continuity of cellular work [1]. The repeated induction that occurs in skeletal muscles during physical performance is the most important part of the muscle remodeling mechanism that has a positive effect on the body [2]. Exercise makes the body experience extraordinary physiological mechanisms, especially the increase in skeletal muscle contraction, which will trigger an increase in ATP demand. This response has an impact on cellular glucose uptake and fatty acid oxidation to produce more ATP and NAD^+, which serves as a fuel supply for sirtuin 1 (SIRT1) [3]. Among the seven types of sirtuin, sirtuin 1 is known to play an important role in the cell signal transduction process, which is involved in metabolic processes in mitochondria, DNA repair,

regulation of inflammation, and cellular aging [4]. One of the deadly non-communicable diseases is metabolic syndrome, which is characterized by overweight patients, high blood glucose levels, high blood pressure, and abnormalities in fat tissue, which has a high risk of mortality worldwide [5]. In patients with type 2 diabetes mellitus (T2DM), metabolic syndrome has an adverse effect on increasing the risk of degenerative diseases such as cardiovascular disease [6]. Chronic hyperglycemia triggered by abnormalities in insulin hormone secretion caused by obesity is a characteristic of people with diabetes mellitus [7]. Statistical results from the International Diabetes Federation in 2021 show that 537 million people have diabetes mellitus in 2021 worldwide, and this number will continue to increase to around 783 million sufferers in 2045 [7]. The beneficial effects of sirtuin make it an interesting gene to study, especially as a therapy in preventing metabolic syndrome and neurodegenerative diseases [8]. Overweight and overeating factors that are not accompanied by increased physical activity are the main causes contributing to T2DM worldwide [9]. In this case, both developed and developing countries are not an exception; insulin resistance, type 2 diabetes mellitus, and obesity are public health problems that should be watched out for [10]. Exercise is a very effective medicine in preventing or reducing these diseases [11]. The activity and expression of sirtuin positively affects the function of mitochondrial organelles in biogenesis but also affects the effectiveness of metabolism and increases the secretion of antioxidant enzymes [12]. Based on the results of the study, it is proven that physical exercise can increase the formation of ROS by increasing the metabolic rate in mitochondria, which has an impact on increasing oxidative stress [13]. Exercise intensity strongly influences exercise-induced oxidative stress [14]. Sport is a strategy in efforts to improve human health status [15]. Tissue damage caused by oxidative stress triggered by exercise will result in an inflammatory process [16]. ROS generated during exercise will affect and induce various signal transductions as a physiological adaptation of skeletal muscle [17]. A temporary inflammation response characterized by changes in various proinflammatory cytokines such as IL-1β, IL-6, IL-10, and TNF-α also occurs as a result of acute physical exercise [18]. Excess ROS will also have an adverse effect on skeletal muscle contractile disorders so that it will also weaken muscle function [13]. Although regular physical exercise increases the production of ROS (reactive oxygen species), the presence of sirtuin also has a beneficial effect on the repair and increase of antioxidants as a body defense system that will protect tissues from damage caused by ROS [19]. Results from studies have highlighted the key role of sirtuin 1 in adipogenesis, and its targets include transcription factors such as peroxisome proliferator-activated receptor gamma (PPARγ) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) [20]. Previous research has partially discussed the impact of physical exercise on increasing SIRT 1, but the information provided still discusses little about the physiological mechanisms that occur during physical exercise in increasing SIRT1 [20]. The important effects of SIRT1 have been discussed, but there is still limited research on the relationship between SIRT1 expression during exercise and how its mechanisms may improve public health. Therefore, in this scientific review, we will discuss and explore in depth how physical exercise influences increased SIRT 1 expression and how its molecular mechanisms promote public health.

METHODS

Study design

To determine how physical exercise impacts SIRT1 levels, this study was conducted by evaluating academic literature. PubMed, Scopus, ScienceDirect, Web of Science, and Embase were search engines used to locate scientific papers. The search terms used were "physical exercise" and "SIRT1." Article selection was based on the following inclusion criteria: English language proficiency, experimental research and studies, and year of publication. Furthermore, articles that did not meet the inclusion criteria, including non-exercise interventions, non-experimental studies, and parameters other than SIRT1, were excluded from our analysis and were subject to exclusion criteria.

Eligibility criteria

The inclusion criteria for this study were met by studies on oxidative stress, physical exercise, and SIRT1 published within the last five years in reputable journals. The only studies excluded from this systematic review were articles published in non-reputable journals. Furthermore, the study did not directly use animal or human samples for experimental testing.

