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REVIEW

Pathogenesis of Musculotendinous and Fascial Injuries After Physical Exercise - Short Review

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Purpose: The identification of sports and physical exercises with injury risk is necessary to preserve the capacity of athletes and people who perform physical education and also to prevent the installation of functional deficiencies.

Methods: We have selected the articles related to the pathogenic mechanisms involved in musculotendinous and fascial injuries produced as a result of physical exercise.

Results and Discussions: The lesional pathogenesis is complex and incompletely clarified. Recent theories put in a new light the mechanisms of muscle pain and tendinopathy production. The accumulation of lactate anion, known to be a residue that induces fatigue and muscle pain, has been reconsidered by some authors. It appears that lactate anion is an excellent fuel for the myocardial fiber. Moreover, the accumulation of lactic acid after intense physical exercise could prevent the inexcitability of the sarcolemma induced by the increased concentration of interstitial K^+. Most of the time, overuse injuries are not limited to muscles. They can cause myofascial, myotendinous or purely muscular injuries. The muscular fascia is more susceptible to injuries produced under the action of large external forces. Also, fascia is more sensitive to pain compared to muscle when external forces act eccentrically. Overloading the tendon and putting it under tension repeatedly is followed by ruptures of the tendon fibers. The regeneration of the degenerated tendon is defective in the context of the inflammation produced by the injury. Tendon fibers undergo a process of fibrosis, scarring, adhesion and heterogeneous calcification. Oxidative stress is responsible for inflammation, degeneration and apoptosis of tenocytes.

Conclusion: The benefits brought by physical education and sports are indisputable, but their practice requires a coordinated program to prevent possible traumatic and overuse injuries.

Keywords: sport muscle injury, musculofascial injury, pathogenesis, stress tendinopathy, delayed onset muscle soreness

Introduction

Prolonged physical exercise promotes health through multiple mechanisms. Muscle contractions during physical exercise remodel the structure of the blood network. Recent studies have demonstrated that mechanical and hemodynamic stimuli mediate angiogenesis. Thus, increasing the speed of blood flow through the vessels during physical effort, stimulates the development of the vascular bed by increasing shear forces. Blood vessels enlarge by stimulating the vascular endothelium with the participation of nitric oxide.[1] The favorable effect of physical exercises was noted also by other researchers. Thus, Hotta et al highlighted that the stretching of muscle fibers repetitively post-exercise brings a benefit to the vascularization of the muscle tissue. They found that daily muscle stretching increases local blood flow through vascular endothelium-dependent vasodilatation and determines angiogenesis.[2] Another study team led by Behnke concluded that the decrease in exercise capacity in the elderly is due to the decrease in blood flow in the striated skeletal

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muscles. Therefore, muscle vascularization in old age can be improved with the help of physical exercise supported by increasing blood flow.[2,3] Despite all these benefits, the practice of sports must be carried out in a controlled environment and according to a predetermined program to prevent the injuries characteristic of each type of sports activity. For the optimal management of musculotendinous and fascial injuries, as well as for the recovery of athletes' capacity, a better understanding of the pathogenic mechanism of traumatic injuries is necessary.[4] Physical exercises with excessive loading of the musculotendinous and fascial tissues can cause injuries grouped into 3 categories, myofascial, myotendinous and muscular, depending on the election areas. Myofascial lesions are located at the level of the fascia, in the epimysium and its deep ramifications, perimysium and endomysium, but they can also affect the insertions between the fascial connective tissues and muscles. Myotendinous lesions affect the two tendons, proximal and distal, or the tendinous insertions of the muscles. The muscle injuries are located at a distance from the fascias and tendons and strictly affect the muscle fibers. The location of the lesion is important for a correct diagnosis and adequate therapeutic management.[4] According to the etiology, injuries associated with sports can be traumatic and through overuse. Regardless of their etiology, sports injuries require medical care and even surgical interventions followed by long-term medical recovery. Because the costs required for medical assistance are burdensome, are responsible for low performance, intense pain and affect the patient's quality of life, the prevention of sports injuries is the target objective.[5]

