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# Combined Physical Activity in the Prevention of Cardiovascular Diseases: From Physiological to Molecular Adaptation Mechanisms

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**ABSTRACT**

*Physical activity is recognized as the most important non-medicinal tool for the prevention of cardiovascular diseases, however, the highest efficiency is demonstrated by the programs combining various types of physical load. The present review summarizes the current scientific data on the effects of combined physical activity, including the aerobic exercises of moderate and high intensity and the muscle strengthening exercises, as well as the ones affecting the system of cardiometabolic regulation. A disclosure is provided for the multi-level adaptation mechanisms, encompassing the physiological, vegetative, hormonal, molecular and epigenetic levels. It was justified that combined training modalities possess the synergetic effects, facilitating the decrease of blood pressure, the increase in the cardiac rhythm variability, the improvement of insulin sensitivity, the decrease of chronic inflammation and the activation of cardioprotective transcription programs. A detailed description was provided for the key molecular pathways participating in the adaptational response (AMP-activated protein kinase, mTOR, PGC-1α, autophagia and the unfolded protein response), as well as the role of exerkines — the signaling molecules produced in response to physical load. Special attention was paid to the epigenetic modifications, including the methylation of DNA, the regulation of microRNA and the telomere stability, as the mechanisms of long-term protection from the cardiovascular diseases. The data provided emphasizes the necessity of introducing the combined modalities of physical activity into the programs of individual and populational prevention. Besides, further research is required on the optimal combination of intensity, extent and patterns of physical load for various population categories for the purpose of maximizing the protective adaptation of the cardiovascular system.*

***Keywords:*** *physical activity; cardiovascular system; prevention; physiological adaptation; epigenetics; exerkines; mTOR; AMP-activated protein kinase; PGC-1α; variability of cardiac rhythm.*

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## INTRODUCTION

Cardiovascular diseases (CVD) remain one of the leading causes of incapacitation, morbidity and premature mortality, representing one of the most severe problems for the modern public healthcare [1]. According to the data from the Global Burden of Disease research conducted in 2022, the global number of fatal outcomes related to CVD, has increased from 12.4 mln in 1990 to 19.8 mln in 2022 [2]. This dynamic change indicates the inextinguishable growth of the CVD burden, with this group of diseases continuing to take the first place among the causes of

# Комбинированная физическая активность в профилактике сердечно-сосудистых заболеваний: от физиологических к молекулярным механизмам адаптации

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**АННОТАЦИЯ**

*Физическая активность признана важнейшим немедикаментозным инструментом профилактики сердечно-сосудистых заболеваний, однако наибольшую эффективность демонстрируют программы, сочетающие различные виды физических нагрузок. В настоящем обзоре обобщены современные научные данные о влиянии комбинированной физической активности, включающей аэробные нагрузки умеренной и высокой интенсивности и упражнения на развитие мышечной силы, на систему кардиометаболической регуляции. Описаны мультиуровневые механизмы адаптации, охватывающие физиологические, вегетативные, гормональные, молекулярные и эпигенетические уровни. Обосновано, что комбинированные тренировочные режимы оказывают синергетическое действие, способствуя снижению артериального давления, повышению вариабельности сердечного ритма, улучшению инсулиночувствительности, снижению хронического воспаления и активации кардиопротективных транскрипционных программ. Детально рассматриваются ключевые молекулярные пути, участвующие в адаптационном ответе (AMPK, mTOR, PGC-1α, аутофагия, UPR), а также роль экзеркинов — сигнальных молекул, продуцируемых в ответ на физическую нагрузку. Отдельное внимание уделено эпигенетическим модификациям, включая метилирование ДНК, регуляцию микроРНК и теломерную стабильность, как механизмам долговременной защиты от сердечно-сосудистых заболеваний. Представленные данные подчёркивают необходимость внедрения комбинированных режимов физической активности в программы индивидуальной и популяционной профилактики. Кроме того, требуется дальнейшее изучение оптимального сочетания интенсивности, объёма и направленности физических нагрузок для различных категорий населения с целью максимизации адаптационных возможностей сердечно-сосудистой системы.*

***Ключевые слова:*** *физическая активность; сердечно-сосудистая система; профилактика; физиологическая адаптация; эпигенетика; экзеркины; mTOR; AMPK; PGC-1α; вариабельность сердечного ритма.*

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mortality and loss of working capacity in the Russian Federation [3].

Notably, the high incidence of CVD is observed not only in the countries with high income level: approximately 80% of all the fatal outcomes related to CVD are registered in the countries with low and medium income level, which emphasizes the omnitude and the multi-aspect nature of this epidemiological problem [4]. In Russia, from the middle of 60s of the past century, a growth was observed in the general mortality, especially the CVD-related one, unlike the stable decrease in the Western countries. The main factors of such growth became the urbanization, the alcoholization and the spreading of risk factors (increased blood pressure, smoking, hypercholesterolemia). From 2003, the mortality was beginning to decrease, mainly due to the decreased spreading of risk factors and improving the accessibility and the quality of medical aid, however, Russia still remains a country with high CVD-related mortality rates with significant regional and gender-associated differences [5].