Procedure

Full text, abstracts, and titles of verified and approved articles were archived to the Mendeley database using Embase, PubMed, Scopus, ScienceDirect, and Web of Science databases. 1,891 publications were found during the first part of the study. In the second step, 1,150 entries were evaluated based on how well the abstract and title met the researcher's requirements. The third stage consisted of verifying 364 items for further processing. We now filtered based on whether the issue was acceptable for the overall discussion or not. After careful consideration, 9 papers that met the inclusion criteria were selected for this systematic review. This study supports the assessment of standard operating procedures using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Figure 1).

RESULTS AND DISCUSSION

Table 1 shows the studies related to the effect of physical exercise in increasing SIRT1 expression.

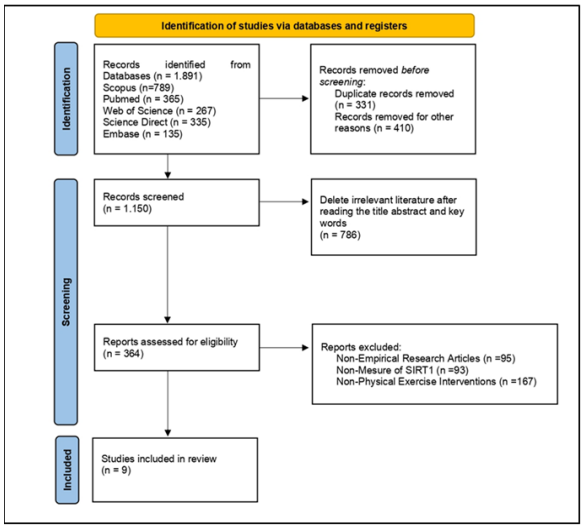

Figure 1: PRISMA flowchart of the article selection process.

Physical exercise regulates oxidation reactions by increasing the levels of free radicals in the body, such as ROS (reactive oxygen species), and regulates the defense system of the body by increasing endogenous antioxidant levels [29]. In addition, oxidative stress that increases during exercise is also caused by the levels of free radicals in the body being higher than the levels of antioxidants [30]. Acute aerobic physical exercise is a fundamental aspect of exercise that can improve people's health by increasing the work system of the cardiovascular system and increasing cardiac output so as to increase the metabolic system to meet the performance of the musculoskeletal system [31]. Aerobic physical exercise can affect maximal oxygen uptake in an effort to increase ATP production in mitochondria, which can benefit the increase in oxidative capacity and have an impact on reducing muscle fatigue after physical exercise [32]. Regular exercise is known to prevent skeletal muscle aging as well as prevent sarcopenia, which is age-related loss of muscle mass [33]. Physical exercise has also been shown to increase skeletal muscle contraction and improve muscular endurance [34]. Malondialdehyde (MDA) is one of the biomarkers of oxidative stress caused by physical exercise [35]. Research results from Souissi *et al*. (2020) proved that there was an increase in MDA levels after physical exercise. Key enzymes that assist the body's defense system in counteracting free radicals are glutathione peroxidase (GPX), superoxide dismutase (SOD), and catalase (CAT) [35]. SOD is an endogenous antioxidant that functions in converting H2O2 into H2O and is also assisted by glutathione peroxidase and catalase [21]. Increased oxidative stress during exercise also has a positive effect on increasing SIRT expression. Besides that, SIRT is also involved in the process of biogenesis, improving mitochondrial function, and increasing body antioxidants [12]. The results of a study in 20 healthy men who performed running training on a treadmill with moderate and high intensity were shown to increase SIRT1 expression after the intervention [29]. A report from Souissi *et al*., 2020, proved that intermittent physical exercise at 75% VO_{2max} can significantly increase MDA levels [36]. Regular aerobic physical exercise can reduce oxidative stress by increasing antioxidant levels in the body, making the body healthier [37]. Previous research findings suggest that 8 weeks of physical therapy and HIIT positively impacted the metabolic profile of participants with metabolic syndrome (MetS) compared to a control group. This short-term period of physical therapy and HIIT, combined with a reduction in cardiometabolic risk factors, increased SIRT1 levels in women with MetS [38]. Studies of metabolic disorders have sparked interest in the role of the mammalian SIRT1 protein (encoded by the SIRT1 gene), as this protein plays a role in important physiological functions such as glucose metabolism and lipid breakdown [39]. Only a few studies have investigated the effects of different types of physical activity on serum SIRT1 levels. For example, Ferrara et al. reported that six weeks of HIIT training increased SIRT1 activity levels [40]. Studies have revealed that exercise causes an increase in SIRT1 activity and protein levels [41]. Another study conducted by Jia et al. reported that sustained, moderate-intensity exercise can increase SIRT1 levels in people with heart disease [42]. Contrary to the findings of this study, Ma et al. showed that four weeks of high-intensity exercise training did not affect SIRT1 levels in healthy men [43], and Marton et al. showed that physical exercise did not significantly affect serum SIRT1 levels [44]. Therefore, further exploration through experimental studies is warranted, and we are interested in pursuing this in the future. However, this systematic review provides a snapshot of the literature showing that physical exercise supports SIRT1 upregulation. SIRT is an NAD^+-dependent deacetylase that has important roles in regulating oxidative stress, transcription, metabolism, DNA repair, and cell cycle progression [29]. Another report is that 30 overweight women participated and contributed to the training protocol, namely the 20 m shuttle run with a maximum speed of 30 seconds carried out 3x a week for 10 weeks of treatment. The results of the study prove that there is an increase in SIRT1 levels after physical exercise [30]. As we age, we experience a decline in body function, which, if not matched with regular physical exercise, will trigger an increase in inflammation that will adversely affect the development of various diseases [45]. In people with obesity, SIRT1 levels in the blood are decreased [46]. Existing evidence reports that high-intensity interval training has favorable benefits on increasing the expression of SIRT1, PGC-1α, and CAT, which also makes it a low-cost treatment for overweight and obesity [47]. A study on recreational runners (18-35 years) practicing given an aerobic physical exercise using an ergometer until fatigue and reached their maximum performance proved that there was an increase in SIRT1 expression after undergoing physical exercise [31]. Measurement of SIRT1 in blood samples in the future can be a special method to be studied further, especially with regard to obese patients who are undergoing pharmacological and non-pharmacological treatment [48].

