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Effects of Physical Exercise on Mitochondrial Biogenesis of Skeletal Muscle Modulated by Histones Modifications in Type 2 Diabetes

Hellen Barbosa[1], Wael Ramadan[2]*, Júlia Matzenbacher dos Santos[3], Sandra Aparecida Benite-Ribeiro[4]

[1]Pós-Graduação em Biociência Animal, Universidade Federal de Jataí, Jataí, Goiás, Brazil; [2]Department of Sports Training, Faculty of Physical Education, Mansoura University, Mansoura, Egypt; [3]Department of Health Promotion and Development, School of Nursing, University of Pittsburgh, Pittsburgh, PA, United States; [4]Unidade Acadêmica Especial de Ciências Biológicas, Universidade Federal de Jataí, Goiás, Brazil

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***Correspondence:** Wael Ramadan, Department of Sports Training, Faculty of Physical Education, Mansoura University, Egypt. E-mail: dr.wael2050@gmail.com
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Abstract

Epigenetic modification in skeletal muscle induced by environmental factors modulates several metabolic pathways that underlie Type 2 diabetes mellitus (T2DM) development. Mitochondrial biogenesis is a vital process for maintaining lipid metabolism homeostasis, as well as epigenetic modifications in proteins that regulate this pathway were detected in T2DM subjects' skeletal muscle. Physical exercise affects several metabolic pathways attenuating metabolic deregulation observed in T2DM. The pathways that regulate mitochondrial homeostasis are critical components for understanding such beneficial effects of physical exercise. Consequently, in this research, we investigate the epigenetic mechanisms characterizing mitochondrial biogenesis in the skeletal muscle in T2DM, focusing on histone modifications and the mechanisms by which physical exercise delays or inhibits T2DM onset. The results indicate that exercise enhances metabolism in cells by increasing enzymes of the antioxidant system, AMPK and ATP-citrate lyase activity, acetyl-CoA concentration, and enhancing the acetylation of histones. A key mediator of mitochondrial biogenesis, including peroxisome proliferator-activated receptor gamma coactivator 1 alpha coactivator-1α, seems to be upregulated by exercise in T2DM. This factor positively modulates the skeletal muscle mitochondrial biogenesis, which improves energy metabolism and glucose homeostasis, inhibiting or delaying insulin resistance and further T2DM.

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic condition defined by above-normal glycemic levels caused first by insufficient insulin action in target tissues and more advanced stages of the reduction of insulin synthesis [1]. T2DM has recently reached dangerous global rates, with an approximate global incidence of 8.4%, or 451 million individuals in 2018. This figure is expected to rise to 693 million patients by 2045 [2].

Unhealthy eating habits and sedentarism are modifiable risk factors that highly induce overweight and obesity. High concentrations of triglyceride lipase (TGL) in adipocytes lead to inflammation in tissues because of macrophage migration into fat tissues [3]. This inflammatory condition induces alterations in cellular metabolism and mitochondrial homeostasis, which affects glucose uptake, leading to resistance to insulin [4], [5].

Dysfunction of mitochondria induces the increase of oxidative stress, which is substantially linked to T2DM as well as insulin resistance. Over the past decades, it has been indicated that the molecular mechanisms underlying T2DM are epigenetic modifications, usually associated with lifestyle and alterations in gene expression modulating mitochondrial homeostases [6], such as myocyte enhancer factor-2 (MEF2), mitochondrial transcription factor (TFAM), and nuclear respiratory factor 1 (NRF1), as well as peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC1α) [7]. Mitochondrial biogenesis is substantially regulated by a signaling pathway and depends on proteins transcribed in the cell nucleus and transported to mitochondria. Down regulation of PGC1α has been related to the development of insulin resistance in skeletal striated muscle [8], [9]. The expression of PGC1α is lower in the skeletal muscle of individuals with T2DM than in healthy individuals [10].

Numerous epidemiological investigations have linked the positive impact of physical exercise in the regulation of metabolic illnesses for decades [11], [12]. These studies have shown that exercise alleviates

low-density lipoprotein as well as TGL and elevates high-density lipoprotein, which is an efficient molecule in the removal of cellular cholesterol [13]. Moreover, the inflammatory process of tissues resulting from lipid deposition and oxidative stress can be attenuated by physical exercise [14].

Because epigenetic changes are reversible and possibly tempting to pharmaceutical research aimed at the regulation of metabolic illnesses, there has been a growing interest in evaluating them. The present review attempts to categorize scientific as well as academic research on histone epigenetic modifications, homeostasis, and mitochondrial biogenesis impairment found in T2DM, culminating in changes in the metabolic characteristics of this pathology and the potential effects of exercise to reverse these changes.

Methods

This review presents a synthesis of studies from the past decade that evaluated the relationship between epigenetic modifications and T2DM and physical exercise effect on histone epigenetic alternations of gene expression associated with the regulation of cell metabolism. The recommended report items for meta-analysis (PRISMA), as well as systematic review procedures, were utilized [15]. Animal and human clinical and laboratory research, as well as non-randomized trials, were included in the study. Studies with a pharmacological intervention focused on other metabolic pathways or that evaluated epigenetic modifications in pathologies not related to metabolic syndrome were excluded from the study. The articles published in the interval between 2009 and 2020 in the MEDLINE database (PubMed) were included in the study, yielding 1237 articles, reaching 162 papers after analyzing the inclusion criteria. Finally, 68 articles were included as per the flow chart in Figure 1 [15].

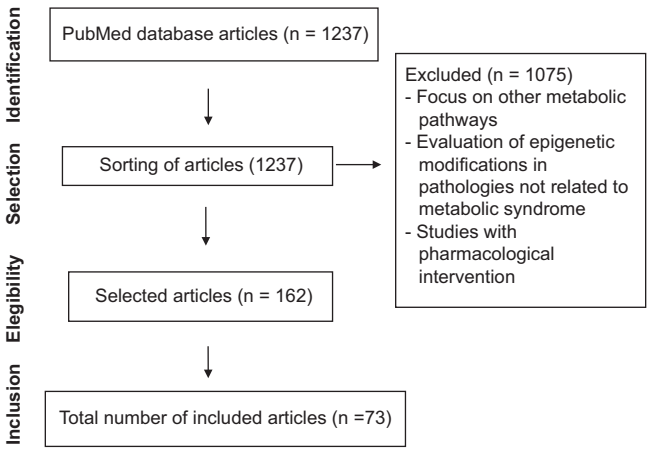

Figure 1: Schematic diagram of article selection according to Prism methodology

Discussion

Histones and epigenetic modifications

Because they mediate related-chromatin proteins' recruitment, reversible alterations in histone structure are critical for modulating the connection between histone as well as DNA. Four types of histones involve nuclear DNA. H2A, H2B, H3, and H4 histones are involved in nuclear DNA and are crucial for genome structure when changed following translation, affecting chromatin and hence gene expression [16]. This structural structure is integrally engaged in all DNA-related functions such as DNA repair, transcription, and replication [17].