Cardiovascular diseases develop under the influence of a whole spectrum of complex factors, among which, special place is taken by the behavioral and the modifiable determinants, including the insufficient physical activity, the non-balanced nutrition, chronic stress, abnormal sleep modes and the effects of unfavorable factors from the environment. Insufficient physical activity, in particular, is recognized as one of the key global risk factors of CVD, associated with significant increase of the relative risk of general and cardiovascular mortality [6].

According to the actual global review [7], the incidence of insufficient levels of physical activity is 26.3% of the general population. This problem takes the central place in the list of modifiable behavioral risk factors, according to the recommendations from the American Heart Association (AHA), set forth in the Life's Essential 8 concept, along with the control of blood pressure, lipid profile, glucose level, normalization of the body weight and smoking cessation.

Despite the recognized efficiency of physical activity in the context of preventing CVD, there still remains a disputable issue on the optimal distribution and combination of various types of physical load — moderate, intensive or muscle strength oriented — from the point of view of the cardioprotection. In one of the most representative cohort studies based on the data from the National Health Interview Survey (NHIS) [8], it was found that the best decrease in the risk of cardiovascular mortality was observed in cases of combined use of all the three types of physical activity. This emphasizes the necessity of adding the strength exercises to the aerobic activity of moderate and high intensity as a part of CVD prevention strategy.

Similar conclusions were reported by M. Hollings et al. [9], pointing out the progressive muscular exercises promote to the improvement of cardiorespiratory stamina — one of the most significant predictors of survival rate in patients with ischemic heart disease. Thus, multicomponent physical training sessions including the aerobic and strength exercises play a key role in primary prophylaxis and decreasing the global CVD burden.

We have arranged a comprehensive analysis of the existing data on the effects of various types of physical activity (moderate and high intensity aerobic, as well as muscle-building exercises) on the cardiovascular wellness with an accent to the mechanisms of their action in a context of primary prevention of cardiovascular diseases.

### Methodology of searching and selecting the research works

The analysis included the scientific literature published from 2000 until 2024 in the international databases — PubMed, Scopus, Web of Science, as well as at the Google Scholar and eLIBRARY platforms.

To select the relevant sources, we used the following key words and logical operators: "physical activity" AND "cardiovascular adaptation", "combined exercise" AND "prevention of cardiovascular disease", "molecular mechanisms" OR "epigenetics" AND "exercise", "autonomic nervous system" AND "training", "exerkines" OR "PGC-1α" OR "AMPK" OR "mTOR".

From the initial sample of more than 600 publications, a total of 72 sources were selected, reflecting the most significant and recent data on the topic.

## A REVIEW OF THE ADVANTAGES OF COMBINED PHYSICAL ACTIVITY COMPARING TO THE ISOLATED EXERCISE PATTERNS

Modern cardiology and preventive medicine are more and more actively investigating physical activity as an integral part of the combined prevention of CVD. The systematic participation in physical activity is recognized as one of the most effective and accessible instruments of modifying the risk factors, associated with CVD and premature mortality. However, for achieving the maximal therapeutic and preventive effect, more and more attention is paid not only to the extent and the regularity of physical activity, but also to its structure, intensity and diversity.

According to the recommendations on the primary prophylaxis of CVD, presented in 2019 [10], the adults are recommended to devote not less than 150 minutes a week to physical activity of moderate intensity, or 75 minutes for high intensity, or their equivalent combination. These recommendations, being aimed at decreasing the risk of developing CVD, reflect the universal approach to the prevention, however, they insufficiently enlighten on the proven benefits of supplementing the training program with exercises aimed at strengthening the skeletal muscles. According to the number of epidemiological and interventional researches, specifically the combined model of physical activity, including the aerobic and strengthening components, is associated with the most significant decrease in the risk of both the cardiovascular and the total mortality [8, 11].

Physiological mechanisms lying at the roots of such effects are various. Moderate physical activity is generally associated with an increase of the total energy usage, with the normalization of the lipid and glycemic profile, with the decrease in the quantity of visceral fat and with the improvement of the arterial tone [12], while the highly intensive load significantly effects the development of cardiorespiratory stamina, which is an independent predictor of survival rate, regardless of the gender, the age, the body mass index and ethnicity [13, 14].

The clinical and populational research works confirm that combining the exercises of various intensity provides a synergetic effect. For example, even moderate physical activity promotes to the decrease of cardiometabolic risk, however, its combination with intensive physical exercises demonstrates significantly more pronounced decrease in the CVD mortality [15]. Moreover, the benefit remains even in case of a minimal life style modification: for example, when changing the sedentary behavior to mild activity during the day combined with regular sessions of aerobic exercises [16].

