Original Article: Investigation of Types of Neuropathies in the Brain and Nerves

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ABSTRACT

Peripheral neuropathy is the result of damage to nerves outside the brain and spinal cord and often causes weakness, numbness and pain, usually in the hands and feet. It can also affect other parts and functions of the body such as digestion, urination and blood circulation. The peripheral nervous system is responsible for sending information from the brain and spinal cord to other parts of the body. Also, peripheral nerves send sensory information to the central nervous system. Peripheral neuropathy can be caused by severe injuries, infections, metabolic problems, hereditary causes, and exposure to toxic substances, one of the most common causes of which is diabetes. People with peripheral neuropathy usually experience throbbing, burning, or tingling pain, and in many cases, symptoms improve. Especially if the cause is a treatable problem. Medicine can also reduce the pain of peripheral neuropathy. There are different types of peripheral neuropathy caused by different causes. These cases range from carpal tunnel syndrome to nerve damage due to diabetes. All types of peripheral neuropathy as a group are especially common in people over 55 years of age. This condition affects 3-4% of people in this group. Neuropathies are usually categorized based on the problems they cause and their causes. There are also terms that indicate how severe the nerve damage is.

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Introduction

Hotocatalysts Damage to the peripheral nerves causes a series of cascade events related to cellular and molecular metabolic changes in the damaged area. These changes are called Wallerin's transformation (degeneration), which is also extended to the cell body of neurons in the form of retrograde reactions and causes the swelling of the cell body, the transfer of the nucleus to the peripheral part, and the disappearance of Nissl bodies. will be Immediately after peripheral nerve damage, calcium enters Schwann cells, which causes the primary proliferation of these cells.

Schwann cells not only destroy the damaged myelin sheath, but also remove dead cells from the damaged area. During this stage of myelin phagocytosis, Schwann cells also secrete cytokines and chemokines, which attract immune cells to the damaged area [1-3].

Also, calcium enters the axoplasm of damaged axons, where it activates Calpain, which is a protease necessary for axon transformation. On the other hand, the entry of calcium in the axon at this stage is also necessary for the formation of new growth buds. Therefore, a very appropriate balance of calcium will be very effective for nerve regeneration. For this reason, calcium inhibitors may accelerate axon growth. In the next stage, macrophages accumulate in the damaged area, some of them are internal tissue macrophages, and the other part, which constitutes the majority of them, infiltrates the damaged area from the general blood circulation. The last immune cells that infiltrate the damaged area are T lymphocytes that produce pro-inflammatory and anti-inflammatory cytokines. These cytokines can increase or inhibit the function of macrophages [6, 7]. Therefore, the inflammation process occurs during nerve damage.

The most important cells involved in valerian transformation are Schwann cells and macrophages, which communicate with each other through the cytokine network and control phagocytosis and the release of nerve growth factors, which lay the groundwork for the regeneration of the damaged area. provide Achillea millefolium is a perennial aromatic plant belonging to the composite family. Several pharmacological and biological effects such as anti-spasmodic, anti-viral and anti-tumor effects have been proven for this plant [8, 9].

In some studies, the extracts of this plant have shown protective effects against oxidative stress and inflammation in tissues such as liver and stomach. Also, its aqueous extracts have reduced inflammatory responses and myelin sheath injuries in experimental autoimmune encephalomyelitis.

Peripheral nerve damage accounts for about three percent of injuries to patients. These injuries greatly affect a person's performance and lead to things like lack of sensation and lack of movement. Therefore, it is necessary to carry out extensive research to determine how to influence the inflammatory responses and increase the repair of the damaged peripheral nerve and improve its function (Figure 1).