Materials and Methods

This systematic review used a PubMed, Google Scholar and Web of Science databases search for scientific with the help of the keywords: sports muscle injury, musculofascial injury, pathogenesis, stress tendinopathy, delayed onset muscle soreness. We collected information about the pathogenesis of muscle, tendinous and fascial injuries after overuse in the physical education and sports program, with the aim of a better, focused understanding of these issues. A brief review of the mechanisms involved in the pathogenic process was prepared.[5] We have selected 19 qualitative articles related to the pathogenic mechanisms involved in musculotendinous and fascial injuries produced as a result of physical exercise (Table 1), which represented the most relevant results of our database search. We have such cited each included study and present its characteristics. As an exclusion criterion, articles that were published earlier than 1985 were excluded. The exclusion criteria also included articles that did not assess musculoskeletal injuries, nor sports related injuries; duplicates of articles in the same journal, published abstracts and articles not published in English were also excluded. The study variables included and were based on the ones from the previous studies analyzed.

Table 1 Scientific Articles That Described the Pathogenic Mechanism of Sports Injuries

Year of Publication	Author	Pathogenic Mechanism
2019	Wilke et al[4]	Experimental electrical stimulation shows that fascia is more sensitive to pain than muscle under the eccentric action of external forces
2019	Schleip et al[6]	The muscle fascia shows a small degree of contraction due to the myofibrils in its structure. The painful fascia has greater thickness and is rigid.
2021	Wilke et al[7]	DOMS is caused by stimulation of the proprioceptors in the muscles
2009	Gibson et al[8]	Experimental irritation of the extensor digitorum longus fascia in rats with overload of this muscle was significantly more painful compared to naive rats.
2018	Zugel et al[9]	Tendon fibrosis is caused by excess collagen produced by fibroblasts stimulated by TGFβ under the action of substance P in the context of post-injury inflammation.
2019 2012	Bangsbo et al[10] Bandschapp et al[11]	The lactate anion is not a residue. Its accumulation does not cause, but rather contributes to the onset of muscle fatigue. The decrease in cellular pH caused by the accumulation of lactic acid after intense exercise could prevent the inexcitability of the sarcolemma induced by the increased concentration of interstitial $K.^{+}$

(*Continued*)

Table 1 (Continued).

Year of Publication	Author	Pathogenic Mechanism
2006	Shireman et al[12]	MCP-1 activates and modulates macrophages; it intervenes in tissue repair after ischemia caused by fascial inflammation.
2014	Wang et al[13]	Macrophages accumulate in injured muscles. Tissue repair is initiated by local stem cells that participate in angiogenesis.
2010 2013	Fedorczyk et al[14] Gao et al[15]	Inflammatory cells accumulate in overworked muscles and tendons and release cytokines. Macrophages induce an increase in the level of substance P which decreases muscle strength.
2018 2009	Aicale et al[16] Abate et al[17]	Overstrain of the tendon causes small tears in the structure of the tendinous fibers. The damaged tendon shows hypoxia, fatty, hyaline, fibrinoid or mucoid degeneration.
2022 2020	Lui et al[18] Xu et al[19] Li et al[20]	Dysregulated expression of nesfatin-1 in the context of obesity induces heterotopic ossification in the damaged tendon structure. Tendon fibers are more affected by local hyperthermia than by zonal microvascular alteration.
2006	Sharma et al[21]	Tendon healing is promoted by MMPs and TIMPs that intervene in collagen degradation and remodeling.
2007	Murrell et al[22]	iNOS, eNOS and bNOS intervene in tendon healing by amplifying collagen production and are overexpressed in the injured tendon.
2003	Petersen et al[23]	VEGF stimulates angiogenesis and mediates tendon repair through the overexpression of MMPs.

Results

Muscle injuries caused by overuse are almost always accompanied by fascia injuries due to the tight connection between the two structures.[6] The fascial tissue in the human body creates a network that actively participates in musculoskeletal biomechanics. For a long time it was believed to be a passive, almost inert structure. Newer studies have shown that the fascia has a role in taking over and redirecting external forces to the muscles. Moreover, the muscular fascia actively contracts by means of myofibroblasts whose density differs by region.[6] Immunohistochemical analysis of myofibroblast density by staining human α-SMA cells after autopsy, showed that the lumbar fascia has a higher myofibroblast density than the plantar fascia and fascia lata. The measurement of mechanical force on rat fascias demonstrated the presence of a degree of fascial contraction. Myofascial tension is mediated by myofibroblasts and influences muscle and skeletal dynamics. Fascial pain was associated with a greater thickness on ultrasound examination and a limitation of the shearing movement of the fascial tissue that induces stiffness affecting dynamics and posture. Recent studies have noted that H1 histamine receptors located on the surface of fascial myofibroblasts could represent a therapeutic target for modulating fascial tissue contractility.[6]