The meta-analysis of interventional studies [17] has shown that active physical load decreases the levels of inflammatory markers, normalizes the parameters of cardiac rhythm variability and promotes to the decrease of blood pressure. These effects are especially pronounced when combining the aerobic and strength-building exercises, while the strength exercises itself promote to the improvement of metabolic homeostasis, to the decrease of insulin resistance and to the increase of muscle mass, which is of major importance at the elderly age. For this age group, the additionally recommended are the balance and coordination exercises, promoting to decreasing the risk of falling and concomitant incapacitation [18].

From the point of view of pathophysiology, the intensity of loading directly affects the degree of intensity of the adaptational processes. The randomized research works have found that intensive physical activity promotes to more significant increase in the heart rate and lactate level, while the moderate load shows a stable effect on the vascular reactivity and microcirculatory network. Besides, physical activity of various intensity can variously affect the expression of microRNA, participating in re-modeling of vessels and in the arteriogenesis, which opens new perspectives in a context of molecular medicine [19, 20].

Special attention should be paid to the data obtained using the accelerometry method, indicating that changing even 5 minutes of sedentary lifestyle to high intensity activity may lead to the improvement of body constitution, to the increase in the level of fat-free body weight and to the improvement of cardiorespiratory functions, especially in children and adolescents [21]. In younger adults with excessive body weight, it was proven that moderate and high-intensity physical activity is more effective than the mild one in terms of improving the cardiometabolic wellness [22]. At the same time, it should be taken into account that, for the majority of the population, especially for individuals from the older age group, high-intensity exercises can be less acceptable, which is why specifically the reasonable combination of exercises of various intensity and patterns is the most practicable strategy.

As shown by the comparative research works, moderate and intensive exercises similarly affect the decrease of the total and cardiovascular mortality, however, specifically the intensive physical activity, to a greater extent, is associated with a decrease in the oncological mortality [23]. This additionally underlines the multisystemic effect of physical activity and the topicality of the individualized approach to compiling the training programs.

The combined training models demonstrate not only the preventive, but also the therapeutic potential. A cohort study based on the data from the National Health Interview Survey in the USA (NHIS) [8] has demonstrated that the most significant decrease of cardiovascular mortality was observed among the individuals, combining aerobic exercises of various intensity with strength exercises. Detailed results were obtained during the controlled clinical research [24], where the 12-weeks program,


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including the cardio- and strength-related components, has lead to a significant decrease in the values of heart rate at rest, the blood pressure, the body weight and the fat mass, as well as to the improvement of maximal oxygen consumption ($VO_2$ max).

Thus, the necessity of revising the existing guidelines becomes evident with an accent to structural diversity of physical activity. The inclusion of the provisions concerning the significance of combined physical activity into the official recommendations shall allow for increasing the efficiency of both the primary and the secondary prevention of CVD, as well as the degree of patients' compliance to healthy lifestyle. The formation of a holistic approach based on the integration of various types and levels of physical activity must become an integral part of the modern programs of preventing and rehabilitation for CVD.

Combined physical activity (aerobic+strength-building) provides more intensive cardiometabolic and preventive effects comparing to the isolated types of exercises. Combining various types of exercises promotes to synergetic effects on the cardiovascular system, decreasing the mortality and improving physiological adaptation.

## HORMONAL ADAPTATION TO PHYSICAL ACTIVITY: METABOLIC AND ENDOCRINE EFFECTS

Physical activity causes a number of systemic positive effects on the metabolic health of the human, largely thanks to its regulating effects on the hormonal homeostasis [25]. One of the key endocrine effects of the regular motor activity is the increase in the sensitivity of the target tissues to insulin, especially when performing exercises aimed at developing muscle strength and increasing the muscle mass [26].

It was found that regular physical activity promotes to the modulation of the transduction of insulin signals in the skeletal muscles [27], stimulating the biogenesis of the mitochondria and the remodeling of muscle tissue by means of the activation of a number of molecular signaling pathways, including the endothelial nitric oxide synthase (eNOS), the peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α) and the mitofusin [28–30]. These mechanisms play the key role in increasing the oxidative capabilities of the muscles, improving both the metabolic flexibility and the insulin sensitivity [31].

Physiologically, eNOS increases the perfusion of tissues, sensitive to insulin, such as the myocardium and the skeletal muscles, by this enhancing the delivery of glucose and other metabolites [32]. Moreover, during the randomized controlled research, it was shown that 10-weeks strength-building training course promotes to the improvement of localizing the neuronal nitric oxide synthase (nNOS) in the skeletal muscles, which is critically important for the effective vasoregulation [33].

Physical activity also activates the expression and the translocation of GLUT4 (glucose transporter type 4), providing an increased uptake of glucose by muscle cells and facilitating its accumulation as glycogen [34, 35]. Even a single training session (for example, 45–60 minutes of riding a bicycle at 60–70% of $VO_2$ max) induces the translocation of GLUT4 to the cellular membrane in the skeletal muscles in patients with type 2 diabetes mellitus [36]. This mechanism forms the basis of improving glycemic control in the given category of individuals.

