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MECHANISMS OF PROTECTIVE ACTION OF PHYSICAL ACTIVITY ON THE OCCURRENCE, CLINICAL COURSE, AND FUNCTIONAL RECOVERY FROM ISCHEMIC STROKE

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In this paper, a review of literature was done regarding the mechanisms of impact of physical activity on the incidence of cerebrovascular disease - ischemic stroke (IS), on the degree of neuronal damage and clinical picture and degree of functional recovery after IS.

The mechanisms by which physical activity protects against IS are multifactorial. The protective effects are most often related to vascular risk factor modification, reduction of neuronal apoptosis, cerebral edema and infarction volume. Physical activity increases the levels of some biohumoral factors with important protective functions for cell growth and neuroplasticity. Physical activity stimulates neurogenesis and angiogenesis, prevents blood-brain barrier dysfunction, reduces inflammatory response, and controls glutamatergic excitotoxicity. In this manner it improves cerebrovascular function, increases nerve tissue tolerance to hypoxia, and reduces the degree of damage, thereby improving clinical presentation and providing a higher degree of functional recovery, reducing also the rates of mortality from IS. Furthermore, physical activity leads to enhanced brain tissue tolerance to ischemia, mediated by increased levels of protective heat shock proteins. Physical activity causes an increase in the level of TNFα, reducing the expression of its receptors over time and limiting in this manner inflammatory damage in the pathogenesis of IS, in which TNFα plays a crucial role. Physical activity is important for the prevention of overweight and obesity, which are recognized as the leading causes of IS.

A large number of studies have demonstrated a protective effect of physical activity on the incidence, course and outcome of IS. Physical activity, even at early ages, reduces vascular risk factors and obesity, thus preventing IS. The mechanisms of prevention are mediated by a complex effect on metabolic processes. *Acta Medica Medianae 2017;56(3):70-76.*

Key words: *physical activity, stroke*

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Introduction

Stroke is the leading cause of morbidity, death and permanent disability worldwide. About 80% of strokes are ischemic strokes (IS), while the rest are hemorrhagic strokes. The highest percentage of patients after an IS have got disabilities as the result of pyramidal lesions, spasticity, cognitive impairments, or speech disturbances. Up to 40% of IS survivors are dependent on someone else's care and assistance. More than 30% of these patients even after four years have some social activity disorder.

It has been shown that the basis of quality of life reduction after IS appears to be the consequence of cardiorespiratory dysfunction. Muscle weakness results from the accumulation of fat in the muscle, greater expression of inflammatory cytokines involved in muscular atrophy, and reduced number of functional capillaries in the myofibrils. Increased levels of proinflammatory molecules, impaired glycemic control and insulin metabolism, as well as autonomic dysfunction, are recognized as the basis of cardiorespiratory failure. Complete recovery after IS occurs only in a small percentage of survivors (1-3).

Modifiable and non-modifiable risk factors for both types of stroke are well known. Non-modifiable factors are age, gender, race, genetic predisposition. Modifiable risk factors can be mo-

dified by any medical intervention (pharmacotherapy or surgical intervention) and among these there are carotid occlusive disease, arterial hypertension, coagulopathy and others; there are also the risk factors that can be altered by changing one's habits and lifestyle (physical activity, smoking, alcohol, etc.). One of the most important variable factors is obesity. Prevention of obesity in childhood is still a significant preventive measure for the prevention of adult obesity and its consequences, including IS. It has been shown that obese children have a four times greater risk of developing obesity in adulthood, and a low level of physical activity is a significant recognized factor in this process (4).

Modern guidelines for IS prevention put an emphasis on the recognition of high-risk groups and risk factor modification. Physical activity is an im-portant component of the prevention (1, 2). The mechanisms of IS prevention are not quite understood. On the one hand, physical activity reduces vascular risk factors that are important for IS to occur (3). On the other, physical activity improves the response to ischemia and thus reduces the size of infarction at the same time reducing the severity of clinical picture (1, 3). There are few studies that examine the link between physical ac-tivity and small blood vessels changes in the brain (5). There are open questions regarding the pre-ventive effects of physical activity in view of its intensity level and target-tissues, and the extent to which physical activity improves recovery after IS.

In this paper, a review of literature was done regarding the mechanisms of influence of physical activity on the incidence of IS, impact of physical activity on the degree of neuronal damage and clinical picture and the degree of functional recovery after IS.