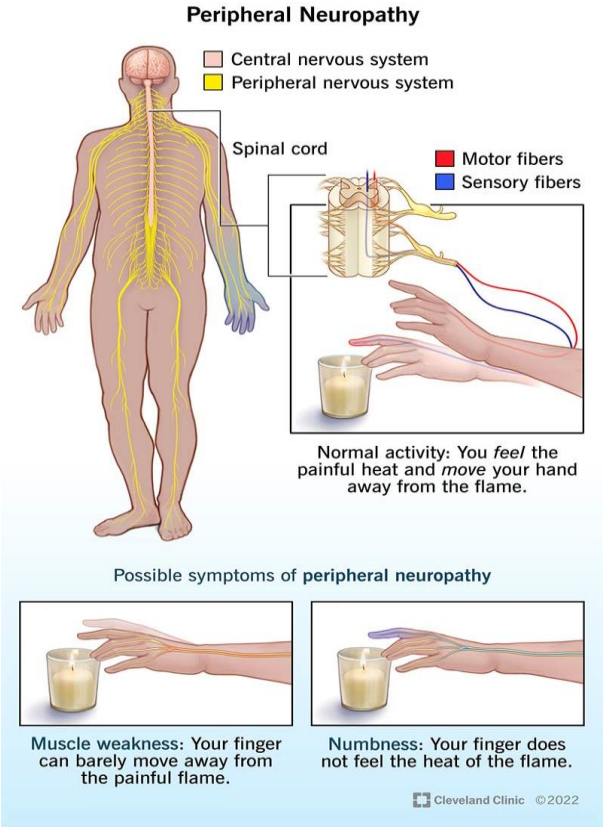

Figure 1. Investigation of Types of Neuropathies in the Brain and Nerves

There are many reports about the anti-inflammatory, antioxidant and healing effects of Achillea millefolium, but the neuroprotective role of the alcoholic extract of this plant has not been investigated. Therefore, the aim of this experimental study is to investigate the neuroprotective effect of the ethanolic extract of Achillea millefolium plant against retrograde transformation of the sciatic nerve after its compression in rats. The anti-inflammatory effect of Achillea mile folium alcoholic extract compounds can be another important factor to protect neurons in this study. These anti-inflammatory effects are caused by the large amounts of sesquiterpenes and the presence of proazolin and azulen in the extract of this plant. Currently, it is known that part of the immune response is controlled by cytokines produced by macrophages. Studies by Lopes et al. in 2005 showed that essential oil of Achillea mile folium causes macrophages to produce moderate amounts of TNF-α. and produce H_2O_2. The production of pro-inflammatory cytokines and reactive oxygen species in sufficient amounts is involved in local and natural defense and immunity. It seems that the anti-inflammatory compounds of the studied plant have helped to protect neurons by regulating the activity of macrophages and preventing excessive production of inflammatory factors [10].

It should be noted that in the study of Lopes et al., the use of commercial azuline compared to Achillea mile folium essential oil produced higher amounts of TNF-α and has become H_2O_2. On the other hand, the study of Benedek et al. in 2007 revealed a new part of the mechanism of anti-inflammatory activity of the alcoholic extract of Achillea mile folium.

This study showed that at least part of the anti-inflammatory effects of this plant is due to the inhibitory activity of protease enzymes including human neutrophil elastase, matrix metalloproteinase-2 and matrix metalloproteinase-9. One of the compounds in Achillea mile folium is a flavonoid called Quercetin, whose anti-inflammatory, anti-swelling and antioxidant effects have been proven.

Its anti-inflammatory effect is exerted by inhibiting the production of pro-inflammatory cytokines and prostaglandins. Quercetin's neuroprotective effects have been proven in animal studies with brain and spinal cord injuries [11].

This compound reduces the number of macrophages in the injury site and reduces the effects of inflammation. It also reduces the release of chemical mediators such as histamine at the site, and through the reduction of myeloperoxidase in the damaged area, it reduces the apoptosis of nerve cells and protects them. Neuropathic pain is a complex and often debilitating condition that affects the quality of life of many people who have had moderate or severe pain for years. These conditions are difficult to treat and typically only 40% to 60% of people with these conditions achieve partial pain relief. Neuropathic pain is pain caused by damaged nerves [12]. This is different from pain messages that travel along healthy nerves through damaged tissue. Neuropathic pain is often treated with different medications that are used for pain caused by damaged tissue. Medications that are sometimes prescribed to treat neuropathic pain can have devastating side effects, and as a result, people are now trying herbal products instead to help relieve pain. In the studies of Zincic et al. (2010) and Welin et al. (2009), antioxidant compounds such as melatonin and N-acetylcysteine have accelerated and promising effects on the regeneration of the sciatic nerve after crushing and cutting it.