Table 1: Results of the effect of physical exercise in increasing SIRT1 expression

Author	Sample Characteristics	Study Design	Intervention	Results
(Cho *et al*., 2022) [21]	20 healthy men participated in were divided into two treatment groups: a moderate-intensity exercise group and a high-intensity exercise group.	Experimental	Performed running training on a treadmill. The moderate intensity group ran with 65% VO2Max, the high intensity group ran with 85% VO2Max.	There was an increase in SIRT-1 expression in all groups after the physical exercise intervention.
(Ghasemi *et al*., 2020) [22]	30 overweight young women aged 20-30 years were divided into 3 treatment groups. These were green tea + HIIT, HIIT + placebo, and without treatment groups.	Experimental	The training protocol was a 20m shuttle run with a max speed of 30 sec. The training protocol was 3x a week for 10 weeks.	There was an increase in the highest SIRT-1 levels in the HIIT + green tea group after 10 weeks of treatment.
(Potthast et al., 2020) [23]	63-75 recreational runners aged 18-35 years were divided into 3 groups. The 1st was omnivore consumption+ exercise, lacto-ovo vegetarian+ exercise, vegan+exercise.	Cross-sectional	The test protocol used a bicycle ergometer until exhaustion. The sample was also given verbal motivation to reach their max performance.	There was the highest increase in SIRT-1 expression in the omnivore group.
(Amirsasan *et al*., 2019) [24]	44 overweight and sedentary women were divided into 4 groups. The 1st was Pilates training, the 2nd was turmeric supplementation, the 3rd was Pilates training+ turmeric supplementation, the 4th was control without intervention.	Experimental	Pilates training with 40% - 70% intensity for 60 minutes per session, 3 x a week for 12 weeks of treatment.	There was an increase in SIRT-1 expression in the treatment groups. However, the highest increase occurred in the pilates training+turmeric group.
(Wasserfurth *et al*., 2021) [25]	134 participants aged between 50 and 70 were divided into 4 groups: control group, exercise only group, exercise and diet counseling group, exercise and Calanus finmarchicus oil supplementation group.	Experimental	Exercise training was conducted for 12 weeks at the fitness center; the intensity gradually increased.	There was a significant increase in SIRT-1 expression in the 3 exercise intervention groups.The highest increase occurred in the exercise+Calanus finmarchicus oil group.
(Sadek MD *et al*., 2019) [26]	40 male Wistar rats were divided into 4 groups: control group without treatment, diabetic group without exercise, post-diabetic exercise group, and pre-diabetic exercise group.	Experimental	Swim training in individual tanks filled with water for 1 hour per day, 5x a week for 4 weeks.	SIRT-1 expression activity increased in the group with exercise intervention.
(Shi *et al*., 2023) [27]	75 rats aged 6 months were divided into 5 groups: normal control, control with Alzheimer, chlorogenic acid+ Alzheimer, aerobic exercise+ Alzheimer, aerobic exercise+ Alzheimer+chlorogenic acid.	Experimental	Treadmill training with warm-up 6m/min for 5 minutes, exercise 9 m/min and 13 m/min for 28 min, cool down 6m/min for 4 min, total training 5 times a week. The total duration of acclimatization+formal training is 9 weeks.	There was the highest increase in SIRT-1 expression in the group with exercise + chlorogenic acid intervention.
(Baskaran *et al*., 2022) [28]	40 Kyoto Wistar and SHR rats aged 12 weeks were divided into 5 groups: Kyoto Wistar rat control group, SHR rat control group, SHR+exercise group, SHR+VH-4 protein use, SHR+VH-4 protein use+ exercise.	Experimental	Rats were allowed to swim in a plastic tank with a height of 50 cm. Animals were trained to swim for 20 min in the 1st week, 40 min in the 2nd week, 60 min in the 3rd week, during weeks 4, 5, 6, 7, and 8 were trained for 60 min.	There was the highest increase in SIRT-1 expression in the SHR + exercise group.
(Aird *et al*., 2021) [2]	28 healthy male subjects were divided into 3 groups: fasting group (FAST), WPC-fed (WPC), or WPH-fed (WPH).	Experimental	3 weeks of 3 times a week physical training. SIT training included 4 to 6 "all-out" Wingate cycle sprints each session (4 sprints in sessions 1-3, 5 in sessions 4-6, and 6 in sessions 7-9), with the identical warm-up, cool-down, and recovery intervals for each session.	There was the highest increase in SIRT-1 expression in the WPC group.