Because of several of these alterations, histones' N terminal structure affects their connection with DNA. Adding the acetyl group to these amino acids neutralizes their positive charges. This mechanism reduces the bond between DNA phosphate groups as well as histones, causing chromatin to relax. Acetylated chromatin areas are often linked with active transcription. Hypo acetyl areas, on the contrary, make chromatin thicker and contribute to a less active transcription process. Histone acetyltransferases (HAT) is the key enzyme for catalyzing acetyl group loading from histones, whereas histone deacetylase (HDAC) is responsible for removing these acetyl groups (Figure 2) [17].

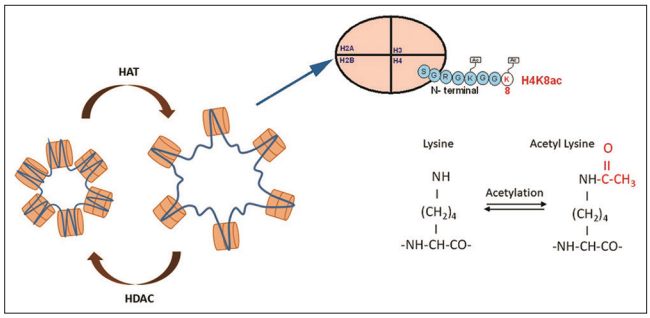

Figure 2: Acetylation of histone 4-lysine 8 by the addition of an acetyl group in the positively charged amino acid residues in the N-terminal portion of the histone, catalyzed by the enzyme histone acetyl transferase that weakens the histone DNA bond, and thus relaxing chromatin and increasing transcription. The deacetylation promoted by the enzyme histone deacetylase will result in reduced transcription

Aside from deacetylation as well as acetylation, there is histone methylation (Figure 3), a process in which terminal areas such as lysine (K) may be methylated once, twice, or three times, resulting in activating specific gene phenotypes and suppressing others. The monomethylated (H3K9me) histone 3 lysine 9 results in activated expression, whereas double or triple methylation, stimulates gene expression suppression [18].

Oxidative stress, inflammation, and histone acetylation

T2DM is induced by insulin action or secretion defects in peripheral tissues. Contributing factors

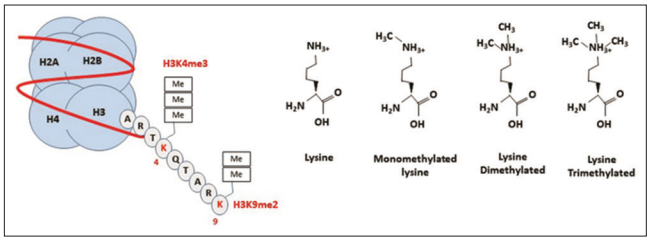

Figure 3: Methylation of histone 3 lysine 9 and histone 3 lysine 4 histones. Mono, di, or trimethyllation of the amino acids methyl group (-CH3) can occur in the N-termin waste. Monomethylation and trimethylation of H3K4me result in increased expression, while di and trimethylation results and silencing of gene expression

such as poor eating habits, obesity, and sedentarism, obesity was proven as causes of oxidative stress and inflammatory processes, as well as accumulating fat tissues [19], [20], [21], which can evolve into insulin resistance and T2DM. Following a high-fat diet (HFD) and/or elevated body weight, mostly adipose tissue causes elevated reactive species of oxygen (ROS) secretion. The exacerbated oxidative stress as well as activated proinflammatory cytokines, including TNF-α, IL6, and IL1, impede insulin signaling through suppressing PI3K as well as the signal transducer and activator of transcription 3 [22]. The associations between ROS and the inflammatory process are usually intensified in T2DM and trigger local and systemic chronic inflammation [23]. Prattichizzo *et al*. illustrated the inflammation impact on T2DM progression; even in a non-obese population with poor dietary habits, the induced inflammatory process might lead to epigenetic alternations associated with metabolic diseases, such as T2DM. In addition, they propose that intervention through antioxidants and physical exercise can be the optimum method to alleviate the inflammation-induced process as well as oxidative stress that results in T2DM [24].

ROS is generated endogenously through mitochondria respiration and exogenous oxidizing agents and affects a wide range of biological processes through various mechanisms [25]. Different hypotheses have been proposed regarding the responses of the components that can affect epigenetic machinery, such as HDACs and HATs classes. Few prior investigations focus on oxidative stress and inflammation impact on such epigenetic modifications in skeletal muscle [26]. In other tissues, there is evidence of the effect of chronic oxidative stress modulating the pattern of epigenetic modifications to histones. A clinical study with adipocytes of normal-weight, obese, diabetic, or non-diabetic showed that T2DM and overweight are associated with global epigenetic modifications of histones, including the trimethylation of histone 3 lysine 4 (H3K4me3) and di-methylation of histone 3 lysine 4 (H3K4me2), damaging the metabolic homeostasis. H3K4me3 was 40 percent more elevated in overweight and diabetic individuals' adipocytes than in overweight as well as average-weight non-diabetics. H3K4me2 level was 37% lower in overweight individuals' adipocytes compared to average weight. By comparing the overweight cohort (T2DM as well as non-diabetic) individuals, the H3K4me2 level was substantially diminished compared to normal-weight individuals' adipocytes [27]. In another study on mice oocytes, Bisphenol AF (BPAF), commonly used in industrial products such as cans and plastic, was shown to consistently increase ROS associated with histones modifications, methylation, and acetylation. In addition, it was observed decreased expression of H3K9me3 and H3K27ac caused by BPAF exposure and mediated by extensive oxidative stress [28].

Therefore, analysis of the effect of oxidative stress associated with systemic inflammations on methylation or acetylation patterns of histones in skeletal muscle with T2DM contributes to interpreting the detrimental effect of this deregulation on the epigenetic mechanisms that cause T2DM and comorbidity development [29], [30]. When cellular ROS increases, the compensatory response of mitochondria is increased biogenesis mediated by PGC1α, a regulatory factor related to mitochondrial biogenesis that modulates antioxidant defense expression in cells. PGC1 α elevates MnSOD/SOD2 and catalase levels, preventing cellular death related to the failure of mitochondria. Nevertheless, PGC1α levels are downregulated under inflammatory conditions, resulting in an enhanced inflammatory response, allowing inflammatory infiltration in the cells [31].

In fact, in chronic diseases, such as T2DM, it has been described to reduce the expression of PGC1α and increase inflammatory response [32], [33]. Furthermore, PGC1 α expression is reduced in aging muscles and linked to systemic inflammations in mice [34] and humans [24], [29], [30]. Besides, PGC1α translocation from cytosol to the mitochondria has been demonstrated to be modulated by AMPK, as illustrated by Smith *et al*. (2013) that in humans, mice, and rat translocations of PGC1α to the mitochondria, stimulated by muscle contraction, we are dependent on AMPK activation [35]. Consequently, it can be hypothesized that AMPK could be a correlation between metabolic status in diabetes and biogenesis.

