Extracorporeal Shock Waves in Metabolic Inflammation

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Abstract

The presentation of this paper provides a comprehensive overview of the challenges associated with metabolic syndrome in clinical practice, while highlighting the innovative role of extracorporeal shock waves as a therapeutic tool to manage metabolic inflammation. A multidisciplinary approach is emphasized, suggesting that collaboration among different areas of expertise is essential to improve patient health outcomes.

Keywords: Metabolic inflammation, Oxidative stress, Extracorporeal shock waves

Introduction

Metabolic disorder is a complex health condition characterized by the simultaneous presence of multiple risk factors, including abdominal obesity, hypertension, insulin resistance, dyslipidemia, and low-grade chronic inflammation. These factors not only increase the likelihood of developing cardiovascular diseases, type 2 diabetes, and strokes but are also interconnected with a cascade of inflammatory and oxidative processes that can adversely affect tissue regeneration. Obesity plays a central role in this context, as it is associated with the activation of inflammatory pathways that exacerbate insulin resistance and worsen metabolic comorbidities [1, 2].

Chronic inflammation resulting from metabolic syndrome (MS) is not a temporary response but a persistent state that can directly interfere with tissue healing and regeneration. The often-overlooked low-grade chronic inflammation can compromise the effectiveness of conventional treatments, such as extracorporeal shock wave therapy (ESWT). This therapy, commonly used in musculoskeletal medicine, has shown potential to reduce pain and promote tissue repair. However, the interaction between MS and the response to shock wave treatment can significantly influence therapeutic outcomes [3, 4].

In this article, we will discuss the impact of MS on inflammation and how ESWT may be a promising approach in managing metabolic inflammation. We will analyze the evidence supporting this therapeutic combination and the relevance of a multidisciplinary approach that considers both metabolic health and local treatments to optimize clinical outcomes. By exploring this intersection between MS and therapeutic interventions, we aim to provide insights that may contribute to better management strategies for patients affected by this complex condition [4].

Metabolic Syndrome

MS is characterized by the combination of various risk factors that, when present simultaneously, increase the likelihood of developing cardiovascular diseases, strokes, and type 2 diabetes [1, 2]. The main manifestations of this condition include the presence of abdominal obesity, indicating fat accumulation in the waist area, as well as hypertension, which is elevated blood pressure. Other important indicators are high blood glucose levels, which can manifest as insulin resistance or fasting glucose levels above 100 mg/dL [3]. MS is also marked by elevated triglyceride levels and low levels of high-density lipoprotein (HDL), commonly known as "good" cholesterol [4]. To diagnose MS, specific criteria from various guidelines can be utilized, but in general, an individual must present at least three of the mentioned characteristics [1, 5]. MS is linked to a variety of risk factors generated by unhealthy lifestyles, such as unbalanced diets, chronic emotional stress, changes in sleep quality, lack of physical activity, and genetic predispositions [4, 6, 7].

Various elements contribute to the development of MS, and evidence indicates that oxidative stress, in conjunction with chronic inflammatory conditions, plays a central role in the progression of these diseases [4,6,7]. The imbalance between reactive oxygen species (ROS) and antioxidants, which often favors oxidants, results in

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Submitted Date: 06 August 2024, Review Date: 24 September 2024, Accepted Date: 12 November 2024 & Published: 30 December 2024

Journal of Regenerative Science | Available on www.jrsonweb.com | DOI:10.13107/jrs.2024.v04.i02.147

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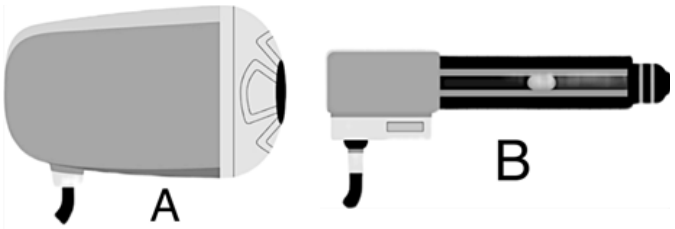

Figure 1: (A) Focused shock wave generator: Deep penetration and (B) radial pressure wave generator: Superficial penetration.

oxidative stress, leading to disruptions in cellular signaling processes, as well as causing damage to cells and molecules [8, 9]. Obesity is a significant risk factor for this condition, illustrating a strong correlation between these diseases. Oxidative stress and inflammation are critical factors that contribute to metabolic comorbidities, such as hyperlipidemia, hypertension, and glucose resistance, culminating in metabolic dysfunctions [10]. The treatment of this condition generally requires lifestyle modifications, including adopting a healthy diet, improving sleep quality, and increasing physical activity. Studies indicate that interventions such as weight loss and the adoption of Mediterranean diets, combined with increased physical activity, can significantly reduce the risk of developing MS [10, 11].