It seems that one of the most important factors that caused neuron protection in the present study by increasing the density of alpha neurons is the antioxidant compounds found in Achillea mile folium, which there are many reports about [13]. Studies by Vitalini et al. in 2011 using spectrometric, NMR and HPLC methods showed that flavonoids, flavonol glycosides and chlorogenic acids in the alcoholic extract of Achillea mile folium have significant antioxidant effects. These compounds are free radical scavengers and remove these potentially harmful factors that cause tissue destruction and damage to DNA and cell death [14].

Symptoms of peripheral neuropathy

Each of the nerves of your peripheral system has a specific task. As a result, the symptoms depend on the type of nerve involved. Nerves are classified into the following groups:

- ❖ Sensory nerves that perceive sensations such as temperature, pain, vibration or touch through the skin.
- ❖ Motor nerves that control muscle movement.
- ❖ Autonomic nerves that control functions such as blood pressure, sweating, heart rate, digestion and bladder function.

Signs and symptoms of peripheral neuropathy may include the following:

- ✓ The gradual onset of numbness, tingling, and tingling in the hands and feet that extends to the upper arm and upper leg.
- ✓ Sharp, sharp, throbbing and burning pain.
- ✓ High sensitivity when touched.
- ✓ Pain when doing things that shouldn't be painful. For example, foot pain when bearing weight or when they are under the blanket.
- ✓ Lack of coordination and falling.
- ✓ muscle weakness
- ✓ The feeling of having gloves or socks when you don't have them.
- ✓ Paralysis, in case of involvement of motor nerves [18].

In case of autonomic nerve involvement, the signs and symptoms are:

- ✓ Heat intolerance.
- ✓ Excessive sweating or inability to sweat.
- ✓ Problems related to digestion, bladder and intestines.
- ✓ Low blood pressure that causes dizziness or lightheadedness.

Peripheral neuropathy can involve one nerve (mononeuropathy), involve two or more nerves in different parts of the body (multiple mononeuropathy), or involve several nerves (polyneuropathy). Carpal tunnel syndrome is an example of mononeuropathy. Most people with peripheral neuropathy have polyneuropathy [19].

Causes of peripheral neuropathy

Peripheral neuropathy is nerve damage that has several causes. Diseases that can cause peripheral neuropathy include:

1- Autoimmune diseases: This case includes Sjogren's syndrome, lupus, rheumatoid arthritis (joint rheumatism), Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy syndrome and vessel inflammation (vasculitis).

2- Diabetes: This is the most common reason. Among people with diabetes, more than half of them will have some kind of neuropathy.

3- Infection: This case includes certain viral and bacterial infections such as Lyme disease, shingles, Epstein-Barr virus, hepatitis B and C, leprosy, diphtheria and HIV.

4- Hereditary disorders: Disorders such as Charcomaritoth disease are types of hereditary neuropathy.

5- Tumor: Glands, cancerous and non-cancerous tumors can develop on the nerve or put pressure on the nerve. Polyneuropathy may also occur due to some cancers related to the body's defense system. These cases are a type of degenerative disorder called paraneoplastic syndrome.

6- Bone marrow disorders: This case includes the presence of abnormal protein in the blood, a type of bone cancer, lymphoma and the rare disease of amyloidosis.

7- Other diseases: This case includes kidney diseases, liver diseases, connective tissue disorder and hypothyroidism.

8- Alcohol consumption: Improper diet and alcohol consumption will cause vitamin deficiency.

9- Exposure to toxins: Toxic substances include industrial chemicals and heavy metals such as lead and mercury.

10- Medicines: Certain medicines, especially medicines used to treat cancer, can cause peripheral neuropathy [20].

11- Injury or pressure on the nerve: injuries such as injury caused by a motorcycle accident, fall or exercise can cause a cut or damage to peripheral nerves. Pressure on the nerve can be caused by wearing a splint or using an elbow crutch or by continuous movements such as typing.

12- Vitamin deficiency: B group vitamins (including B-1, B-6 and B-12), vitamin E and niacin are essential for nerve health. In many cases, there is no known cause for this disease.

Discussion

Comparison of central and peripheral nervous system lesions

Due to the presence of the blood-brain barrier, the passage of macrophages to the damaged tissues and the clearing of cellular debris in the central nervous system occurs slowly. In addition, the substances secreted in neuroglia cells are different in the central and peripheral nervous system, which causes differences in the repair process of these two systems [25]. One of the biggest differences between these two devices is that in the central nervous system, axons do not have the ability to regenerate and repair. In addition, there are factors in the central nervous system that can prevent axon repair, such as glycosaminoglycans, which are present in the extracellular matrix environment of the central nervous system [26].