AMPK is a significant energy sensor that contributes to cellular energy homeostasis. The inhibition or reduction of mitochondrial function leads to diminished ATP as well as elevated ADP and AMP activation AMPK. Hence, AMPK maintains metabolic energy balance, triggering the production of energy as well as suppressing the processes consuming energy. In energy metabolism, AMPK inhibits glucose synthesis and stimulates hepatic fatty acid oxidation and ketogenesis, stimulates the oxidation of fatty acids, glucose uptake, inhibition of cholesterol, and triacylglycerol synthesis. In adipocytes, it inhibits lipolysis and lipogenesis and modulates pancreatic insulin secretion [36]. In people as well as animals with

metabolic syndrome and T2DM, it is evident that AMPK activity is impaired. On the contrary, the physiological or pharmacological activations of AMPK can improve insulin sensitivity and metabolic homeostasis [37]. Besides, in ROS-activated biogenesis mitochondria, the activation of AMPK is required for PGC1α transcription in skeletal muscle [38].

Regarding the link between AMPK and mitochondrial biogenesis, the AMPK translocates from the cytoplasm to the nuclei, promoting the regulation of transcription through histone acetylation, activating particular HAT and therefore triggering acetylation of histone as well as PGC1α transcription. In addition, nuclear AMPK might induce phosphorylation of HDAC and HDAC4, as well as HDAC5, eliciting their transportation from nuclei and consequently triggering the reactions of histone acetylation through the inhibition of HDAC.

The activation of AMPK might raise the acetyl CoA level as well through cholesterol syntheses and fatty acid suppression [39]. In this way, the histone acetylation or deacetylation depends on coenzyme metabolism, responding to the metabolic status because acetyl-CoA is used as a building block for lipid acetylation as well as synthesis [40], [41]. In mammalian cells, the major carbon source is glucose; thus, Acetyl-CoA secretion can occur through glucose by the enzyme ATP-citrate lyase (ACL), which triggers mitochondrial-derived citrate conversion into acetyl-CoA as well as oxaloacetate [42]. ACL in skeletal muscle contributes to homeostasis and mitochondrial biogenesis and enhances mitochondrial respiration [43].

Wellen *et al*. (2009) showed that ACL is a primary acetyl-CoA source for overall histone acetylation in many mammalian cell types under normal growth circumstances and may be directly connected to the pool of citrate-derived acetyl-CoA generated by ACL. Furthermore, silencing ACL or HAT (GCN5) resulted in a substantial decrease in histones H4, H3, and H2B acetylation and the diminished overall histone acetylation detected when lowering ACL silenced through inhibiting HDACs. As a result, in the absence of significant histone deacetylation, ACL activity has a less effect on core histones' net acetylation. Other important findings of the group were that under intracellular glucose deprivation conditions, such as in T2DM, the oxidation of fatty acids leads to mitochondrial acetyl-CoA production, but not nucleocytoplasmic acetyl-CoA. Similarly, supplying cells with fatty acids did not promote histone acetylation, leading the authors to conclude that only nucleocytoplasmic acetyl-CoA is available to be involved in the acetylation of histones [44]. Acetyl-CoA produced from the oxidation of fatty acids as well as pyruvate oxidation in the mitochondria cannot diffuse across phospholipid membranes, and mitochondrial citrate is transferred from the tricarboxylic acid cycle to the nucleus and cytosol through the citrate transporter. Nucleocytosolic citrate is subsequently reconverted to acetyl-CoA ACL and employed in histone acetylation processes [45]. Furthermore, the glucose transporter type 4 (GLUT4) expression was reduced by acetylating histones H4 and H3 at the GLUT4 promoter and remarkably diminished when ACL was silenced and may be restored by acetate [44].

Aside from the effects of AMPK and Acetyl-CoA on HAT, HDAC inhibitors can modulate the expression of genes expression through suppressing histone deacetylation and were found to have anti-diabetic as well as anti-obesity properties. Lee *et al*. (2020) demonstrated the molecular mechanism characterizing the protective impact of class I HDAC suppression under lipotoxic conditions on the tissues of skeletal muscle in mice fed HFD and increased fructose drinking water compared to control results. The used diet elevated the protein expression of HDAC3, in addition to impairing the oxidation of mitochondria, inducing elevated mitochondrial ROS secretion as well as accumulated TG. Besides, extended exposure promoted elevated expression of insulin resistance as well as inflammatory cytokines, while a Class I HDAC inhibitor substantially diminished lipotoxicity, restricting the expression of inflammatory cytokines and insulin resistance, along with increased expression of PGC1α and TFAM, restoring mitochondrial biogenesis [46].

Figure 4 demonstrates a schematic model of oxidative stress impact associated with the inflammatory process [47] AMPK activity and acetyl CoA concentration reduced in the cytoplasm, common in T2DM disease, on histone acetylation processes, leading to impairment in the mitochondrial biogenesis through deregulation of HAT and HDAC activity [48], [49]. This process damages histone acetylation and may affect the mitochondrial biogenesis cascade's gene transcription and regulatory factors, such as PGC1α [39], [42]. In contrast, ROS concentration balance improves the HAT activity leading to the transcription these factors as well as genes.

Physical exercise, oxidative stress, and inflammation

ROS levels rise in response to physical exertion, triggering intracellular alterations. The amount of ROS produced is determined by the intensity, duration, and kind of physical activity done. Nonetheless, tissue damage induced by exercise promotes various processes for healing the damaging tissues as well as skeletal muscle. Exercising regularly causes a physiologic adaptation through the activation of the antioxidant mechanism mediated by hydrogen peroxide (H_2O_2) and superoxide (O_2^-) that triggers the activation of the catalase (CAT) of the antioxidant system, superoxide dismutase of manganese (MnSOD), and glutathione peroxidase (GPx), as well as enzyme superoxide dismutase (SOD). These enzymes donate electrons or atoms to the ROS and become stable