Special significance is gained by physical activity aimed at developing the muscle strength, for it promotes to the increase of muscle mass — the main glucose depot in the organism — and to the improvement of its metabolic quality [37, 38]. Thus, only two sessions of progressive strength-building sessions a week, even with no additional interventions in the diet, significantly improve the sensitivity to insulin, decrease the fasting glucose level and reduce visceral obesity in elderly men with type 2 diabetes mellitus [39].

The efficiency of physical training is also observed in persons with pre-diabetes, as well as among those who are in the high-risk group in terms of developing type 2 diabetes. The network meta-analysis [40], including the data from 13 randomized controlled studies, has shown that 12-weeks programs of physical activity combining aerobic and strength-building exercises significantly decrease the level of glycated hemoglobin, (HbA1c) in persons with impaired glucose tolerance. Moreover, regular physical activity, both combined with controlling the body weight and in the autonomous mode, was proven to promote the prevention or significant delay of the manifestation of type 2 diabetes mellitus [41, 42].

Special attention deserves the role of catecholamines — adrenalin and noradrenalin — in the regulation of the metabolism and the cardiovascular functions in response to physical load. These hormones are synthesized by the medullary substance of the adrenal glands and they are released in response to acute stress, including physical activity [43]. The stimulation of β-adrenoreceptors with catecholamines increases the rate and the strength of heart contractions, dilates the arterioles in the skeletal muscles and enhances the accessibility of metabolic substrates [44].

Catecholamines also modulate the functions of the immune system, in particular, the activity of T- and B-lymphocytes, the synthesis of cytokines and antibodies, which is of significant meaning both for the immuno-metabolic regulation and for systemic anti-inflammatory response [45]. Besides, they provide the mobilization of fatty acids and glucose, required for supporting the energy needs of the skeletal muscles during the long-term physical activity [45, 46].

The level of catecholamines production directly correlates with the level of physical training: among the individuals training the stamina, the findings include higher capabilities to adrenalin secretion, which was denominated as the phenomenon of "sports-related adrenal cortical hyperplasia" [44]. Moreover, regular physical activity induces the adaptation of the sympathoadrenal system, increasing the sensitivity of peripheral adrenoreceptors and the efficiency of response reactions to physical load [47], which additionally contributes to the improvement of the regulation of blood pressure, of glycemic control and of the lipid metabolism. Table 1 summarizes the main hormonal effects of physical activity [26–47].

Thus, hormonal adaptations induced by regular physical activity, are implemented by means of the multi-level mechanisms — from the molecular activation of insulin-dependent signaling pathways to systemic modulation of catecholamine activity and vascular regulation. These processes not only promote to the improvement of metabolic and hormonal status, but also play the key role in the prevention and control of chronic non-infectious diseases, including type 2 diabetes mellitus and CVD. Thus, the integration of aerobic and strength-building components of physical activity into the structure of everyday activities is a justified strategy of preserving the hormonal balance and metabolic wellness at all the stages of life.

Regular physical activity promotes to the improvement of hormonal background and metabolic wellness due to the increase of sensitivity to insulin and due to the activation of anabolic signaling pathways. These adaptations decrease the risk of developing

Table 1

**Hormonal effects of physical activity**

| Hormonal effect | Mechanism of action | Type of physical activity | Source |
|---|---|---|---|
| Increasing the sensitivity to insulin | Activation of signaling pathways in the muscles (eNOS, PGC-1α, mitofusin); stimulation of biogenesis in mitochondria | Strength-building, aerobic | [26–31] |
| Improvement of circulation in the target organs | Increased activity of eNOS and nNOS | Aerobic, strength-building | [32, 33] |
| Translocation of GLUT4, increased glucose usage | Increased expression of GLUT4 and its translocation to the cell membrane | Aerobic, especially with high intensity | [34–36] |
| Increasing the muscle mass and metabolic activity of the muscles | Growth of muscle mass, increased the reserves for glucose utilization | Strength-building | [37–39] |
| Decreased insulin resistance in pre-diabetic individuals | Combined adaptation: decrease of fat mass, improvement of HbA1c | Combined (aerobic+ strength-building) | [40] |
| Prophylaxis of type 2 diabetes among the persons of the risk group | Physical load, decrease in the body weight, dietary intervention | Aerobic, strength-building | [41, 42] |
| Stimulation of the secretion of catecholamines | Activation of the adrenal glands and of the sympathetic nervous system in response to physical load | Intensive | [43–45] |
| Improvement of the functions in the cardiovascular system via the β-receptors | Increased heart rate, force of contractions, vasodilation | Aerobic, intervallic | [44] |
| Increased lipolysis and oxidation of fats | Increased catecholamine response; mobilization of energy substrates | Intensive | [45, 46] |
| Increasing the sensitivity of the adrenoreceptors | Long-term adaptation of the sympathoadrenal system | Regular aerobic and strength-building | [47] |

*Note*. eNOS/nNOS — endothelial/neuronal nitrogen oxide synthase; PGC-1α — peroxisome proliferator-activated receptor-gamma coactivator-1α, regulator of mitochondrial biogenesis; GLUT4 — glucose transporter, type 4; HbA1c — glycosylated hemoglobin.