Preventive role of physical activity

Modern guidelines for IS prevention recommend at least 30 minutes of moderate to intense physical activity per day in order to reduce the risk of IS (6). In the study of Reimers et al. (2), it has been shown that physically active subjects of both genders and of different ages had a 25% lower risk of IS, in comparison to the less physically active subjects. Respondents who were moderately physically active also had a lower risk for IS, although there are no clear identified association between the types of physical activities and their preventive effects (7).

While increased physical activity correlates with a greated reduction of IS risk, the exact preventive doses of physical activity are not clearly defined. In most studies, the volume of physical activity was defined over time (hours per week), or by intensity (measured in kilocalories), or metabolic equivalents (during the week) (2). Most of the studies that have measured the extent of physical activity through two levels (more and less physical activity) have shown that subjects with more physical activity have a higher degree of reduction of IS risk. In the studies that measured the extent of physical activity through multiple levels, it has been shown that subjects with moderate and higher levels of physical activity have the greatest protective effect against IS. It was also shown that the volume of physical activity is a significant factor related to the duration of physical activity (1). Some results indicate that moderate, but not intense physical activity, reduces the risk of small blood vessel damage in the brain (8). There are results which indicate a clear-cut link between moderate and ideal physical activities and the reduction of risk for different stroke subtypes (lacunar and non-lacunar) (9). The scale proposed by the American Heart Association was used in this study to estimate the intensity of physical activity (10) (Table 1). There are no results which clearly link the duration of the physical activity with the reduction of risk for IS. It has been shown that the protective effects of physical activity on IS incidence are similar in both women and men, with those with more extensive physical activity having a lower IS risk, compared to those engaging in less extensive physical activity. However, the largest number of studies that have followed three or more levels of physical activity have found that respondents with moderate physical activity have a lower IS risk compared to those with more extensive physical activity. Moreover, active physical activity is almost twice as effective in the prevention of IS compared to passive physical activity. This could be the consequence of a greater intensity of active compared to passive physical activity (11).

Table 1.: American Heart Association's ideal cardiovascular health guidelines for adults aged 20 years and above (10)

Level of physical activity	
Poor	0 min/week of moderate or vigorous exercise
Intermediate	1–149 min/week of moderate intensity or 1–74 min/week of vigorous intensity or 1–149 min/week of moderate and vigorous intensity
Ideal	≥150 min/week of moderate intensity or ≥75 min/week of vigorous intensity or ≥150 min/week of moderate and vigorous intensity

Influence of physical activity on the incidence of small vessels damage in the brain is not clearly defined. In one study, it has been shown that physically active patients have twice as often small blood vessels injuries in the brain as seen on MRI, compared with physically inactive subjects (12).

The mechanisms of the protective effects of physical activity

Protective effects of physical activity are most frequently related to the modification of vascular risk factors, such as hypertension and type 2 diabetes mellitus (DM 2). In the study of Mora et al. (13), changes in the markers of vascular function, such as homocysteine, hemoglobin A1C, CRP and other markers have been evaluated during physical activity, and it has been shown that decrease in the levels of these markers may be useful in assessing the IS prevention mediated by physical activity. Physical activity is also important in the reduction of neuronal damage and at the same time in the reduction of the severity of neurological expression (14). The results of experimental studies have shown that physical activity, at least two to three times a week (training on a treadmill for a period of 30 minutes) for four weeks, exerts a beneficial effect on the clinical picture and the speed of recovery after an IS. These mechanisms are mediated by the reduction of neuronal apoptosis, edema of the brain, and reduction of infarction volume. The most favorable effects were observed immediately after exercise (15, 16).

Although rare, there are cases of IS occurring during physical activity. In a series of these cases, an absence of classical risk factors for IS has been shown, but the presence of cervicocervical arterial dissection (in more than 80% of such cases) has been identified as the leading cause of IS (17).

The mechanisms by which physical activity mediates IS prevention are multifactorial. It was shown that exercise increases the levels of BDNF, which has important protective function in cell growth and neuronal activity. Physical activity stimulates neurogenesis and angiogenesis, reduces neuronal apoptosis, prevents dysfunction of the blood brain barrier, supresses inflammatory response and suppresses glutamatergic excitotoxicity (18). In this way it improves cerebrovascular function, increases the tolerance of nerve tissue to hypoxia and reduces the degree of damage to the nervous tissue, and thereby improves IS clinical presentation and provides a better degree of functional recovery reducing mortality rates (1). Physical activity leads to brain tissue preconditioning (increased tolerance to ischemia), which is mediated by increased levels of protective heat shock proteins (19). Physical activity causes an increase in the level of TNFα, which over time reduces the expression of its receptors, and thus reduces inflammatory damage in the pathogenesis of IS in which TNFα plays a major role (20).