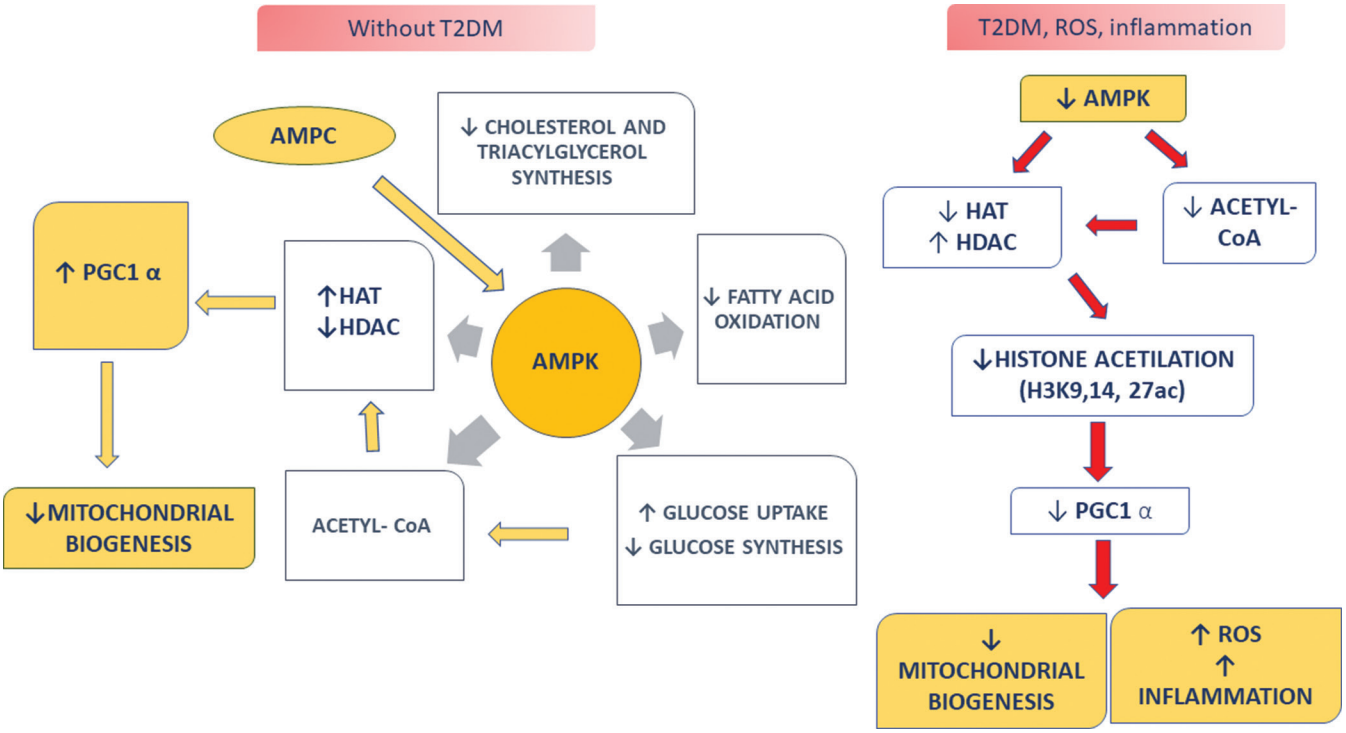

Figure 4: The effect of type 2 diabetes mellitus, oxidative stress, and inflammation on histones (H3K9, H3K14 e H3K27) acetylation. (a) In the subject without type 2 diabetes mellitus, AMP-activated protein kinase (AMPK) activity is normally regulated, thus it stimulates energy metabolism, inhibits glucose synthesis, and stimulates hepatic fatty acid oxidation and ketogenesis. AMPK stimulates fatty acid oxidation, glucose uptake, inhibition of cholesterol, and triacylglycerol synthesis. In adipocytes, it inhibits lipolysis and lipogenesis. AMPK also promotes the increased nucleocytoplasmic concentration of acetyl-CoA and makes it available to participate in the mechanism of histone acetylation. AMPK stimulates specific histone acetyltransferases (HAT), increasing histone acetylation and proliferator-activated receptor γ coactivator-1α (PGC1α) transcription. Moreover, nuclear AMPK can phosphorylate Type 2A histone deacetylases (HDACs) inhibiting it, supporting the histone acetylation, PGC1α transcription and mitochondrial homeostasis and biogenesis and (b) When T2DM is established, increased reactive oxygen species and inflammatory process are exacerbated, and there is a decline in AMPK activity and Acetyl-CoA available in the nucleocytoplasmic compartment, generated by ATP-citrate Lyase, this results in diminished HAT as well as elevated HDAC activity. Therefore, it results in reduced histones acetylation, PGC1 expression, and impaired mitochondrial homeostasis and biogenesis. Dysregulation of PGC-1α alters the redox homeostasis in cells and exacerbates inflammatory response. During inflammation, low levels of PGC-1α downregulate mitochondrial antioxidant gene expression, induce oxidative stress, and impair mitochondrial biogenesis

since they metabolize the ROS in excess and maintain homeostasis [50]. In addition, oxidative stress caused by long-term exercise results in the stimulation of stress-activated protein kinase (SAPK) signaling, which increases the expression of genes and coactivator transcription in the skeletal muscle like MEF2 and PGC1α [51].

Ristow *et al*. (2009) demonstrated the effect of increased stress caused by physical exercise on PGC1α expression in humans. In the study, they were included 20 subjects previously trained and 20 untrained. About 50% of the previously trained and untrained received antioxidant supplementation (ascorbic acid and Vitamin E), and all subjects practiced physical exercise for 4 weeks. Physical exercise improved insulin resistance by elevating ROS mitochondrial formation in skeletal muscle to promote the expression of PGC1α and SOD, and GPx. Furthermore, antioxidant supplements blocked the exercise-dependent formation of reactive oxygen species and the metabolic health effects of physical exercise [52].

Besides the impact of moderate long-term physical exercise in reducing oxidative stress, physical exercise also has beneficial effects on the inflammatory process. Several epidemiologic investigations reveal that increased physical activity effectively reduces low-level systemic inflammation in metabolic syndrome, diabetes, and obesity, in addition to healthy people [53], [54], [55], [56]. However, the effects of intensity, duration, and the kind of physical exercise are still controversial. Prolonged high-intensity exercise has been demonstrated to cause muscle damage and increased inflammation-markers as IL6 and neutrophils and macrophages infiltrating. Nevertheless, moderate regular physical exercise can induce physiological adaptation and promote an anti-inflammatory phenotype, including an increased PGC1α expression in skeletal muscle, an important initial mechanism involved in mitochondrial adaptations to physical exercise, coordinated by increased activation of AMPK [57], [58], [59].

AMPK activity increases in skeletal muscle with heavy exercise, and a reduced ATP/ADP ratio simultaneously increases AMPC, and this can occur either by inhibiting ATP production or by accelerating ATP consumption mediated by physical exercise [59]. In the mitochondria, the increased AMPK function stimulates