Nanoparticles in the treatment of ischemic central nervous system diseases

A stroke caused by a lack of blood supply to a part of the brain is a type of neurological disorder. Production of free radicals is one of the common symptoms in stroke [27]. Some nanoparticles have the potential to inhibit reactive oxygen species in stroke. Nanoparticles of platinum and cerium oxide, due to their antioxidant properties, have been promising answers for the recovery and treatment of stroke [28]. These nanoparticles mimic the activity of antioxidant enzymes and destroy free radicals [30]. The use of these nanoparticles significantly reduces the volume of the damaged area. The use of gold nanoparticles in the treatment of stroke depends on the size of the nanoparticles. A study showed that gold nanoparticles with a size of 20 nm reduced the volume of the damaged area, while the same nanoparticles with a size of 5 nm can cause damage to nucleic acids by accumulating in the nucleus. Therefore, the antioxidant property depends on the size of nanoparticles [31]. Also, in another study, it was shown that cerium oxide nanoparticles reduced the death of rats by reducing the induction of nitric oxide synthesis in the hippocampus of rats [32]. In research conducted by Estevez and his colleagues, the effect of cerium oxide nanoparticles on animal models of stroke was investigated. In mice treated, nanoparticles by inhibiting peroxynitrite played a very important role in reducing damage caused by stroke. Also, in this research, the death of nerve cells was evaluated by the release of lactate dehydrogenase and it was observed that the death of nerve cells caused by excess glutamate was reduced by treatment with this nanoparticle [29]. Nanomaterials can also be used as gene transfer carriers to intervene in nervous system diseases [33]. Because although gene transfer by virus has been successful in the promotion and survival of brain cells, but due to the issues of safety, high biocompatibility, effective penetration into the cell and its nucleus, and precise targeting, the use of some nanoparticles for gene transfer is suggested. becomes [34]. Research showed that the use of nanoparticles causes the neutrophils that cause the immune response to be inhibited and to prevent severe brain damage in brain models [35]. It has also been shown that increased Nestin protein is effective in post-injury repair mechanisms. Also, this protein is expressed in large amounts during the early stages of development of the peripheral and central nervous system [36]. Researchers showed an increase in the number of cells expressing Nestin as a result of treatment

with silver nanoparticles in mouse models of stroke, which indicated the effectiveness of these nanoparticles in neurogenesis.

Alzheimer

Alzheimer's disease (AD) or amnestic disease is a type of brain disorder with gradual weakening in which the functions and mental abilities of the patient are degraded [37-39]. In Alzheimer's disease, a recent event usually occurs first, and unfortunately, a cause or a suitable treatment is not available. Accumulated evidence supports the hypothesis that oxidative stress produced by different mechanisms may be among the main factors promoting neurodegeneration [40]. The accumulation of amyloid plaques is one of the known causes of Alzheimer's disease, which is found in all parts of the brain of these patients, and in laboratory environments, beta amyloid is used to induce Alzheimer's disease in mice [41]. In their research, D'Angelo et al found that treatment with cerium oxide nanoparticles protects brain neurons against oxidative stress induced by beta amyloid.