Wilke and his study team observed that overuse can affect both the fascia and the muscle, because the fascia is molded on the muscle, making the two structures tightly joined. An exaggerated stretch of the muscle has an impact on the fascia and can be followed by ruptures of the fascial tissue. We can say that post-overuse injuries cannot be limited to muscles only. This result contradicts the opinions of other authors who note that intense physical exercise mainly affects the skeletal muscles. Moreover, Wilke appreciates that the ratio - isolated muscle injury: myo-fascial injury, is 1:8. It seems that the border between the muscle fibers and the fibrous connective tissue is the most susceptible to injury. The authors propose the term "myocollagenous strain injury" instead of "muscle strain injury" because it better expresses the type of affected tissue. The elective localization of lesions at the myotendinous junction is explained by the transmission and absorption of forces at the time of muscle contraction. Approximately one third of the injuries are located in the epimysium, fascia or at their junction with the muscle. There are opinions that the connection structures between the muscle fibers, respectively the muscle bundles and the connecting connective tissues (endomysium, perimysium, epimysium) intervene in the transmission of forces, their absorption and distribution. This assumption is supported by the frequent identification of perimuscular thecal injuries during sports activities with sudden movements. Although the fascia is resistant to the action of elongation and deformation forces, it becomes vulnerable to the sudden action of large external forces. Wilke and his study team concluded that the fascia contributes to the distribution of external forces to the muscles, and if the forces are greater than the tolerance of the fascia, it can degrade.[4]

The most common clinical manifestation following sustained physical effort is muscle pain. The excessive demand of muscle groups during intense and sustained physical exercise is followed by muscle pain accompanied by stiffening of the affected tissue. Delayed onset muscle soreness (DOMS) is a clinical entity that begins in the first hours after physical exercise and is accentuated in 1–3 days.[7] Classic theories regarding the pathogenesis of muscle damage blame the inflammation produced by the excess of lactate anions, but newer research shows a deterioration of the entire myofascial connective tissue.[4,8] It was believed that DOMS is only the result of the stimulation of proprioceptors in the muscles that cause a modified response through spinal motoneurons, followed by the limitation of muscle strength in the injured area.[7,9] Experimental evidence shows that fascia is more sensitive to pain compared to muscle when external forces act eccentrically. DOMS appears to be caused by fascia rather than muscle. Experimental electrical stimulation of the fascia caused much greater pain than muscle stimulation. The proven fascial nociception could direct therapeutic management towards new perspectives in sports traumatic pathology.[4] Another study team led by Gibson obtained similar results. They observed that the irritation of the fascial tissue of the extensor digitorum longus in rats that suffered an overload of this muscle was significantly more painful compared to naive rats. Therefore, DOMS is mainly caused by the fascia rather than the muscles.[8]

Skeletal striated muscle fibers produce lactic acid during contraction as well as at rest. The amount of lactic acid produced at rest and during small efforts is very small. The resulting lactic acid is absorbed by the tissues so that the blood level of the lactate anion is maintained at very low values. Lactic acid is found mainly in the form of lactate and results from glycolysis of glycogen deposits or glycolysis of glucose molecules from the blood. Lactate level increases with the intensity of physical effort. In the case of trained muscles, the accumulation of lactate in the blood is lower because the mitochondria of muscle fibers have a greater capacity to produce energy stored in adenosine triphosphate (ATP) molecules. The blood lactate is absorbed by the myocardium, the kidney tissue and other muscles, after which it is transformed into energy, while the liver takes the lactate and converts it into glucose. It is considered that lactate is not a residue. Most of the lactate molecules dissociate into a lactate anion and a proton, H^+. The dissociation of lactate induces an increase in the concentration of H^+, realized by a decrease in pH with a tendency to acidosis. The accumulation of lactate anions and hydrogen ions causes muscle fatigue indirectly, by increasing the release of potassium ions from the contracting muscles. In other words, the accumulation of lactate anion does not cause, but rather contributes to the appearance of muscle fatigue. In the case of athletes, physical training has the benefit of an increased capacity to transport and buffer the lactate anion and H^+.[10]