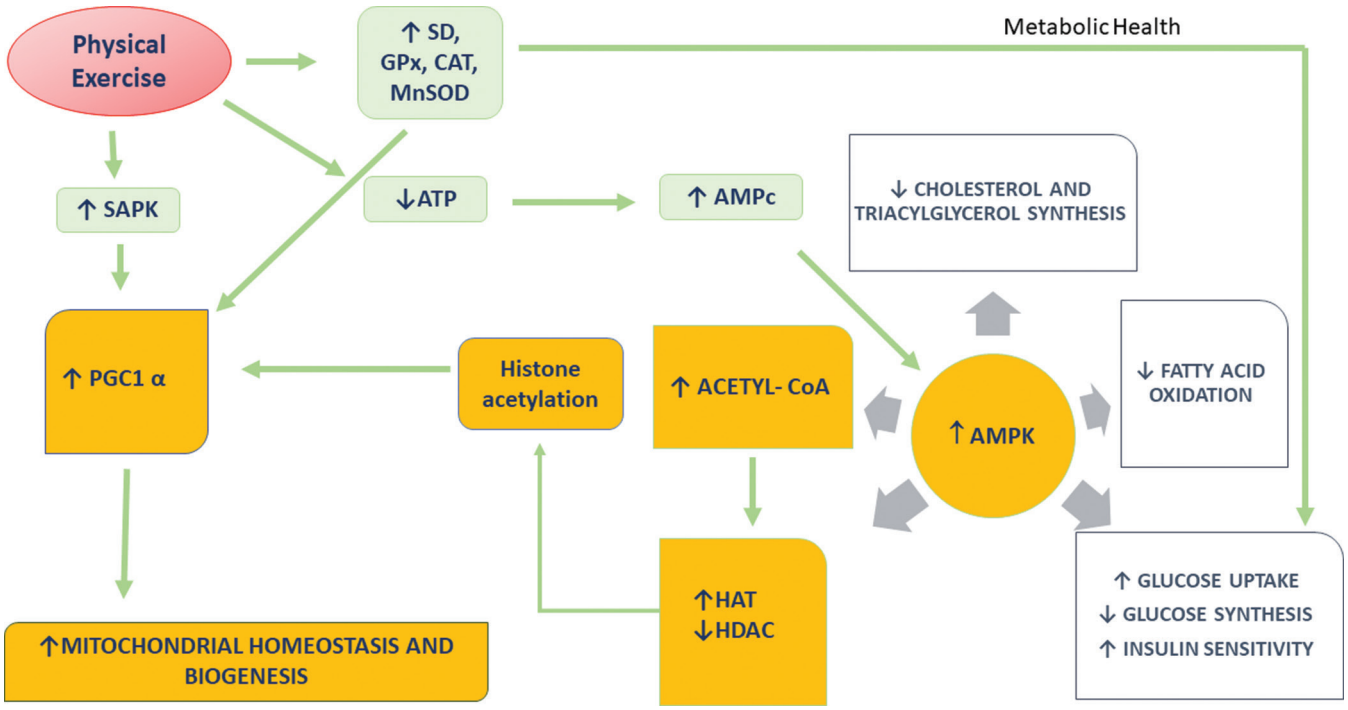

Figure 5: Mechanism in which regular exercise can improve the biogenesis and mitochondrial homeostasis in the skeletal muscle. Exercise elevates oxidative stress that triggers the physiological adaptation, producing enzymes of the antioxidant system, such as superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT) and superoxide dismutase of manganese, CAT, and stress-protein kinase (SAPK) of the antioxidant system that reduces reactive species of oxygen. SOD, GPx, and SAPK increase insulin sensitivity and proliferator-activated receptor γ coactivator-1α (PGC1α) expression. Reduced ATP/ADP ratio increases intracellular AMPc that activates AMP-activated protein kinase (AMPK). AMPK enhances histone acetyltransferases activity and histones acetylation. AMPK also stimulates ATP-citrate lyase that increases Acetyl-CoA concentration, providing acetate to the histone acetylation. Increased histone acetylation enhances de PGC1α expression and mitochondrial biogenesis and homeostasis

the PGC1α expression and the signaling cascade, such as increased NRF1 and TFAM expression that culminates with mitochondrial biogenesis [60], [61].

Besides increasing AMPK activity, exercise can increase skeletal muscle acetyl-CoA levels through the effect of contraction on calcium-calmodulin/dependent protein kinase CaMKK [62], which activates AMPK. Therefore, AMPK can enhance ACL activity [59]. However, the ACL functions in skeletal muscle mediated by physical exercise are poorly understood. Figure 5 demonstrates a schematic drawing of the effects of physical exercise.

Epigenetic modifications and physical exercise in histones

Several scientific studies have been conducted in recent decades to investigate the impact of epigenetic

Table 1: Types of physical activity

Reference	Type of physical activity	Tissue/Experimental model	Biogenesis/Signalling	Effect on histones	Metabolic effect
McGee *et al.* [65]	Acute exercise, 60-min cycling session	Vast side muscle/ humans	RNApol II active; MPK and CaMK II activated. HDAC class II (4 and 5) exported from the core.	↑ H3K36ac	H3K36ac increases transcriptional activity. HDAC class II (4 and 5) exported from the core by activation of AMPK and CaMKII, prevents the suppression of acetylation.
Lochmann *et al.* [18]	Acute exercise, race for 60 min, being: 35 rpm/20 min; 40 rpm/30 min; 45 rpm/10 min	Quadriceps muscle/ mice	↑ Total PGC1α expression and isoforms	↑ H3K4me3 at the place where the transcription begins	↑ Mitochondrial biogenesis and oxidative metabolism
Joseph *et al.* [66]	Short-term exercise, 15 days of swimming	Gastrocnemius muscle/ Wistar rats	CaMKII activation. ↑ NRF1 and MEF2	↑ H3 acetylation at the NRF1 gene site	↑ Transport and capture of glucose
Masuzawa *et al.* [67]	Acute exercise, running: 24 m/min for 20 min	Plant and soleus muscles/Wistar rats	↑ mRNA expression from PGC1 2 h after the race	↑ H3K27ac or↑RNA pol II	Activation of the transcription of PGC1α in the rapidly contracting muscle fibers due to increased mobility of H3k27ac-induced RNApol II, improving oxidative metabolism
Ohsawa *et al.* [64]	Long-term exercise, Running: Group 1: 30 min/day, 4 days/ week, 8 weeks; Group 2: 15 min/day, 4 days/ week, 8 weeks; Group 3: 60 min/day, 4 days/ week, and 4 weeks	Plant muscle/Wistar rats	↑ citrate activity synthase in group 3	Variations in the acetylation of H3 and H4K20me3 between groups	↑ H3 and↓H4K20me3 acetylation in group 1, without stimulation of mitochondrial metabolism. An increase in the daily amount of exercise, group 3, caused a slight increase in mitochondrial metabolism.

PGC1α: Peroxisome proliferator-activated receptor γ coactivator-1α, NRF1: nuclear respiratory factor 1, MEF2: myocyte enhancer factor-2, HDAC: Histone deacetylase, AMPK: AMP-activated protein kinase.

changes induced by physical activity. Physical exercise contributes to extrapolating generations, maintaining health, and improving metabolic offspring [63]. Despite the reported promising effects of acute exercise presented in Table 1, we assumed that chronic exercise adaptation must be examined in an attempt to comprehend physical exercise's molecular impacts on epigenetic changes.

Among the analyzed articles (Table 1), Ohsawa *et al*. [64] assessed the impact of long-term physical activity (Table 1), while the other research investigated its impacts on the skeletal muscle following one session of exercising [18], [65], [66], [67] or a short exercise interval (15 days). All studies indicated an enhancement in mitochondrial biogenesis-related functions such as activation of gene transcription, glucose uptake, and oxidative metabolism. This impact was mediated by epigenetic alterations such as acetylation of H3K36ac histones as well as methylation of H3K4me3 histones, demonstrating the underlying processes of enhanced T2DM metabolic regulation.