In this research, the effects of cerium oxide nanoparticles on known signaling pathways in the survival of neurons such as the signaling pathway (Brain derived neurotrophic factor; BDNF) and (Extracellular signal regulated kinase 5; ERK5) were investigated and the results obtained on the neurotrophic role of this emphasized nanoparticles as a factor that can modulate the important pathways of neuronal cell survival [42]. Also, Das et al investigated the antioxidant and neuroprotective properties of cerium oxide nanoparticles in spinal cord injuries. In this research, it was observed that treatment with this nanoparticle causes the growth and survival of nerve cells in the spinal cord. It is possible that the existence of different capacities of cerium such as Ce3+ and Ce4+ can act as an antioxidant and remove free radicals from the tissue [20]. Among the factors that cause the accumulation of beta amyloid proteins, we can mention metal ions such as copper and iron, which increase with age in the brain [43]. Nanoparticles can remove metals from the body or prevent their undesirable functions through their specific bonds [44]. Nanogels have received attention due to their high stability, ability to respond to external stimuli, high and accurate loading of active substances such as drugs. In Alzheimer's disease, nanogels are also used to prevent the accumulation of amyloid beta plaques [45]. In research that investigated the effects of silver nanoparticles on Alzheimer's disease, the results showed that the surfaces of silver nanoparticles can act as a nano chaperone and inhibit the formation of amyloid fibers. As a result, the medicinal use of these nanoparticles can be useful for the treatment of Alzheimer's disease [46]. Dowding J and his colleagues showed that cerium oxide nanoparticles can switch between their Ce3+ and Ce4+ states and thus are able to remove superoxide anions and hydrogen peroxide. Also, these nanoparticles accumulate in the outer membrane of mitochondria and prevent the collapse of the mitochondrial structure due to the toxicity caused by beta amyloid. Therefore, cerium oxide nanoparticles have antioxidant properties and drug treatment by this nanoparticle can prevent the destruction and death of nerve cells in Alzheimer's disease [47].

Parkinson

Parkinson's disease (PD) mainly affects brain dopaminergic cells [48]. Parkinson's is a multifactorial cascading disease that typically affects people over the age of 65. Loss of dopaminergic neurons leads to tremors, speech and memory impairment [49]. A subset of patients appears to follow an autosomal dominant inheritance pattern, although in most cases the inheritance pattern is undetectable [50]. Researchers used a method based on nanoparticles to prevent neurodegeneration in animal models of Parkinson's disease to transfer plasmids containing desired genes to the brain. This approach discovered a gene therapy-based approach to treating Parkinson's disease that had the potential to repair faulty genes. Iron oxide nanoparticles, by affecting the interaction of neurons and surrounding cells, play a significant role in increasing the regeneration capacity of neurons after spinal cord injury.

The ability of magnetic iron oxide nanoparticles to track the migration of leukocytes and track cells inside the body can be useful in the study of

central nervous system lesions such as Parkinson's, stroke, brain tumors, epilepsy and Alzheimer's. Stressed or disabled neurons need more energy to survive and repair and improve their function. Improving metabolic pathways and improving levels of adenosine triphosphate and nicotinamide adenine dinucleotide are among the characteristics of nanoparticles on the brain [51]. For example, introducing a suspension containing gold nanoparticles into the body of rats has been effective in improving the symptoms of Alzheimer's and Parkinson's disease [52].

Multiple sclerosis

Although the cause of multiple sclerosis is unknown, it seems to be caused by gene and environment interactions, and diet, sunlight, infections, and genetics are important factors in MS patients. Despite promising advances in the understanding of modern diseases, precise details about inflammatory processes are still not available [56]. MS is an inflammatory disease that destroys the central nervous system, especially in adults, which causes numbness and loss of vision. In the early definitions of MS disease, it was described as a disease in which inflammation around blood vessels and damage to myelin are seen [57].

It has been identified in more than 2 million people worldwide, mainly based on medical history and clinical examination of the patient [58]. This disease has become a model for the study of immunology and research on the nervous system and is measured using the diagnosis and evaluation of the response to therapeutic agents. Nanoparticles are programmable biological materials that have a very high ability to transport and deliver targeted drugs and help to connect therapeutic proteins and restore damaged circuits. For example, researchers were able to control MS and reduce its complications by using iron nanoparticles [59-61].

Given the currently available surface modification techniques, nanoparticles have the ability to deliver not only traditional drugs and molecules or diagnostic agents, but also nucleic acids. Also, nanoparticles have more control over the release of substances [59]. This method is very effective and practical especially in diseases of the central nervous system. Obstruction of blood flow in narrow vessels and increased production and accumulation of reactive oxygen species in MS lead to activation of macrophages and apoptosis in oligodendrocytes. The use of nanoliposomes in modern drug delivery systems, while having many structural similarities to biological membranes, can show fewer side effects and better treatment process in the target tissue with controlled release and accurate targeting. In research, the use of nanocarriers such as nanoliposomes have shown promising results in improving MS symptoms [61].