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metabolic syndrome and type 2 diabetes mellitus, especially when adding the strength-building exercises.

## VEGETATIVE ADAPTATION TO REGULAR PHYSICAL ACTIVITY

Physical activity acts as an important stimulus for vegetative restructurisation, facilitating the development of stable neurophysiological changes, directed at increasing the efficiency of cardiovascular, metabolic and respiratory regulation. The adaptational processes in the vegetative nervous system play the key role in providing the homeostatic resistance of the organism to physical load of various intensity and duration.

The vegetative nervous system functions by means of two complementary segments — the sympathetic and the parasympathetic nervous systems. The activation of sympathetic nervous system initiates the so-called “fight or flight” reaction, accompanied by the acceleration of the cardiac rhythm, by elevation of blood pressure, by vasoconstriction and the decrease in the gastro-intestinal motor activity. On the contrary, the parasympathetic nervous system implements the reparative processes at rest, decreasing the frequency of heart contractions, facilitating the vasodilation, activating the secretion and the peristaltic motions in the digestive tract [48].

One of the key markers of vegetative tone used in clinical practice and sports medicine is the variability of the cardiac rhythm — the reflection of the degree of variation of the intervals between the consecutive heart contractions [49]. The low level of cardiac rhythm variability is significantly associated with elevated risk of sudden cardiac death, cardiac failure, hypertension and metabolic disorders, including type 2 diabetes mellitus.

One of the most important adaptations to regular physical activity, regardless of its modality, is the increase of parasympathetic tone with a simultaneous decrease in the activity of the sympathetic segment. These changes, occurring with preserved normal functions of the sinusal node, are due to the increased vagus modulation of the heart rate, facilitating its decrease at rest and the increase in the cardiac rhythm variability [50]. Such a parasympathetic shift is considered as the marker of high-level functional adaptation of the cardiovascular system and of decreasing the risk of developing CVD [51].

It was found that regular physical activity, especially of aerobic type, leads to an increase in the cardiac rhythm variability, both among the individuals with already diagnosed CVD and among the healthy individuals, which confirms its multi-purpose effects on the vegetative balance [52]. At the same time, neurophysiological adaptations occur also at the level of central regulation, in particular, in the rostral ventrolateral part of the medulla oblongata, playing the key role in the modulation of the sympathetic tone. These changes promote to the decrease of hyperactivation in the sympathetic nervous system, which is especially characteristic for persons with chronic stress and cardiometabolic disorders [53].

Moderate and intensive physical activity improves the sensitivity of the sympathetic nervous system to physiological stimuli, increasing the efficiency of responses upon physical loading due to more rational use of energy resources and due to the mobilization of catecholamines [54, 55], which is accompanied by an increase in the cardiac output, by vasodilation in the skeletal muscles, by the improvement of glucose transport and by an increased lipolysis.

Interestingly, but even at rest after regular aerobic exercises, a decrease is observed in the sympathetic activity, while when using the submaximal physical lead, a more energy efficient regulation of the vegetative is achieved, which indicates increase of the total vegetative efficiency [54, 55].

The vegetative adaptation is also characteristic for the strength-building exercises. Systematic exercises aimed at developing muscle strength, promote to the activation of the pituitary-hypothalamic-adrenal axis, providing a modulation of the production of cortisol, with the findings also including a decrease in its levels at rest and the suppression of the chronic inflammatory response [55]. The decrease in the levels of cortisol has a positive effect, for its chronic hyper-secretion correlates with the development of insulin resistance, arterial hypertension and atherogenic dyslipidemia — the main components of metabolic syndrome [56].

Regular muscle core strengthening exercises improve the sensitivity of β-adrenoreceptors in the skeletal muscles, enhancing the effect of catecholamines and facilitating the finer regulation of the vascular tone and metabolic processes [47]. Besides, strength-building activities promote to the increase in the cardiac rhythm variability, which indicates the restoration of the vegetative balance, similar to the one observed in cases of aerobic activities [57].

Thus, regardless of the type of physical activity, its regular conduction forms a favorable vegetative adaptation, including the increase of the vagus effects in the heart, the decrease of the sympathetic activation, the improvement of hormonal and neurovascular regulation. The totality of such changes promotes to decreasing the risk of cardiometabolic disorders, to the improvement of the general stress resistance and to the increase of the functional reserves of the organism.