The mechanism of producing muscle fatigue issued divergent opinions among the authors. The increased level of K^+ at the level of the interstitium affects the transmission of the electrical depolarization of the sarcolemma by law of proximity and is the basis of muscle fatigue. Newer theories claim that lactic acidosis inhibits the coupling of excitation with contraction to a small extent and the low pH induced by the lactate anion has a negligible effect on the contractility of skeletal striated fiber under homeothermic conditions. Studies have shown that lactate anion is not a useless waste at the tissue level. There are also opinions that emphasize that the lactate anion represents an excellent fuel for the myocardial fiber. The decrease in pH in the cell caused by the accumulation of lactic acid after intense physical exercise could prevent the inexcitability of the sarcolemma induced by the increased concentration of interstitial K^+.[11]

Fascial tissue injuries reduce sports performance and can develop a wide range of musculoskeletal disorders. A better understanding of the pathogenic process of musculotendinous and fascial injuries is useful for directing management. The presence of collagen fibers in the structure of the fibrous tissue of the muscular fascia, both loose and dense, allows an integrative functioning of the muscular system.[9] In a broad sense, the fascial tissue includes several structures with a clearly defined role, such as: aponeuroses, fascias of the viscera, ligaments, tendons and other connective tissues (endomysium, epimysium, perimysium), septa, retinacula and joint capsules.[24] Sustained physical exercise produces tissue damage followed by inflammation that induces acute and chronic tissue ischemia.[9] The local inflammatory process has an important role in the development of the network of collateral arterioles and in muscle regeneration. The mechanism is not very clear, but it seems that a chemokine, Monocyte chemoattractant protein-1 (MCP-1), also called C-C motif chemokine ligand 2 (CCL2), is involved in the activation and modulation of macrophages and implicitly in tissue repair after ischemia through its receptor C-C chemokine receptor type 2 (CCR2).[12] Similarly, Wang demonstrated using transgenic mice as experimental models, that macrophages accumulate in injured muscles. Skeletal striated muscles

have a great capacity for regeneration. Tissue repair involves the recruitment of inflammatory cells and then angiogenesis in which local stem cells participate.[13] Macrophages and other inflammatory cells at the site of the injury release cytokines with inflammatory potential, especially interleukin (IL)-1β, IL-6 and tumor necrosis factor alpha (TNFα), proportionally to the intensity of the overload. Infiltration with macrophages is accompanied by an increase in the level of substance P in the affected muscles and tendons and correlates with a decrease in muscle strength.[9,14,15] Destroyed cells are phagocytized within the immune response.[14] The accumulation of cytokines sensitizes nociceptors that stimulate the synthesis of substance P. After the mechanical overload, but also throughout regeneration, substance P induces an increased level of transforming growth factor beta (TGFβ) which stimulates fibroblasts from the damaged tendon to produce excess collagen. As a result, collagen deposition increases in the fascial tissue and fibrosis occurs. Nerve fibers are embedded in areas of microfibrosis and the pain is amplified.[9] Non-steroidal anti-inflammatories reduce inflammation and promote tissue regeneration if administered before exercise.[25,26]

Along with the muscle fascicles, the tendon takes the force load and is susceptible to injuries. Tendinopathy produced by overuse is accompanied by pain and swelling of the tendinous fibers. It is followed by a decrease in tolerance to physical exercise, and over time tendinous degeneration sets in. Overloading causes small breaks in the structure of tendinous fibers as a consequence of reducing the diameter and density of collagen fibers with the loss of parallelism between the fibers.[16] The term "tendinitis" was replaced by "tendinosis" which better expresses the degenerative nature of the lesion, but the general term "tendinopathy" is more convenient and accepted by most authors. Tendon fibers are affected during the aging process by reducing arterial blood flow that induces hypoxia, affects metabolism and determines the formation of free radicals. The affected tendon becomes painful during movements, limiting activities, and sometimes the pain can be present even at rest. An intense activity or a sudden movement can cause the sudden rupture of the inflamed tendon.[17]