Nanoparticles in the treatment of peripheral nervous system diseases

Considering that various mechanisms play a role in the repair of peripheral nerves, as a result, various molecular signals can be effective in these processes. These signals can play a role in these complex processes separately or in cooperation with each other using specific methods such as specific expression or deletion of genes in nerve tissue cells or using specific antibodies. Several factors can cause peripheral nerve damage. In addition to causing changes in the axon of damaged neurons, damage to peripheral nerves can also cause dysfunction of the organs related to them [56]. Today, it has been shown that the target organ has a supportive effect on motor neurons by secreting trophic factors, without which the preservation and survival of these neurons is impossible. With nerve damage, neurons are deprived of these trophic factors, and in most cases, in addition to the death of neurons, the organ associated with these nerves also atrophies.

Conclusion

Diabetic neuropathy (DN) is one of the disorders that follows diabetes and includes peripheral nerve disorders in people with diabetes mellitus, which can lead to pain symptoms and loss of sensation. This disease is associated with

structural changes in peripheral nerves, including axonal atrophy, demyelination, reduction of nerve fibers and slow regeneration of nerve fibers. In general, diabetic neuropathy is a descriptive term that includes a spectrum of clinical syndromes that include different anatomical distributions, treatment courses, and possibly different pathological mechanisms. The most common clinical syndromes involving diabetes are classified into two categories: diffuse and focal neuropathy. Diffuse neuropathy includes peripheral diabetic neuropathy and autonomic diabetic neuropathy, which are very common and progressive. In peripheral diabetic neuropathy with increasing duration and severity of diabetes, sensory deficits usually overshadow motor nerve function and appear first in the lower parts of the body, and its symptoms vary depending on the type of fibers involved. Peripheral diabetic neuropathy is considered as the most known form of diabetic neuropathy due to its high prevalence. Peripheral diabetic neuropathy affects both sensory and motor parts, but the dominant disorder is manifested in sensory function.

While focal diabetic neuropathies are usually rare, they are less common and increase sharply at first and are self-limiting within six to eight weeks, and are more likely to occur in the elderly. In general, diabetic neuropathy occurs as a result of damage caused by hyperglycemia to nerve cells and neuronal ischemia caused by a decrease in vascular-neural flow stimulated by hyperglycemia. Neuropathy caused by diabetes involves different anatomical distributions, treatment courses, and possibly different etiological mechanisms. The creation of pathological conditions and neurodegeneration in sensory neurons is caused by the disruption of the neuron's cytoskeleton structure following the phosphorylation of Na instead of neurofilaments in the place of the nerve cell, which leads to the disruption of the neuron structure. Weakness of sensory neurons in the dorsal root ganglia (DRG) leads to destruction of peripheral axons in these neurons as well as central sensory neurons. Disorders in these neurons can lead to factors such as neuropathic pain, hyperglycemia, and sensory organ syndrome. In fact, in sensory neurons, Na phosphorylation instead of neurofilaments is the main reason for the emergence of neurodegenerative conditions.

On the other hand, the local changes that exist after injury are related to the function of immune cells, the development of macrophages and T cells. Increased synthesis, expression, and release of cytokines such as IL-6, IL-1, and TNF-α are among the causes of failure in sensory neurons, which cause spontaneous firing of nerve messages from sensory neurons. In pathological conditions such as diabetic neuropathy, the amount of nerve destruction exceeds nerve sprouting. It has been reported that after nerve injury, peripheral neurogenesis is impaired in streptozotocin (STZ)-stimulated diabetic rats. This disorder is caused by deficiencies in one or more sets of nerve processes, including delay in the initiation of germination, reduction in the amount of germination, and disturbance in the swelling of nerve fibers. Streptozotocin causes permanent hyperglycemia and hyperinsulinemia in diabetic animals, and finally, the entry and accumulation of excess glucose in neurons causes destructive metabolic pathways. In various models of rats and other animal samples following the development of diabetes, the symptoms of diabetic neuropathy have overlapped with the appearance of these destructive conditions in neurons, which first involve sensory neurons and then motor neurons. Oxidative stress generated under diabetic conditions is involved in the development of pancreatic beta cell dysfunction. Due to the relatively low expression of antioxidant enzymes such as catalase (CAT) and superoxide dismutase (SOD), pancreatic beta cells may be vulnerable to free radical attack when the system is under oxidative stress. In many previous studies, it has been stated that ß-cell dysfunction causes long-term exposure of cells to glucose or free fatty acids or a combination of both. Destruction of insulin-secreting ß-cells of the pancreas following STZ injection causes a sharp decrease in insulin levels and therefore hyperglycemia. Diabetes also leads to a decrease in the capacity of antioxidant defense in peripheral nerves. During diabetes, hyperglycemia, and finally, the

increase in glycosylation of molecules, the change in protein kinase C activity and the increase in mitochondrial superoxide production cause an increase in oxidative stress due to an increase in the production of free radicals. Under normal conditions, the amounts of activated oxygen species and antioxidants are in a balanced state.