Conclusion

PGC1α expression control maintains a strong association with mitochondrial function, being essential in mitochondrial biogenesis and avoiding the metabolic deregulation related to T2DM. Physical exercise can reverse the epigenetic modifications found in T2DM, stimulating the expression of PGC1α, mediated by increased histone acetylation and transcriptional activity. The mechanisms underlying histone acetylation seem to be related to oxidative stress, the systemic inflammatory process, and the metabolic state of cells. Exacerbated oxidative stress and inflammatory processes common in T2DM impair cell signaling processes related to mitochondrial biogenesis, for example, reducing the activation of AMPK and the concentration of Acetyl-CoA. The stimulus for the expression of PGC1 is impaired. Long-term physical exercise stimulates physiological adaptation by synthesizing antioxidants, reducing the inflammatory process, and increasing ATP expenditure, which will cause increased AMPK activity. Increased AMPK stimulates histone acetylation and Acetyl-CoA concentration, which is a substrate for the activity of HAT to histones acetylation, resulting in an enhanced expression of PGC1α. However, investigations on the long-term impact of physical activity are fundamental to interpreting the comprehensive mechanism, which is the best types, frequency, and duration that have the most significant potential to induce increased mitochondrial biogenesis.

Declarations

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Hooper PL, Balogh G, Rivas E, Kavanagh K, Vigh L. The importance of the cellular stress response in the pathogenesis and treatment of Type 2 diabetes. Cell Stress Chaperones. 2014;19(4):447-64. https://doi.org/10.1007/s12192-014-0493-8
   PMid:24523032
2. Cho NH, Shaw JE, Karuranga S, Huang Y, Fernandes JD, Ohlrogge AW, *et al*. IDF diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract. 2018;138:271-81. https://doi.org/10.1016/j.diabres.2018.02.023
   PMid:29496507
3. Milagro FI, Mansego ML, De Miguel C, Martínez JA. Dietary factors, epigenetic modifications and obesity outcomes: Progresses and perspectives. Mol Aspects Med. 2013;34(4):782-812. https://doi.org/10.1016/j.mam.2012.06.010
   PMid:22771541
4. Benite-Ribeiro SA, Putt DA, Santos JM. The effect of physical exercise on orexigenic and anorexigenic peptides and its role on long-term feeding control. Med Hypotheses. 2016;93:30-3. https://doi.org/10.1016/j.mehy.2016.05.005
   PMid:27372853
5. Benite-Ribeiro SA, Rodrigues VA, Machado MR. Food intake in early life and epigenetic modifications of pro-opiomelanocortin expression in arcuate nucleus. Mol Biol Rep. 2021;48(4):3773-84. Available from: https://www.link.springer.com/10.1007/s11033-021-06340-x [Last accessed on 2021 Oct 20].
6. Santos JM, Moreli ML, Tewari S, Benite-Ribeiro SA. The effect of exercise on skeletal muscle glucose uptake in Type 2 diabetes: An epigenetic perspective. Metabolism. 2015;64(12):1619-28. https://doi.org/10.1016/j.metabol.2015.09.013
   PMid:26481513
7. Stepto NK, Benziane B, Wadley GD, Chibalin AV, Canny BJ, Eynon N, *et al*. Short-term intensified cycle training alters acute and chronic responses of pgc1α and cytochrome C oxidase IV to exercise in human skeletal muscle. PLoS One. 2012;7(12):e53080. https://doi.org/10.1371/journal.pone.0053080
   PMid:23285255
8. Santos JM, Tewari S, Benite-Ribeiro SA. The effect of exercise on epigenetic modifications of PGC1: The impact on Type 2 diabetes. Med Hypotheses. 2014;82(6):748-53. https://doi.org/10.1016/j.mehy.2014.03.018
   PMid:24703492
9. Santos JL, Krause BJ, Cataldo LR, Vega J, Salas-Pérez F, Mennickent P, *et al*. PPARGC$_1$A gene promoter methylation as a biomarker of insulin secretion and sensitivity in response to glucose challenges. Nutrients. 2020;12(9):2790. https://doi.org/10.3390/nu12092790
   PMid:32933059