In some cases, the use of medications may also be necessary to manage associated comorbidities. This syndrome is particularly concerning as it is linked to type 2 diabetes and cardiovascular diseases, increasing the risk of developing diabetes by up to five times and doubling the likelihood of experiencing heart problems [12, 13].

MS is characterized by interconnected risk factors that manifest in a pro-inflammatory, pro-thrombotic, and atherogenic state [3,5,13,14]. Obesity stands out as the primary risk factor for type 2 diabetes, present in approximately 90% of diagnosed cases [13, 14]. Central obesity, defined by a waist circumference exceeding 102 cm in men and 88 cm in women, is especially alarming as it is associated with low-grade inflammation that can lead to insulin resistance and metabolic disorders [15]. Insulin resistance, which negatively affects glucose metabolism, can trigger various complications, including hyperglycemia, hypertension, and dyslipidemia [12-15].

Changes in lipid levels are crucial in the onset of insulin resistance and MS. The primary diagnostic criteria include fasting triglycerides exceeding 150 mg/dL and HDL levels below 40 mg/dL. Patients with this syndrome often exhibit hemostatic changes that elevate the risk of cardiovascular diseases. Obesity can be both a cause and a consequence of oxidative stress, which intensifies as a result of excessive lipid and carbohydrate intake, leading to the formation of superoxides [15-17].

Oxidative stress and chronic inflammation are central to the pathophysiology of the syndrome, with imbalances between oxidants and antioxidants impairing cellular and regulatory functions [18-20].

Oxidative stress, caused by ROS, plays important roles in biological processes such as cellular signaling, immune defense, metabolic regulation, stress adaptation, and apoptosis. These ROS are primarily produced by mitochondria and the enzyme NADPH oxidase, which has a dual role in the body; it is essential for defense against infections but may pose potential risks when its activity is unregulated, contributing to the onset of insulin resistance and metabolic dysfunction. While ROS are essential at moderate levels, their excess can lead to processes that contribute to inflammation, cellular injury, and impairment of endothelial function, conditions that promote the progression of MS and its comorbidities. ROS are crucial for cellular health and the overall well-being of the organism [20].

The activation of pro-inflammatory transcription factors, such as nuclear factor-kappa B (NF-κB), is fundamental in mediating immune and inflammatory responses, contributing to an environment that promotes insulin resistance. This occurs when the liver, muscle, and adipose tissue cells do not respond adequately to insulin, leading the pancreas to increase insulin production to compensate, resulting in hyperinsulinemia. This can cause inflammation, increased glucose production in the liver, and excessive fat storage, contributing to abdominal obesity, dyslipidemia, and type 2 diabetes [18-20].

Obesity promotes the infiltration of M1 macrophages, which release pro-inflammatory cytokines, resulting in a chronic inflammatory state that impairs metabolic response [19,20]. Oxidative stress and inflammation are interconnected, forming essential components in the pathophysiology of obesity-related conditions such as insulin resistance and atherosclerosis [19, 21].

The gut microbiota plays a crucial role in health, with dysbiosis, or microbial imbalance, being associated with increased oxidative stress and low-grade systemic inflammation [22].

Possibly, in situations where we have systemic inflammation, whether due to external agents such as vaccination or internal agents such as meta-inflammation that generates inflammatory changes in the intestinal wall, there will be adjuvant factors that trigger changes or breakdown of the integrity of our body's natural barriers, such as the hematoencephalic [22].

Dysbiosis, an imbalance in the composition and function of the bacteria residing in the intestine, caused by high-fat diets, obesity, and type 2 diabetes mellitus, among others, increases blood levels of lipopolysaccharides (LPS) produced by Gram-negative microorganisms. This induced inflammation creates systemic inflammation in peripheral tissue, triggered by this metabolite through the activation of Toll-like receptor 4 (TLR4) signaling [23].

To promote the management of MS through the modulation of the gut microbiota, several dietary interventions can be considered. First, the inclusion of functional prebiotics such as fructooligosaccharides, galactooligosaccharides, and other oligosaccharides, inulin, and lactulose, along with the conscious consumption of probiotic products and the use of postbiotics such as short-chain fatty acids (SCFAs), polyunsaturated fatty acids, and phenolic compounds, constitute well-balanced measures aimed at not only improving the diversity of the gut microbiome but also restoring the symbiotic balance of the species [24].