When the balance is disrupted to increase reactive oxygen species, especially during intense exercise, it causes oxidative stress. In fact, oxidative stress occurs in the biological system when the production of reactive oxygen species exceeds the capacity of antioxidant defense. Oxidized byproducts of free radicals cause damage to proteins, lipids and nucleic acids. Impaired function of proteins with impaired mechanism function slows down the speed of axon transmission and reduces the support of neurotrophies. Neurotrophies refer to a group of secreted proteins that are produced by structures in the nervous system. The most important neurotrophies are brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF), which play a direct role in reducing the incidence of Alzheimer's disease and Parkinson's disease, respectively. GDNF monomer with a molecular weight of 15 kDa, which is made in the substantia nigra and released into the striatum, protects dopaminergic neurons from damage caused by toxins, thereby improving motor function. More precisely, by binding to the GFRα2 receptor, GDNF causes the expression of anti-apoptotic proteins and the increase of antioxidant enzymes, and in this way, it is known as an important maintenance factor for dopamine-producing neurons.

Many studies have stated that moderate levels of oxidative stress and pro-inflammatory factors increase the expression of neurotrophies in the brain through the activation of nuclear factor kappa B (NF-KB). Nuclear factor kappa B is a member of the family of inducible nuclear factors, which is expressed in a variety of cells in the central nervous system, such as microglia, astrocytes, and neurons, and mediates neurotrophic responses caused by proinflammatory cytokines and oxidative products. cries the formation of reactive oxygen species causes the activation of various stress-sensitive intracellular signaling pathways, including NF-κB, mitogen-activated protein kinase (P38MAPK), and protein kinase C. Activation of these cell signaling cascades is not only associated with the development of diabetic complications, but also with insulin resistance and pancreatic beta cell dysfunction. Among these cellular cascades, the NF-KB pathway plays a central role as a mediator of immune and inflammatory responses. Excessive levels of free radicals cause damage to cell proteins, cell membrane lipids, nucleic acids and sudden cell death. Various mechanisms have been proposed to participate in the synthesis of these free radicals in diabetes. Glucose oxidation is the main source of free radicals. By increasing intracellular oxidative stress, advanced glycation end products (AGEs) activate nuclear factor kappa B. Thus, upregulation of target-controlled generation of NF-κB is improved [30]. Nuclear factor kappaB is responsible for regulating the expression of a large number of genes that lead to the reduction of diabetic complications. Although radical species caused by oxidative stress in high amounts cause oxidative damage, it has been found that hydrogen peroxide (H_2O_2) in moderate levels causes a series of very important physiological events such as angiogenesis, through the activation of NF-κB. Expression of antioxidant enzyme and expression of neurotrophies. In this regard, Sen and Parker (1996) stated that H_2O_2 is the strongest stimulus for NF-KB activation, and increasing catalase expression decreases NF-KB activation and increasing Mn-SOD expression due to the conversion of superoxide to (H_2O_2) increases NF-κB activation. According to the above explanations, the majority of evidence shows that oxidative stress is involved in the increase of cardiovascular diseases, high blood pressure and diabetes. Once free radicals are released, damage is done to the host cell composition and antioxidant defenses are widely deployed to protect against damage induced by reactive oxygen species. This wide range of active antioxidants in the human body, which includes enzymatic and non-enzymatic antioxidants, is supplied from the diet, including

the main reactive species produced in superoxide cells.