Some authors consider that post-exercise injuries are caused by several intrinsic and extrinsic traumatic factors. The extrinsic factors are represented by fatigue and error in training, wrong running techniques, inadequate surface of the playing field, excessive effort on a hilly surface, low environmental temperature of the exercising space, inadequate equipment and footwear. Intrinsic factors refer to some pathological conditions of the athlete, such as the elements of the metabolic syndrome: obesity, arterial hypertension, diabetes, hyperuricemia, dyslipidemias. Most of the time, the tendon is subjected to inflammatory and degenerative changes at the same time. The affected tendon changes its bright white color, becoming gray on its entire surface or only partially. Almost always, the painful tendon shows degenerative changes in the histological examination such as hypoxia, mucoid, hyaline, fibrinoid, myxoid or fatty degeneration. Metaplasia of tendinous fibers to fibrocartilage or bone is very rare. Sometimes tendinous fibers can present calcifications. Degenerative changes of the tendon can often be found in healthy people over 35 years old, without symptoms. Painful degenerated tendon can often be accompanied by the formation of new blood vessels through the proliferation of existing ones. The formation of neo-vessels is found especially in tendons that have a synovial sheath. Intratendinous neovascularization was observed on power Doppler and color ultrasound. Histologically, the acute process presents a fibrinous exudate and intensively proliferating fibroblasts. Inflammatory processes appear in the first 3–7 days after the onset of the injury and coexist with the regenerative and degenerative processes in tendinopathy. Early on, monocytes and macrophages phagocytize the necrotic areas, then other inflammatory cells, mainly neutrophils, accumulate at the site of the injury. Platelets are activated and chemotactic and vasoactive substances are released.[16,17] Acute tendinous injury accompanied by persistent inflammation involves significant oxidative stress that is complicated by fibrosis, scarring and adhesion of the tendon. It has been experimentally demonstrated that stem progenitor cells in the tendon can differentiate into tenocytes; fibrosis is reduced and tendon fibers are repaired when oxidative stress is inhibited. During physical effort, but also after traumatic injuries, the tendon produces reactive oxygen species that support tendon inflammation and lead to its damage. Oxidative stress increases the expression of cytokines with inflammatory potential, IL and TNFα, which mediate the release of reactive oxygen species in tendinous fibers by means of an enzyme with oxidative activity, nicotinamide adenine-dinucleotide phosphate-oxidase (NOX). Thus, a vicious circle is created that self-maintains inflammation, degeneration and apoptosis of tenocytes. The prognosis of tendinopathy is unfavorable when comorbidities are associated: obesity, diabetes and dyslipidemia. Hypertrophied adipocytes, hyperplastic adipose tissue as a whole provide high levels of reactive oxygen species that maintain oxidative stress as a pro-inflammatory element. Obesity induces a small degree of systemic inflammation. Newer studies have shown that nesfatin-1 is an adipokine with dysregulated

expression in obesity. This adipokine activates the mTOR kinase pathway and blocks autophagy and thus tendon metabolism is affected. Autophagy is a mechanism that involves lysosomes in cellular defense through the selective degradation of intracellular structures and damaged proteins. Lysosome-dependent autophagy prevents oxidative stress.[18] In the context of obesity, deregulated expression of nesfatin-1 induces heterotopic ossification in the tendon structure.[18,19]

As a result of overuse, ligaments and tendons can suffer potentially disabling ruptures and heal poorly.[18] Failed tendon regeneration goes through several stages and is based on the process of fibrillogenesis through collagen production by activated fibroblasts supported by neovascularization. Overloading the tendon and putting it under tension repeatedly breaks the cross-links between the collagen fibers that slide between them and destroy the tissue. The weakening of collagen cross-links is accompanied by the alteration of the blood vessels of the tendon. The overstressed tendon heats up a lot to 43–45°C and the tendinous fibers are destroyed by intratendinous hyperthermia. Studies have shown that a temperature higher than 42.5°C fibroblasts are destroyed.[16,17] It is appreciated that tendinous fibers are more affected by local hyperthermia than by zonal microvascular alteration.[16,17,20]