Exercise has been shown to increase MDA levels as a biomarker of oxidative stress triggered by increased ROS during physical exercise [49]. In addition, exercise also increases the expression of SIRT1, which affects the increase of biogenesis in mitochondria 12. During physical exercise the mitochondrial organelles also go through a phase of adaptation to exercise [43]. Many studies have reported that SIRT1 expression plays an important role in oxidative stress responses triggered by physical exercise [31]. The results of a study on 44 overweight women who did Pilates training with an intensity of 40% - 70% for 60 minutes per session 3x a week for 12 weeks proved that there was an increase in SIRT1

expression [32]. Endurance physical training has been shown to increase skeletal muscle contraction activity and AMPK and induce SIRT1 expression [32]. The results of another study in 134 research participants aged 50-70 years participating in a 12-week exercise study at a fitness center proved that there was an increase in SIRT1 expression after physical exercise [33]. Of the many types of sirtuins, SIRT1 and SIRT3 are often studied and are the subject of discussion because of their beneficial impact on many metabolic energy processes, especially those caused by physical exercise, in addition to regulating systemic adaptation caused by exercise [18]. SIRT3 and SIRT1 contribute to the regulation of mitochondrial biogenesis and fatty acid oxidation, while SIRT1 is also involved in the regulation of glucose homeostasis [33]. Another research report on 40 Wistar albino rats participating in a study with a swimming training intervention in individual tanks filled with water for 1 hour per day, 5x a week for 4 weeks, proved that there was an increase in SIRT1 expression after being given a physical training intervention [34]. The results of the next study on mice given swimming physical exercise intervention also proved to be able to increase SIRT1 expression [21]. Over the last decade physical exercise has become an important part of experimental clinical studies in order to improve health and longevity due to its positive effects [50]. There are two types of sports activities, namely sports with aerobic endurance and sports with anaerobic endurance [47]. Aerobic exercise is defined as any activity that uses major muscle groups and relies on aerobic metabolism to form adenosine triphosphate (ATP) as the main energy supply for the body [51]. The following is a picture of the mechanism by which physical exercise increases SIRT1 expression (Figure 2).