10. Cao S, Li B, Yi X, Chang B, Zhu B, Lian Z, *et al*. Effects of exercise on AMPK signaling and downstream components to PI3K in rat with Type 2 diabetes. PLoS One. 2012;7(12):e51709. https://doi.org/10.1371/journal.pone.0051709
    PMid: 23272147
11. Barrón-Cabrera E, Ramos-Lopez O, González-Becerra K, Riezu-Boj JI, Milagro FI, Martínez-López E, *et al*. Epigenetic modifications as outcomes of exercise interventions related to specific metabolic alterations: A systematic review. Lifestyle Genom. 2019;12(1-6):25-44. https://doi.org/10.1159/000503289
    PMid:3154624
12. Di Liegro I. Genetic and epigenetic modulation of cell functions by physical exercise. Genes(Basel). 2019;10(12):1043. https://doi.org/10.3390/genes10121043
    PMid:31888150
13. Søndergaard E, Poulsen MK, Jensen MD, Nielsen S. Acute changes in lipoprotein subclasses during exercise. Metabolism. 2014;63(1):61-8. https://doi.org/10.1016/j.metabol.2013.08.011
    PMid:24075739
14. Pinto PR, da Silva KS, Iborra RT, Okuda LS, Gomes-Kjerulf D, Ferreira GS, *et al*. Exercise training favorably modulates gene and protein expression that regulate arterial cholesterol content in CETP transgenic mice. Front Physiol. 2018;9:502. https://doi.org/10.3389/fphys.2018.00502
    PMid:29867549
15. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med. 2009;6(7):e1000097. https://doi.org/10.1371/journal.pmed.1000097
    PMid:19621072
16. Karlić R, Chung HR, Lasserre J, Vlahoviček K, Vingron M. Histone modification levels are predictive for gene expression. Proc Natl Acad Sci U S A. 2010;107(7):2926-31. https://doi.org/10.1073/pnas.0909344107
    PMid:20133639
17. Lochmanová G, Ihnatová I, Kuchaříková H, Brabencová S, Zachová D, Fajkus J, *et al*. Different modes of action of genetic and chemical downregulation of histone deacetylases with respect to plant development and histone modifications. Int J Mol Sci. 2019;20(20):5093. https://doi.org/10.3390/ijms20205093
    PMid:31615119
18. Lochmann TL, Thomas RR, Bennett JP, Taylor SM. Epigenetic modifications of the PGC-1α promoter during exercise induced expression in mice. PLoS One. 2015;10(6):e0129647. https://doi.org/10.1371/journal.pone.0129647
    PMid:26053857
19. De Souza CT, Araujo EP, Bordin S, Ashimine R, Zollner RL, Boschero AC, *et al*. Consumption of a fat-rich diet activates a proinflammatory response and induces insulin resistance in the hypothalamus. Endocrinology. 2005;146(10):4192-9. https://doi.org/10.1210/en.2004-1520
    PMid:16002529
20. Abraham NG, Brunner EJ, Eriksson JW, Robertson RP. Metabolic syndrome: Psychosocial, neuroendocrine, and classical risk factors in Type 2 diabetes. Ann N Y Acad Sci. 2007;1113:256-75. https://doi.org/10.1196/annals.1391.015
    PMid:17513461
21. Eriksson JW. Metabolic stress in insulin's target cells leads to ROS accumulation - A hypothetical common pathway causing insulin resistance. FEBS Lett. 2007;581(19):3734-42. https://doi.org/10.1016/j.febslet.2007.06.044
    PMid:17628546
22. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest. 2003;112(12):1796-808. https://doi.org/10.1172/JCI19246
    PMid:14679176
23. Oguntibeju OO. Type 2 diabetes mellitus, oxidative stress and inflammation: Examining the links. Int J Physiol Pathophysiol Pharmacol. 2019;11(3):45-63.
    PMid:31333808
24. Prattichizzo F, De Nigris V, Spiga R, Mancuso E, La Sala L, Antonicelli R, *et al*. Inflammageing and metaflammation: The yin and yang of Type 2 diabetes. Ageing Res Rev. 2018;41:1-17. https://doi.org/10.1016/j.arr.2017.10.003
    PMid:29081381
25. Liu Y, Hernández-Ochoa EO, Randall WR, Schneider MF. NOX_2-dependent ROS is required for $HDAC_5$ nuclear efflux and contributes to $HDAC_4$ nuclear efflux during intense repetitive activity of fast skeletal muscle fibers. Am J Physiol Cell Physiol. 2012;303(3):334-47. https://doi.org/10.1152/ajpcell.00152.2012
    PMid:22648949
26. Whetstine JR, Nottke A, Lan F, Huarte M, Smolikov S, Chen Z, *et al*. Reversal of histone lysine trimethylation by the $JMJD_2$ family of histone demethylases. Cell. 2006;125(3):467-81. https://doi.org/10.1016/j.cell.2006.03.028
    PMid:16603238
27. Jufvas Å, Sjödin S, Lundqvist K, Amin R, Vener A, Strålfors P. Global differences in specific histone H_3 methylation are associated with overweight and Type 2 diabetes. Clin Epigenetics. 2013;5(1):15. https://doi.org/10.1186/1868-7083-5-15
    PMid:24004477
28. Ding ZM, Jiao XF, Wu D, Zhang JY, Chen F, Wang YS, *et al*. Bisphenol AF negatively affects oocyte maturation of mouse *in vitro* through increasing oxidative stress and DNA damage. Chem Biol Interact. 2017;278:222-9. https://doi.org/10.1016/j.cbi.2017.10.030
    PMid:29102535
29. Luc K, Schramm-Luc A, Guzik TJ, Mikolajczyk TP. Oxidative stress and inflammatory markers in prediabetes and diabetes. J Physiol Pharmacol. 2019;70(6):809-24. https://doi.org/10.26402/jpp.2019.6.01
    PMid:32084643
30. Karachanak-Yankova S, Dimova R, Nikolova D, Nesheva D, Koprinarova M, Maslyankov S, *et al*. Epigenetic alterations in patients with Type 2 diabetes mellitus. Balkan J Med Genet. 2015;18(2):15-24. https://doi.org/10.1515/bjmg-2015-0081
    PMid:27785392
31. Rius-Pérez S, Torres-Cuevas I, Millán I, Ortega ÁL, Pérez S, Sandhu MA. PGC-1 α, inflammation, and oxidative stress: An integrative view in metabolism. Oxid Med Cell Longev. 2020;2020:1452696. https://doi.org/10.1155/2020/1452696
    PMid:32215168
32. Patti ME, Butte AJ, Crunkhorn S, Cusi K, Berria R, Kashyap S, *et al*. Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: Potential role of PGC1 and NRF1. Proc Natl Acad Sci. 2003;100(14):8466-71. https://doi.org/10.1073/pnas.1032913100
    PMid:12832613
33. Burgos-Morón E, Abad-Jiménez Z, Marañón AM, Iannantuoni F, Escribano-López I, López-Domènech S, *et al*. Relationship between oxidative stress, Er stress, and inflammation in Type 2 diabetes: The battle continues. J Clin Med. 2019;8(9):1385. https://doi.org/10.3390/jcm8091385
    PMid:31487953
34. Sczelecki S, Besse-Patin A, Abboud A, Kleiner S, Laznik-Bogoslavski D, Wrann CD, *et al*. Loss of Pgc-1α expression in aging mouse muscle potentiates glucose intolerance and systemic inflammation. Am J Physiol Endocrinol

Metab. 2014;306(2):157-67. https://doi.org/10.1152/ajpendo.00578.2013
PMid:24280126