In addition, adherence to the Mediterranean diet has proven beneficial, as has the reduction of refined sugar and trans-fat intake, which can disrupt the balance of the microbiota. The incorporation of fermented foods is also advantageous, as it nourishes the gut microbiota. Supplementing the diet with omega-3 fatty acids may further enhance gut health. Furthermore, reducing stress and maintaining adequate hydration are factors that significantly contribute to the balance of the microbiota. It is important to emphasize that these practices should be tailored to individual needs and, ideally, carried out under the guidance of a specialized professional [25].

Factors Increasing in Metabolic Syndrome:

1. ROS (Reactive Oxygen Species)
2. M1 Macrophages (Pro-inflammatory)
3. TGF-β (Transforming Growth Factor Beta)
4. TNF-α (Tumor Necrosis Factor Alpha)
5. MCP-1 (Monocyte Chemoattractant Protein-1)
6. IL-6 (Interleukin-6)
7. IL-8 (Interleukin-8)
8. IL-1β (Interleukin-1 beta)
9. Leptin
10. C-reactive Protein (CRP)
11. Resistin
12. Uric Acid
13. Pro-inflammatory Adipokines (Visfatin, RBP4)
14. Chronic low-grade inflammation
15. Gut Dysbiosis

Factors Decreasing in Metabolic Syndrome:

1. Insulin Sensitivity
2. HDL (Good Cholesterol)
3. Endothelial Function
4. Adiponectin (an anti-inflammatory adipokine)
5. Efficient Blood Flow
6. M2 Macrophages (Anti-inflammatory)
7. Tissue Oxygenation
8. Tissue Regeneration Capacity

Figure 2: Factors increasing in metabolic syndrome and factors decreasing in metabolic syndrome. ROS: Reactive oxygen species, TGF-β: Transforming growth factor-beta, TNF-α: Tumor necrosis factor-alpha, MCP-1: Monocyte Chemoattractant Protein, IL: Interleukin.

Inflammation

Inflammation can be classified into various categories that reflect its duration, cause, and mechanism of the inflammatory response. There is a phase where we can consider inflammation as pathological rather than a normal and essential process for injury repair. Given the marked differences between the various types of inflammation in terms of duration, we have acute inflammation, which is an immediate response that lasts from hours to days. This is the body's rapid response to injuries, infections, or irritations, characterized by the presence of classical signs such as heat, redness, swelling, pain, and loss of function. In contrast, chronic inflammation develops when acute inflammation is unresolved, resulting in a persistent state lasting longer, which can range from weeks to years. Between these two lies subacute inflammation, representing an intermediate state lasting several weeks [18-21,26].

Often associated with tissue damage and fibrosis, low-grade inflammation refers to a reduced intensity and persistent inflammatory response that does not display the typical signs of acute inflammation. It can influence the development of metabolic diseases and is frequently linked to obesity and MS. Meta-inflammation refers to inflammation primarily originating from metabolic factors, such as insulin resistance or excessive fat accumulation; this type of inflammation is commonly observed in states of obesity and is associated with metabolic changes, contributing to the development of chronic diseases. Finally, para-inflammation describes an inflammatory state that occurs in response to metabolic or systemic stressors but does not present in the classic form of inflammation. If the alterations are maintained at elevated levels for extended periods, it can become dysfunctional [21,27].

Let us analyze acute inflammation and low-grade inflammation as distinct entities. The differences between these two forms are so significant that alternative terms have emerged, such as "para-inflammation" and "meta-inflammation," whose definitions encompass inflammation triggered by metabolic factors [24]. In summary, inflammation is not simply a beneficial or harmful phenomenon; it has multiple facets that depend on the context, duration, and intensity of the inflammatory response.

Chronic low-grade inflammation or meta-inflammation is common in metabolic disorders such as obesity, type 2 diabetes, and nonalcoholic fatty liver disease, the prevalence of which is increasing. This inflammation is characterized by low-level inflammatory responses, increased levels of acute-phase proteins, cytotoxicity, and chemokines that trigger endoplasmic and oxidative stress and play a central role in the development of chronic diseases. Adipose tissue serves as a reservoir for cytokines, and its degree of inflammation is related to non-alcoholic fatty liver inflammation [28].

The mechanisms of metabolic inflammation are triggered by various factors, including the accumulation of adipose tissue, especially visceral fat, insulin resistance, mitochondrial dysfunction, oxidative stress, and activation of the innate immune system. For example, macrophages in adipose tissue undergo a phenotypic shift from M2 to pro-inflammatory M1 phenotype, intensifying systemic inflammation [29].