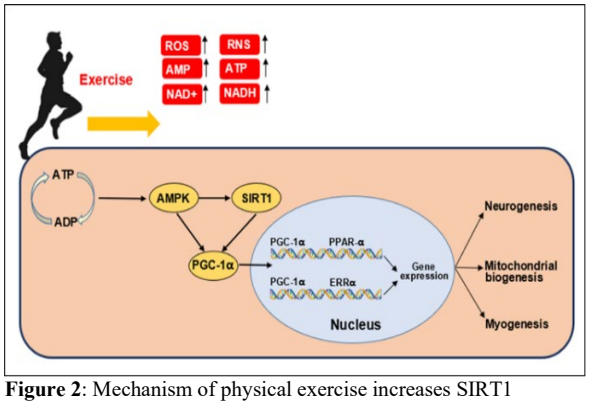

Figure 2: Mechanism of physical exercise increases SIRT1 expression.

Physical exercise has been shown to increase ATP production and also increase energy-forming activity in the mitochondria [51]. One of the modulators of increased exercise signaling associated with physiological adaptation is AMP-activated protein kinase (AMPK), which is widely expressed in all cells, tissues, and organs, including skeletal muscle, heart, liver, and adipose tissue [52]. AMPK is an enzyme that has an important role in the regulation of energy balance that exerts effects in increasing glucose uptake, fatty acid oxidation, and mitochondrial biogenesis [53]. AMPK during physical exercise exerts beneficial effects, including increasing fatty acid oxidation and lipolysis in adipose tissue [53]. Sirtuin is involved in various biological cellular activities such as DNA repair, inflammatory response, and metabolism. In addition, sirtuin is also involved in apoptosis and cell secretion and is thus directly involved in influencing the cellular aging process [54]. The results of research on mice that regulate energy restriction have provided evidence that it can delay cellular aging. The mice that were given the calorie restriction intervention lived longer than the normal group [55]. By exercising, the body will increase total energy expenditure, which has the benefit of reducing energy in the body [56]. In addition to regulating various biological signals, SIRT1 can also treat and prevent age-related diseases such as diabetes mellitus, cardiovascular system disorders, and neurodegenerative diseases [54]. Therefore, recent research on AMPK and SIRT1 is needed to provide therapy related to aging [54]. A report from Bayond in 2012 proved that there was an increase in SIRT1 and PGC-1α in rat muscle after being given a 36-week treadmill training intervention, and not only that but also an increase in antioxidant levels [12]. An increase in SIRT1 activity, triggered by an increase in NAD^+ levels, which in turn affects the upregulation of PGC-1α transcriptional activity [53]. On the other side of the response to exercise, SIRT1 also contributes to increased mitochondrial biogenesis through PGC-1α-dependent [12]. Mitochondrial biogenesis function is also very closely influenced by peroxisome proliferator-activated receptor γ coactivator 1α PGC-1α [57]. Thus, the expression of PGC-1α can improve the biogenesis mechanism in mitochondria, which will provide physiological benefits during physical exercise [58]. Of course, in this review, it has been widely described how physical exercise can increase biogenesis in mitochondria and the role of other proteins or genes that are affected by physical exercise. In this review, the author still has limitations on the research that has been done. The discussion that has been written by researchers still discusses only how SIRT1 can be expressed during physical exercise, what the mechanism is, and the stages that affect it. In data, further scientific study is still needed related to the effects of physical exercise on various types of SIRT ranging from SIRT1 to SIRT7. Hopefully, the next discussion can examine physical exercise on gene expression and various other types of genes that are affected so that it can provide broad insight into the repertoire of knowledge and scientific development in the field of physiology.

Strengths and limitations

The advantage of this systematic review is that it only reviewed randomized controlled trials, which are the most reliable type of scientific data, eliminating the possibility of ambiguous cause-and-effect relationships. Furthermore, we also address the limitations of our study, including the small number of studies reviewed, the lack of protocol

heterogeneity, and the limited review of physiological responses. These are indeed limitations of our research. Therefore, we are interested in conducting experimental studies on this topic in the future to further substantiate this. Furthermore, the limited discussion and debate surrounding physiological research demonstrating that physical exercise increases SIRT1 and the underlying mechanisms is a challenge we faced. To improve our understanding and knowledge of the impact of physical exercise on increasing SIRT1 and the theoretical and scientific explanation of the underlying mechanisms, this study is considered crucial.

Conclusion

This review supports that physical exercise can increase SIRT1 expression in an effort to influence increased biogenesis in mitochondria, which will have a positive and beneficial impact on human health.

Conflict of interests

The authors declared no conflict of interest.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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