Superoxide dismutase was discovered in 1969 by McCord and Friedwich. They are the first line of defense against superoxide radicals. Because superoxide dismutase dismutase's superoxide radicals to form hydrogen peroxide and oxygen. Superoxide is mainly formed as a mediator in biochemical reactions. Dismutation of superoxide is catalyzed by superoxide dismutase. Catalase plays an important role in removing hydrogen peroxide. This enzyme exists in peroxisomes and cytoplasm and consists of four subunits and each monomer contains one group. This enzyme very actively and effectively converts hydrogen peroxide into water and oxygen molecules and neutralizes its toxic effects. According to some evidence, increasing physical activity and exercise can strongly influence the pathological factors associated with diabetic neuropathy through the development of vasodilation, reduction of oxidative stress and increase of growth factors [2]. Research results show that diabetes causes a significant decrease in the amount of superoxide dismutase with the abundant formation of superoxide anions, which results in a decrease in the activity of enzymes that remove hydrogen peroxide, such as catalase and glutathione peroxidase.

Therefore, reducing the activity of catalase may lead to some harmful effects caused by superoxide radicals and hydrogen peroxide, but it has been reported that physical exercise can play a protective role by increasing the activity of superoxide dismutase, catalase and glutathione peroxidase enzymes in the cerebral cortex of rats. against oxidative imbalance and brain damage caused by induction of homocysteine. In the research conducted by Powers et al. (2010), Radak et al. (2006) and Chow and Kim (2009), it was also shown that regular endurance sports activity leads to brain plasticity, strengthening of the antioxidant system, and increased regulation of neurotrophies. and prevents the apoptosis of nerve cells. Kluding et al. (2012) stated that probably the change in lifestyle including healthy eating, increasing physical activity and exercise can significantly reduce the prevalence of diabetes and its complications such as neuropathy.

The changes caused by exercise training in neurons are actually caused by changes in energy metabolism, lysosomal activity, RNA biosynthesis, increased acetylcholine transfer and increased sprouting rate following nerve cutting. Therefore, it seems that neurons adapt to decreasing and increasing activity biochemically, and such biochemical changes can help maintain the survival of neurons. Pro-inflammatory agents increase the expression of neurotrophies and protect the brain in both in vivo and in vitro conditions. Tumor necrosis factor alpha (TNF-α) and interleukin 1 beta (IL-1β) are two important pro-inflammatory cytokines that are expressed and produced following the activation of various types of immune cells and structures in the brain such as astrocytes and glial cells. Tumor necrosis factor alpha by binding to the TNF-R receptor on the surface of cells in nerve structures causes the release of the inhibitory protein from the NF-KB complex, which in turn causes the transfer of the p50-p65 dimer from the cytoplasm to the nucleus and binding to the special region. E of the nortrophin gene and in this way, increases the transcription of BDNF and GDNF neurotrophies. Due to their important physiological roles in the brain, BDNF and GDNF neurotrophies affect the cognitive and motor functions of a person, respectively. Studies have reported that the levels of these neurotrophies are low in people suffering from various types of neurological diseases, such as Alzheimer's, Parkinson's, and Huntington's, and studies have used the approaches of injecting neurotrophies and using drugs that stimulate the endogenous production of neurotrophies. In other studies, exercise has been mentioned as a preventive and therapeutic tool for disorders during which neurotrophies decrease and increase their induction in the brain. It has been shown that four weeks of optional exercise training, daily exercise training and every other day and eight weeks of moderate intensity swimming exercise training increase the levels of neurotrophies. Despite this, exercise training for a short period of time (two weeks at a speed of 10 m/min) had no effect on the levels of neurotrophies. Kote et

al. (2011) reported in a study that 4 weeks of step exercise training increases spinal cord GDNF levels in rats with spinal cord injury. It has also been stated that long-term exercise increases the levels of GDNF in the cervical spinal cord of rats through increasing H_2O_2 levels. Most importantly, it is not yet clear what type of exercise works best for people with diabetes. This research aims to answer the question of whether these training protocols change the expression of neurotrophic proteins and nuclear factor kappa B and antioxidant stress indices by testing six weeks of intermittent and continuous aerobic training on diabetic rats.

Do the mentioned proteins and antioxidant indicators create? If there is a change, which method is more effective? If the positive effect of each of the above exercise methods on the mentioned indicators is proven, it is possible to recommend the best exercise approach for improving diabetes. Nuclear factor kappaB is responsible for regulating the expression of a large number of genes that leads to the reduction of diabetes complications, and considering that catalase and superoxide dismutase are among the most key variables affecting NF-κB and antioxidant pressure, in this research have been used.

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