Physical activity is important for the prevention of overweight and obesity. There is evidence of a reciprocal relationship between physical activity and obesity, and it is the explanation for the onset of diseases in which obesity has a key role among physically less active or inactive patients (21). Physical activity and proper hygiene and dietary regime are key in the prevention of obesity and IS. Physical activity in the period of development and growth exerts protective effects on the subsequent occurrence of IS (22). Again, it has been documented that the modern lifestyle is characterized by a lower degree of physical activity than that required and recommended for normal growth and development (23). Overweight and obese children are less physically active and less mobile compared to their normal weight peers. Moreover, boys are more physically active than girls and even at the age of 6 years they have better hypodermic vasomotion (24). On the other hand, obese children are less motivated for physical activity, while normal weights have a higher level of motivation for engaging in physical activity. It creates a vicious circle of obesity in adulthood, and thus the occurrence of complications such as IS. It has been shown that obesity in adolescence could be an useful predictor for the oc-currence of subsequent morbidity (4). Physical activity is associated with an increased loss of energy, which directly prevents obesity and cardiometabolic and vascular complications (25). It is significant that the obese, physically active subjects may have a lower IS risk compared with even those with normal weight (26). In contrast, subjects with a high body mass index (BMI) who are physically active, however, have a higher incidence of DM2, compared to subjects with normal BMI and less physical activity. The fact is that physical activity prevents obesity by increasing energy consumption. On the other hand, obesity causes cardiorespiratory ailments and reduced tolerance of physical exertion, which again restricts physical activity (27). The World Health Organization recommendations propose that children and adolescents aged 5 to 17 years should engage in moderate to intense physical activity for at least 60 minutes a day (28). Taking into account the modern way of life, the recommendations of the national associations propose physical exercise for 35 to 40 minutes per day (29). This would be the prevention of obesity in adolescence and thus the occurrence of IS.

The protective role of physical activity has an influence in the behavioral sphere, too. In experimental conditions it has been shown that the animals active before the occurrence of IS have had a low level of cognitive impairment, compared to those with the same type and location of IS without physical activity before IS. Furthermore, in patients with IS a higher degree of functional recovery was shown in relation to behavioral-cognitive impairment if they were physically active before the occurrence of IS (30, 31).

Physical activity after the IS

Physical activity after the IS has some positive effects on the improvement of cognitive impairment, better stability, mobility, motor strength and overall functionality. Physical activity after an

Table 2.: Overview of recommendations of physical activity after ischemic stroke (modified by Gordon et al, 2004 and Billinger et al, 2014) (36)

Model	Target
Hospitalization and early convalescence (acute phase)	
Low-level walking, self-care activities Intermittent sitting or standing Seated activities Range of motion activities, motor challenges	Prevent hypostatic pneumonia, orthostatic intolerance, and depression Evaluate cognitive and motor deficits Stimulate balance and coordination
Inpatient and outpatient exercise therapy or"rehabilitation"	
Aerobic Large-muscle activities (walking, graded walking, stationary cycle ergometry, arm ergometry, arm-leg ergometry, functional activities seated exercises)	Increase walking speed and efficiency Improve exercise tolerance Increase independence in activities of daily living Reduce motor impairment and improve cognition Improve vascular health and induce other cardioprotective benefits
Muscular strength/endurance Resistance training of upper/lower extremities, trunk using free weights, weight-bearing or partial weight-bearing activities, elastic bands, spring coils, pulleys Circuit training Functional mobility	Increase muscle strength and endurance Increase ability to perform leisure-time and occupational activities Reduce cardiac demands
Flexibility Stretching (trunk, upper and lower extremities)	Increase the range of motion Prevent contractures Decrease the risk of injury Increase the activities of daily living
Neuromuscular Balance and coordination activities Tai chi Yoga Recreational activities using paddles/sport balls to challenge hand-eye coordination Active-play video gaming and interactive computer games	Improve balance, skill reacquisition, quality of life and mobility Decrease fear of falling Improve the level of safety during activities of daily living

IS has a positive impact on the reduction of general weakness and social rehabilitation (32).

Physical activity after an IS should be organized through a special definition of the various components such as the type of exercise (cardiorespiratory, etc.), model (walking, etc.), duration, frequency, intensity, etc. Physical activity after IS should be aimed to correct the deficit incurred after the IS; to prevent a new IS, and to minimize the effect of comorbidities; to maximize the functionality of a survivor and to ensure independent performance of activities of daily living; to accelerate the psychological and social rehabilitation, and to increase the quality of life after in IS (30-32).