The healing is initiated by matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs). Some MMPs degrade collagen, while others intervene in both collagen degradation and remodeling processes.[17,21,27] Murrell noticed that nitric oxide (NO) is synthesized by the nitric oxide synthases family (NOS) which intervenes in tendon healing by amplifying collagen production. Murrell used the rat as an experimental model and observed that the 3 isoforms of NOS, inducible nitric oxide synthase (iNOS), endothelial nitric oxide synthase (eNOS) and neuronal nitric oxide synthase (bNOS) were overexpressed in the injured tendon.[22] Other authors have shown that vascular endothelial growth factor (VEGF) stimulates angiogenesis and could mediate tendon repair by overexpressing the level of MMPs. However, more studies are needed to establish with certainty the role of VEGF in tendon repair processes.[23] Cheron studied the types of injuries by categories of sports activities, football, volleyball, handball, and by different age groups, children, teenagers, young people and adults. The author found that the lower limbs are affected more frequently than the upper limbs regardless of the type of sport, mainly the knees, but also the calves, thighs and hips. In football, the hips were most often affected due to the "shear force" required in this sport. Children presented bursitis and tendinitis most of the time. Adults also presented injuries to the tendons and bursae, synovitis being the second type of injury identified, and the most affected segment was the knee. Periostitis was present in young people, not being found in adults probably due to bone maturity. The study carried out by Cheron noted that overuse injuries are more common than traumatic ones. The identification of sports and physical exercises with a risk of injury is necessary to preserve the capacity of athletes and people who perform physical education and also to prevent the installation of functional deficiencies.[5]

Discussion

The lesional pathogenesis is complex and incompletely clarified. Recent theories put in a new light the mechanisms of muscle pain and tendinopathy production. The accumulation of lactate anion, known to be a residue that induces fatigue and muscle pain, has been reconsidered by some authors. Its accumulation does not cause, but rather contributes to the onset of muscle fatigue. It appears that lactate anion is an excellent fuel for the myocardial fiber. Moreover, the decrease in cellular pH caused by the accumulation of lactic acid after intense exercise could prevent the inexcitability of the sarcolemma induced by the increased concentration of interstitial K^+.[9,10] Most of the time, overuse injuries are not limited to muscles. They can cause myofascial, myotendinous or purely muscular injuries.[4] The muscular fascia is more susceptible to injuries produced under the action of large external forces. Also, fascia is more sensitive to pain compared to muscle when external forces act eccentrically.[17] The muscle fascia shows a small degree of contraction due to the myofibrils in its structure. The painful fascia has greater thickness and is rigid.[5] Overloading the tendon and putting it under tension repeatedly is followed by ruptures of the tendon fibers.[17] The regeneration of the degenerated tendon is defective in the context of the inflammation produced by the injury. Tendon fibers undergo a process of fibrosis, scarring, adhesion and heterogeneous calcification.[16,17,26] Oxidative stress is responsible for inflammation, degeneration and apoptosis of tenocytes (all local processes involved, with fibrosis stemming from pro-inflammatory cytokines, and with apoptosis being an important process even in malignancies).[17,28–30] Traumatic injuries are less common in sports pathology compared to overuse injuries. Injuries are characteristic for different types of sports activities and

preferentially affect certain anatomical segments in different age groups.[5] The identification of sports and physical exercises with injury risk is necessary to preserve the capacity of athletes and people who perform physical education and also to prevent the installation of functional deficiencies.[5]

Conclusion

The benefits brought by physical education and sports are indisputable; the current work allows for an updated literature search results all in a single work which is essential to all sports medicine providers. Muscle contractions during exercise are favorable to angiogenesis, which supports the properties of skeletal muscle. Exercising requires a coordinated program to prevent possible traumatic and overuse injuries. The pathogenesis of these lesions is complex and not fully known. The studies carried out to identify the pathogenic chains involved in sports injuries are useful in guiding the diagnosis, the establishment of new therapeutic management directions and the recovery of functional capacity.

Abbreviations

α-SMA, alpha-smooth muscle actin; DOMS, delayed onset muscle soreness; ATP, adenosine triphosphate; MCP-1, monocyte chemoattractant protein-1; CCL2, C-C motif chemokine ligand 2; CCR2, C-C chemokine receptor type 2; IL, interleukin; TNFα, tumor necrosis factor-alpha; TGFβ, transforming growth factor beta; NOX, nicotinamide adenine dinucleotide phosphate oxidase; mTOR, mammalian target of rapamycin; MMPs, matrix metalloproteinases; TIMPs, tissue inhibitors of matrix metalloproteinases; NO, nitric oxide; NOS, nitric oxide synthases family; iNOS, inducible nitric oxide synthase; eNOS, endothelial nitric oxide synthase; bNOS, neuronal nitric oxide synthase; VEGF, vascular endothelial growth factor.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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