35. Smith BK, Mukai K, Lally JS, Maher AC, Gurd BJ, Heigenhauser GJ, *et al*. AMP-activated protein kinase is required for exercise-induced peroxisome proliferator-activated receptor γ coactivator 1α translocation to subsarcolemmal mitochondria in skeletal muscle. J Physiol. 2013;591(6):1551-61. https://doi.org/10.1113/jphysiol.2012.245944
PMid:23297307
36. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia. 2017;60(9):1577-85. https://doi.org/10.1007/s00125-017-4342-z
PMid:28776086
37. Coughlan KA, Valentine RJ, Ruderman NB, Saha AK. Diabetes, metabolic syndrome and obesity: Targets and therapy dovepress AMPK activation: A therapeutic target for Type 2 diabetes? Diabetes Metab Syndr Obes. 2014;7:241-53. https://doi.org/10.2147/DMSO.S43731
PMid:25018645
38. Irrcher I, Ljubicic V, Hood DA. Interactions between ROS and AMP kinase activity in the regulation of PGC-1α transcription in skeletal muscle cells. Am J Physiol Cell Physiol. 2009;296(1):C116-23. https://doi.org/10.1152/ajpcell.00267.2007
PMid:19005163
39. Salminen A, Kauppinen A, Kaarniranta K. AMPK/Snf1 signaling regulates histone acetylation: Impact on gene expression and epigenetic functions. Cell Sign. 2016;28(8):887-95. https://doi.org/10.1016/j.cellsig.2016.03.009
PMid:27010499
40. Teperino R, Schoonjans K, Auwerx J. Histone methyl transferases and demethylases; can they link metabolism and transcription? Cell Metab. 2010;12(4):321-7. https://doi.org/10.1016/j.cmet.2010.09.004
PMid:20889125
41. Cohen HY, Miller C, Bitterman KJ, Wall NR, Hekking B, Kessler B, *et al*. Calorie restriction promotes mammalian cell survival by inducing the SIRT1 deacetylase. Science. 2004;305(5682):390-2. https://doi.org/10.1126/science.1099196
PMid:15205477
42. Takahashi H, McCaffery JM, Irizarry RA, Boeke JD. Nucleocytosolic acetyl-coenzyme A synthetase is required for histone acetylation and global transcription. Mol Cell. 2006;23(2):207-17. https://doi.org/10.1016/j.molcel.2006.05.040
PMid:16857587
43. Das S, Morvan F, Jourde B, Meier V, Kahle P, Brebbia P, *et al*. ATP citrate lyase improves mitochondrial function in skeletal muscle. Cell Metab. 2015;21(6):868-76. https://doi.org/10.1016/j.cmet.2015.05.006
PMid:26039450
44. Wellen KE, Hatzivassiliou G, Sachdeva UM, Bui TV, Cross JR, Thompson CB. ATP-citrate lyase links cellular metabolism to histone acetylation. Science. 2009;324(5930):1076-80. https://doi.org/10.1126/science.1164097
PMid:19461003
45. Choudhary C, Weinert BT, Nishida Y, Verdin E, Mann M. The growing landscape of lysine acetylation links metabolism and cell signalling. Nat Rev Mol Cell Biol. 2014;15(8):536-50. https://doi.org/10.1038/nrm3841
PMid:25053359
46. Lee SJ, Choi SE, Lee HB, Song MW, Kim YH, Jeong JY, *et al*. A class I histone deacetylase inhibitor attenuates insulin resistance and inflammation in palmitate-treated C_2C_{12} myotubes and muscle of HF/HFr diet mice. Front Pharmacol. 2020;11:601448. https://doi.org/10.3389/fphar.2020.601448
PMid:33362555
47. Tsalamandris S, Antonopoulos AS, Oikonomou E, Papamikroulis G, Vogiatzi G. Risk factors and cardiovascular disease prevention the role of inflammation in diabetes : Current concepts and future perspectives. Eur Cardiol Rev. 2019;14(1):50-9.
48. Khwairakpam AD, Banik K, Girisa S, Shabnam B, Shakibaei M, Fan L, *et al*. The vital role of ATP citrate lyase in chronic diseases. J Mol Med. 2020;98(1):71-95. https://doi.org/10.1007/s00109-019-01863-0
PMid:31858156
49. Lefort N, Glancy B, Bowen B, Willis WT, Bailowitz Z, De Filippis EA, *et al*. Increased reactive oxygen species production and lower abundance of complex I subunits and carnitine palmitoyltransferase 1B protein despite normal mitochondrial respiration in insulin-resistant human skeletal muscle. Diabetes. 2010;59(10):2444-52. https://doi.org/10.2337/db10-0174
PMid:20682693
50. Samjoo IA, Safdar A, Hamadeh MJ, Raha S, Tarnopolsky MA. The effect of endurance exercise on both skeletal muscle and systemic oxidative stress in previously sedentary obese men. Nutr Diabetes. 2013;3(9):e88. https://doi.org/10.1038/nutd.2013.30
PMid:24042701
51. Parker L, Shaw CS, Stepto NK, Levinger I. Exercise and glycemic control: Focus on redox homeostasis and redox-sensitive protein signaling. Front Endocrinol. 2017;8:87. https://doi.org/10.3389/fendo.2017.00087
PMid:2852949
52. Ristow M, Zarse K, Oberbach A, Klöting N, Birringer M, Kiehntopf M, *et al*. Antioxidants prevent health-promoting effects of physical exercise in humans. Proc Nat Acad Sci U S Am. 2009;106(21):8665-70. https://doi.org/10.1073/pnas.0903485106
PMid:19433800
53. Pischon T, Hankinson SE, Hotamisligil GS, Rifai N, Rimm EB. Leisure-time physical activity and reduced plasma levels of obesity-related inflammatory markers. Obes Res. 2003;11(9):1055-64. https://doi.org/10.1038/oby.2003.145
PMid:12972675
54. Beavers KM, Brinkley TE, Nicklas BJ. Effect of exercise training on chronic inflammation. Clin Chim Acta. 2010;411(11-12):785-93. https://doi.org/10.1016/j.cca.2010.02.069
PMid:20188719
55. Kondo N, Nomura M, Nakaya Y, Ito S, Ohguro T. Association of inflammatory marker and highly sensitive C-reactive protein with aerobic exercise capacity, maximum oxygen uptake and insulin resistance in healthy middle-aged volunteers. Circ J. 2005;69(4):452-7. https://doi.org/10.1253/circj.69.452
PMid:15791041
56. Jankord R, Jemiolo B. Influence of physical activity on serum IL-6 and IL-10 levels in healthy older men. Med Sci Sports Exe. 2004;36(6):960-4. https://doi.org/10.1249/01.mss.0000128186.09416.18
PMid:15179165
57. Metsios GS, Moe RH, Kitas GD. Exercise and inflammation. Best Pract Res Clin Rheumatol. 2020;34(2):101504. https://doi.org/10.1016/j.berh.2020.101504
PMid:32249021
58. Zong H, Ren JM, Young LH, Pypaert M, Mu J, Birnbaum MJ, *et al*. AMP kinase is required for mitochondrial biogenesis in skeletal muscle in response to chronic energy deprivation. Proc Nat Acad Sci U S Am. 2002;99(25):15983-7. https://doi.org/10.1073/pnas.252625599

PMid:12444247

59. Fujii N, Hayashi T, Hirshman MF, Smith JT, Habinowski SA, Kaijser L, *et al*. Exercise induces isoform-specific increase in 5' AMP-activated protein kinase activity in human skeletal muscle. Biochem Biophys Res Commun. 2000;273(3):1150-5. https://doi.org/10.1006/bbrc.2000.3073
PMid:10891387
60. Pilegaard H, Saltin B, Neufer DP. Exercise induces transient transcriptional activation of the PGC-1α gene in human skeletal muscle. J Physiol. 2003;546(3):851-8. https://doi.org/10.1113/jphysiol.2002.034850
PMid:12563009
61. Russell AP, Feilchenfeldt J, Schreiber S, Praz M, Crettenand A, Gobelet C, *et al*. Endurance training in humans leads to fiber Type-specific increases in levels of peroxisome. Diabetes. 2014;52(12):2874-81. https://doi.org/10.2337/diabetes.52.12.2874
PMid:14633846
62. Santos JM, Ribeiro SB, Gaya AR, Appell HJ, Duarte JA. Skeletal muscle pathways of contraction-enhanced glucose uptake. Int J Sports Med. 2008;29(10):785-94. https://doi.org/10.1055/s-2008-1038404
PMid:18401805
63. Axsom JE, Libonati JR. Impact of parental exercise on epigenetic modifications inherited by offspring: A systematic review. Physiol Rep. 2019;7(22):e14287. https://doi.org/10.14814/phy2.14287
PMid:31758667
64. Ohsawa I, Konno R, Masuzawa R, Kawano F. Amount of daily exercise is an essential stimulation to alter the epigenome of skeletal muscle in rats. J Appl Physiol. 2018;125(4):1097-104. https://doi.org/10.1152/japplphysiol.00074.2018
PMid:30070609
65. McGee SL, Fairlie E, Garnham AP, Hargreaves M. Exercise-induced histone modifications in human skeletal muscle. J Physiol. 2009;587(24):5951-8. https://doi.org/10.1113/jphysiol.2009.181065
PMid:19884317
66. Joseph JS, Ayeleso AO, Mukwevho E. Exercise increases hyper-acetylation of histones on the Cis-element of NRF-1 binding to the Mef2a promoter: Implications on type 2 diabetes. Biochem Biophys Res Commun. 2017;486(1):83-7. https://doi.org/10.1016/j.bbrc.2017.03.002
PMid:28263745
67. Masuzawa R, Konno R, Ohsawa I, Watanabe A, Kawano F. Muscle Type-specific RNA polymerase II recruitment during PGC-1α gene transcription after acute exercise in adult rats. J Appl Physiol. 2018;125(4):1238-45. https://doi.org/10.1152/japplphysiol.00202.2018
PMid:30113273