Physical activity should be administered early after an IS. Earliest rehabilitation, even in a hospital setting, aims to reduce the negative consequences of being bed-ridden pertaining to inadequate diuresis, loss of sodium and potassium, reduction of circulating fluid volume, immunodepression, increased heart rate, decreased muscle strength, orthostatic intolerance, as well as an increased risk of contracture and deep venous thrombosis (33, 34). Early exposure to gravitational force (occasionally standing and sitting) early after an IS has shown a marked favorable impact on the functional recovery. Impaired stability and decreased bone density at this stage usually lead to a significant increase of the fracture risk. After clinical status stabilization after an IS, the second objective of physical activity is achieving the highest possible level of functional independence, possibly returning to the level of physical activity that approximates the period before the IS. In this sense, physical activity at this stage aims to increase the degree of motor recovery (range of motion, function, stability, muscle strength, etc.). At this stage, cardiovascular exercises are usually used. It has been shown that the application of these exercises for a period of 6 days after the IS up to 6 months after the IS significantly increases the effort tolerance and walking distances compared with IS survivors who have not had this treatment (35).

Physical activity should be individually tailored to each patient, taking into account the diseases present and the degree of functional impairment. According to the recommendations, physical activity should involve mild to moderate aerobic activity and reduction of sedentary lifestyle (33) (Table 2).

Conclusions

A large number of studies have demonstrated protective effects of physical activity regarding the incidence, course and outcome of IS. Physical

activity, even as early as in childhood, reduces vascular risk factors and obesity, which in turn prevents IS. The mechanisms of prevention are mediated by a complex effect on metabolic processes. After an IS, moderate physical activity should be tailored to each of the affected, taking into account the degree of functional impairment, comorbid conditions, and should involve mild to moderate aerobic activity and sedentary lifestyle reduction.

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MEHANIZMI ZAŠTITNOG DELOVANJA FIZIČKE AKTIVNOSTI NA POJAVU, TOK I FUNKCIONALNI OPORAVAK OD MOŽDANOG UDARA

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Cilj ovog preglednog istraživanja bio je da se utvrde mehanizmi uticaja fizičke aktivnosti na pojavu ishemijskog moždanog udara, na nivo oštećenja moždanog tkiva i kliničku sliku oboljenja, kao i na nivo funkcionalnog oporavka posle ovog oboljenja. Mehanizam po kom fizička aktivnost sprečava nastanak moždanog udara je multifaktorski. Zaštitni efekti su najčešće u vezi sa modifikacijom vaskularnih faktora rizika, redukcijom neuralne apoptoze, cerebralnog edema i veličine infarkta. Fizička aktivnost povećava nivoe nekih biohumoralnih faktora, koji imaju značajnu zaštitnu funkciju za rast ćelija i neuroplastičnost. Fizička aktivnost stimuliše neurogenezu i angiogenezu, sprečava disfunkciju krvno-moždane barijere i smanjuje zapaljenski odgovor i kontroliše glutamatergičnu ekscitotoksičnost. Na ovaj način se poboljšava cerebrovaskularna funkcija, povećava tolerancija nervnog tkiva na hipoksiju i smanjuje nivo oštećenja. Na taj način se smanjuju znaci kliničkog ispoljavanja, što rezultira boljim funkcionalnim oporavkom i manjom stopom smrtnosti od moždanog udara. Fizička aktivnost dovodi do povećanja tolerancije moždanog tkiva na ishemiju, posredstvom povećanih nivoa zaštitnih heat shock proteina. Fizička aktivnost povećava nivo TNFα, koji vremenom smanjuje delovanje svojih receptora i na taj način se ograničava zapaljensko oštećenje koje u patogenezi ishemijskog moždanog udara ima najznačajniju ulogu. Takođe, fizička aktivnost je značajan faktor u prevenciji prekomerne uhranjenosti i gojaznosti, koji su vodeći faktori rizika za nastanka moždanog udara. Najveći broj studija je upućivao na zaštitne efekte fizičke aktivnosti za nastanak, tok i ishod moždanog udara. Primena fizičke aktivnosti, čak i u ranom uzrastu, smanjuje vaskularne faktore rizika i na taj način prevenira nastanak moždanog udara. Mehanizmi prevencije posreduju kompleksnim dejstvima u metaboličkim procesima. *Acta Medica Medianae 2017;56(3):70-76.*

Ključne reči: *fizička aktivnost, moždani udar*