**MOLECULAR ADAPTATION TO PHYSICAL ACTIVITY**

Physical activity is a potent trigger for a wide spectrum of molecular adaptational processes, which mediate the positive effects of the motor activity in terms of general wellness. These processes include the activation of multiple intracellular signaling cascades, regulating the cellular homeostasis, energy metabolism, tissue plasticity and stress resistance. The special role in the modulation of the adaptive responses is played not only by the type and the intensity of physical load, but also by the accessibility of nutritive substrates, determining the metabolic direction of cellular regulation [58].

One of the key mechanisms activated in response to physical activity is the activation of autophagia — the evolutionary conservative pathway of disposal and reprocessing of organelles and proteins. Autophagia provides metabolic flexibility and maintenance of cellular homeostasis, playing the critical role in the adaptation to physiological stress related to muscle contractions [59]. Besides, mitochondrial biogenesis, autophagia and mitophagy (selective degradation of mitochondria) form the coordinated response in the tissues with high energy consumption, such as the skeletal muscles and the myocardium, facilitating the increase in the resistance to further load and the improvement of tissue metabolism [60].

In the settings of physical activity, a coordinated activation is observed in the mTORC1 (mechanistic target of rapamycin complex 1) and AMPK (5’ adenosine monophosphate-activated protein kinase) pathways, which reflects the complex integration of anabolic and catabolic signals. Such a convergence of molecular cascades is especially important when combining the strength-building and aerobic exercises, explaining the phenomenon of the so-called “simultaneous training effect” [61].

At the level of transcriptional regulation, physical activity induces the expression of genes, controlling muscle hypertrophy, angiogenesis and remodeling of muscle fibers. It was noted that physical exercises activate both the myogenic and the angiogenic transcription programs, promoting to the complex tissue adaptation, directed at the optimization of delivering oxygen and substrates [62].

The most important role in regulating the cellular response to physical activity is played by the unfolded protein response (UPR), activated in the settings of increased synthetic load. This mechanism allows the cells to manage the stress in the endoplasmatic reticulum, maintaining proteostasis in the conditions of intensified metabolism [63].

The recognized central element of molecular adaptation to physical activity is the Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1α (PGC-1α) — the key regulator of mitochondrial biogenesis. The activation of PGC-1α promotes to the increase in mitochondrial density, to the improvement of the oxidative capabilities of muscle cells and to the resistance to tiredness [64]. The PGC-1α regulation is also associated with the modulation of the expression of genes encoding the antioxidant enzymes, which is important in a context of protection against oxidative stress.

The molecular responses to physical activity demonstrate a complex and multicomponent pattern, which requires a comprehensive analysis. Understanding the integration of the AMPK, mTOR, MAPK (mitogen-activated protein kinases) and UPR signaling pathways along with the transcription factors, activated upon moderate and high intensity physical activity, is critically important for unveiling the mechanisms of cellular adaptation [65]. The mTOR pathway has demonstrated, along with the metabolic functions, an important role in regulating the neuroplasticity, the cognitive abilities and the structural re-organization of neuronal networks in the brain in response to physical load [66], which opens new perspectives of using physical activity as the non-medicinal mean of improving the cognitive status in cases of neurodegenerative and vascular diseases.

The regulation of the expression of genes sensitive to physical activity, including the epigenetic modification, remains an object of active research. Special interest is aroused by the exerkines — the signaling molecules produced by skeletal muscles in response to contractions and showing systemic endocrine-like effects. The exerkines are considered as potential therapeutic agents for cardiovascular, metabolic and neurodegenerative diseases [67].

Thus, physical activity initiates a wide spectrum of molecular mechanisms, promoting to the structurally functional remodeling of tissues, to the increase of metabolic efficiency and stress-resistance. The variety of adaptive responses confirms the necessity of personalized approach in selecting the type and the


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intensity of physical exercises for preventive purposes and for the correction of chronic diseases. The molecular mechanisms of adaptation to physical activity are provided in Table 2 [59–61, 63, 64, 66, 67]. Physical activity also stimulates the key molecular pathways (AMPK, mTOR, PGC-1α, autophagia), promoting to the improvement of the energy metabolism, stress resistance and tissue remodeling (Table 3) [61, 63, 64, 66, 67] — the processes lying in the foundation of metabolic flexibility and of the cardioprotective effect of working out.

## EPIGENETIC ADAPTATIONS IN RESPONSE TO PHYSICAL ACTIVITY

Modern research works strongly confirm that regular physical activity provides a significant epigenetic effect, playing the key role in regulating the genetic expression without changing the primary DNA sequence. These molecular modifications promote to the long-term remodeling of cellular functions, forming the basis for stable improvement of the cardiometabolic profile and of the general physiological status.

Table 2

**Molecular mechanisms of adaptation to physical activity**

| Molecular pathway | Main effects | Source |
|---|---|---|
| Autophagia | Removal of damaged organelles and proteins, maintaining the cellular homeostasis | [59] |
| Mitochondrial biogenesis | Increase in the number of mitochondria, improvement of oxidative metabolism | [60] |
| mTORC1 | Stimulation of protein synthesis, muscle growth, participation in neuroplasticity | [61] |
| AMPK | Activation of catabolism, energy mobilization, stimulation of mitophagy | [61] |
| PGC-1α | Regulation of mitochondrial genes, antioxidant protection, angiogenesis | [64] |
| UPR (unfolded protein response) | Adaptation to metabolic stress, control of proteostasis | [63] |
| Exerkines | Secretion of myokines, systemic regulation of metabolism and vascular functions | [67] |
| mTOR and cognitive function | Memory improvement, neurogenesis, synaptic plasticity | [66] |

*Note*. AMPK — AMP-activated protein kinase, the energy sensor in the cell, activated in the settings of energy deficit; mTORC1 — the main component of the mTOR signaling pathway, regulating the cell growth, protein synthesis and metabolism; PGC-1α — the main regulator of mitochondrial biogenesis and oxidative metabolism in the skeletal muscles; UPR — the response to unfolded proteins, a cellular mechanism of adaptation to stress in the endoplasmatic reticulum; exerkines — the common name for signaling molecules, including the myokines, excreted into systemic circulation in response to physical activity.

Table 3

**The main signaling pathways of adaptation to physical activity**

| Signaling pathway | Activation conditions | Main effects | Source |
|---|---|---|---|
| AMPK | Physical load and energy deficit (increased levels of AMP/ATP) | Activation of catabolism, stimulation of mitophagy, enhanced oxidation of fats | [61] |
| mTOR | Sufficient energy status, especially after exercises | Stimulation of protein synthesis, growth of muscle mass, participation in neuroplasticity | [61, 66] |
| PGC-1α | Increased metabolic activity and aerobic exercises | Increased mitochondrial biogenesis, angiogenesis, antioxidant protection | [64] |
| UPR | Stress in the EPR after intensive workout intensive | Maintaining the proteostasis and adaptation to metabolic stress | [63] |
| Exerkines | Contraction of skeletal muscles | Systemic regulation of metabolism, vascular function, anti-inflammatory effects | [67] |

*Note*. AMPK — AMP-activated protein kinase (energy sensor of the cell); mTOR — the mechanistic target of rapamycin, regulating the growth and the metabolism; PGC-1α — peroxisome proliferator-activated receptor-gamma coactivator-1α, regulator of mitochondrial biogenesis; UPR — unfolded protein response, mechanism of controlling the proteostasis in the EPR after stress; exerkines — signaling molecules excreted by skeletal muscles in response to the contraction; EPR — endoplasmic reticulum.

The epigenetic mechanisms induced by physical activity include the methylation of DNA, the post-translational modifications of histones, the changes within the structure of the chromatin, as well as the regulation of the expression of non-coding RNA, including the microRNA and the long non-coding RNA [68]. These processes promote the activation of protective transcriptional programs aimed at the suppression of inflammatory and proliferative signals, which is of special importance in the prevention of such chronic diseases as atherosclerosis, type 2 diabetes, oncological and neurodegenerative disorders [69].

Physical activity, especially when performed on a regular basis, induces the stable epigenetic remodeling in the cells of the cardiovascular system. These modifications promote to the suppression of atherogenic genes, to decreasing the expression of pro-inflammatory cytokines, to the improvement of endothelial functions and to the enhancement of antioxidant protection [68]. Thus, the epigenetic regulation is considered as one of the central mechanisms, mediating the cardioprotective effects of physical activity.

Data are being accumulated that show that intensive physical activity is capable of preventing DNA damage, of modulating the expression of genes controlling the telomere length and slowing down the epigenetic aging of the organism [70]. These effects are in part caused by the stabilization of methylation in the promotor areas of the genes participating in the regulation of cellular proliferation and apoptosis.

Special interest has the phenomenon of transgenerational epigenetic transition: according to the latest data, physical activity of the parents can affect the epigenetic markers in the germinal cells and, respectively, the expression of genes in the progeny [71]. These changes induced by favorable environmental factors (including the physical load), can be transitioned to the next generations, providing an inheritable resistance to metabolic disorders, cardiovascular and oncology diseases. Such an inter-generational transfer of adaptive phenotypes gives the physical activity the status of not only individual, but also the potentially inter-generational preventive instrument.

Despite the progress in studying the molecular biology of adaptation to physical activity, the insufficiently clear issue is the degree of participation of various types of activity (aerobic, strength-building, intervallic) in the modulation of specific epigenetic targets, however, the aggregate data indicate that each type of physical activity is capable of inducing a unique epigenetic effect, regulating the specific cascades of transcriptional and post-transcriptional changes [72].

Thus, physical activity represents a potent exogenous factor forming a long-term epigenetic remodeling at the level of separate cells, tissues and the organism in general. These changes form the basis of not only the short-term functional adaptation, but also the long-term protection from chronic diseases, facilitating the increase in life expectancy and improving its quality.

Physical activity induces stable epigenetic changes, including the methylation of DNA, modifications of histones and regulation of the microRNA, which promotes to the suppression of inflammation and slowing down the ageing process. These effects provide a long-term protection against cardiovascular and metabolic diseases, also capable of being transferred to the progeny. The epigenetic mechanisms of adaptation to physical activity are provided in Table 4 [68, 70, 71].

## CONCLUSION

The present review summarizes the accumulated scientific data supporting the high efficiency of combined physical activity, including the aerobic exercises of moderate and high intensity combined with the exercises aimed at improving muscle strength. Such a multicomponent strategy demonstrates significant superiority over the isolated types of physical activity by the spectrum of positive physiological adaptations, especially in terms of the cardiovascular system.

Systematic implementation of various forms of physical activity allows for achieving a synergetic effect, expressed as an increase in the cardiorespiratory stamina, improvement of neurovegetative balance, metabolic resistance and decreased inflammatory background. These adaptations play the key role in decreasing the risk of developing cardiovascular diseases and increasing the quality of life in various age groups and clinical groups.

The obtained results are of major importance both for developing the personalized preventive programs and for compiling the populational strategies of improving the wellness. The integration of various types of physical activity into everyday practice shall be considered a central element of combined interventions in the field of public healthcare and cardiology prevention.

Taking into consideration the high clinical and social significance of the data compiled in the present review, it is deemed appropriate to draw the attention of the professional medical communities and of the persons


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Table 4

**Epigenetic mechanisms of adaptation to physical activity**

| Epigenetic mechanism | Mechanism description | Physiological effects | Source |
|---|---|---|---|
| Methylation of DNA | Addition of methyl groups to cytosine residues in the promotor areas of the genes | Decreased expression of pro-inflammatory and atherogenic genes, slowing down ageing | [68, 70] |
| Modification of histones | Acetylation, methylation and other post-translational changes in the histones | Remodeling of chromatin, regulation of DNA accessibility for transcription | [68] |
| Non-coding RNA (miRNA, lncRNA) | Regulation of transcription and translation by means of microRNA and long non-coding RNA | Decreased inflammation; regulation of angiogenesis, metabolism | [68, 71] |
| Methylation of RNA | Changes at the mRNA level, affecting the stability and translation | Plasticity of cell response to work-out, increased adaptation | [68] |
| Telomere regulation | Preserving the telomere length, preventing the chromosomal instability | Slower cell ageing, genome protection | [70] |
| Transgenerational epigenetics | Inheritable changes in gene expression without changing the DNA sequence | Transfer disease resistance to progeny | [71] |

*Note*. miRNA (microRNA) — microRNA, non-coding RNA (regulating the expression of genes at the post-transcription level; lncRNA — long non-coding RNA (taking part in the regulation of transcription and chromatin organization); mRNA (messenger RNA) — matrix RNA (transfers the information on the protein sequence from the DNA to the ribosomes).

responsible for managerial decisions, to the necessity of encouraging and implementing the multi-level models of physical activity in various contexts — from individual prevention to population-scale programs.

The promising direction of further research is the clarification of the optimal ratio of intensity, volume and structural composition of various types of physical activity with taking into consideration the gender, the age, the functional status and the presence of comorbidities for the maximization of the preventive potential with regard to the cardiovascular outcomes.

As for the practical aspect, the obtained data underline the necessity of recommending combined physical activity for the general population: patients should combine aerobic exercises (of moderate and high intensity) with strength-building sessions not less frequent than two times a week, while the physicians should personalize the recommendations with taking into consideration the age, the general fitness level and the presence of chronic diseases, using the objective adaptation markers (for example, variability of cardiac rhythm and carbohydrate metabolism parameters) for monitoring the efficiency of the intervention.

## ADDITIONAL INFORMATION

**Author contributions.** *A.R. Magomedov:* conceptualization and study design, overall scientific supervision, manuscript editing, and approval of the final version of the article; *P.V. Rykova:* methodology, data acquisition and systematization, drafting sections on physiological and molecular adaptation, and contribution to manuscript writing; *B.A. Anokhin:* literature analysis, contribution to sections on hormonal and epigenetic adaptation, and reference formatting; *A.Kh. Melikian:* preparation of tables and illustrative materials, formatting of bibliographic references; *M.A. Agaronian*, *A.G. Sarkisyan*, *E.S. Shimko:* analytical data processing, drafting of the “Introduction” and “Conclusion” sections; *A.Yu. Yusupova*, *E.R. Irgalieva:* scientific editing and critical manuscript review, verification of factual accuracy; *E.M. Bokova:* preparation of the English version of the abstract, keywords, and article title translation; *R.S. Mokaev*, *D.V. Leonova*, *A.Sh. Kendzhametov*: technical support with document formatting, verification of references, and coordination of the final manuscript version. The authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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