In healthy individuals, the gut microbiota maintains intestinal barriers, but obesity causes dysbiosis, leading to the proliferation of potentially pathogenic microorganisms. Interventions to control metabolic inflammation, such as dietary habits and physical activity, show promise in reducing the risk of MS. Diets high in fat promote metabolic dysfunction, while indigestible carbohydrates and exercise can improve glucose homeostasis and reduce inflammatory cytokines. Bariatric surgery is also effective in weight loss and the treatment of metabolic disorders, with mediating effects related to the gut microbiome, provided that nutritional care is observed in both the immediate and late post-operative periods [30].

Chronic inflammation leads to the recruitment and activation of various cells, including growth factors, proteolytic enzymes, angiogenic factors, and cytokines such as transforming growth factor-beta (TGF-β), tumor necrosis factor-alpha (TNF-α), Monocyte Chemoattractant Protein (MCP-1), Interleukin (IL)-6, and IL-8. This inflammatory response results in the deposition of extracellular matrix and an increase in the stiffness of the affected tissue, which hinders the diffusion of oxygen and exacerbates cellular damage, thereby promoting fibrosis [31].

Inflammation and Tissue

The health of the musculoskeletal tissue is of utmost importance for the functionality of the body. The metabolites produced by the gut microbiota play a crucial role in preserving bone health, alongside nutritional and hormonal factors, by facilitating both bone growth and restructuring through the activation of insulin-like growth factor 1. Certain microorganisms could stimulate this production through the innate immune receptor NOD2 directly in the intestine [30-32]. SCFAs are also vital, as they promote the release of intestinal hormones such as glucagon-like peptides (GLP)-1, GLP-2, and peptide YY, which significantly impact bone formation and resorption. Vitamins A, C, D, and K also play direct roles in maintaining bone health by modulating the gut microbiota and affecting intestinal barrier functionality and immune response. Vitamin D is particularly crucial, as it increases the expression of the Vitamin D receptor and helps maintain intestinal barrier integrity; a deficiency in this Vitamin can lead to increased intestinal permeability,

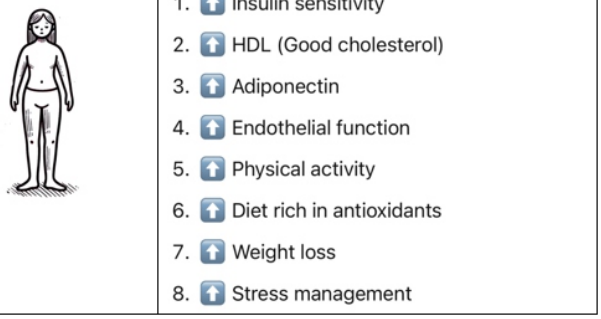

Figure 3: Factors that impromove Metabolic Syndrome. HDL: High-density lipoprotein.

predisposing individuals to inflammation that may be detrimental to bone health [32, 33].

The presence of a leaky gut and chronic low-grade inflammation are intertwined with dysbiosis, decreased sex hormones, and cellular aging. Alteration of the intestinal barrier creates an inflammatory state within the immune system, resulting in the release of cytokines harmful to bone mass and quality. Studies have shown a clear link between intestinal dysbiosis and bone loss, with intestinal barrier dysfunction exacerbating this association. The resulting inflammation leads to an increase in inflammatory cytokines and modifications in the expression of cell junction proteins, compromising the intestinal barrier and facilitating the translocation of harmful microorganisms into the bloodstream [34].

Cellular senescence is also a significant biological process that leads to irreversible cell cycle arrest, often complicating apoptosis and associating with chronic low-grade inflammation. Senescent cells are known to release a range of inflammatory molecules, such as cytokines and chemokines, promoting the aging of adjacent cells through autocrine and paracrine signaling. Regarding bone health, these cells may accumulate DNA damage, limiting their ability to divide and resist apoptosis. The involution of the thymus, which occurs with increasing age, results in decreased populations of naive T and B lymphocytes, while the number of autoreactive T-cells tends to increase, creating an environment that favors inflammation [35].

Moreover, factors secreted by senescent cells, known as SASPs, negatively affect immune cells that interact with bone cells in the marrow. The senescence of mesenchymal stem cells and their differentiation into adipocytes are also influenced by the presence of senescent neutrophils and macrophages, resulting in increased inflammatory cytokines and loss of bone mass. This combination of factors culminates in a significant reduction in the viability of bone cells, further impaired by inflammation and decreased protection that estrogens typically provide [36].

The skin microbiome is a diverse community of microorganisms that inhabit the skin and is essential for maintaining skin health by protecting against infections and modulating immune responses. An imbalance in this microbiome can lead to various dermatological conditions, such as inflammation and rashes. Furthermore, burns often result in hypertrophic scars, which cause discomfort such as pain and itching, and scarring complications are common [37].

Table 1: Biological effects of shock waves
1. Increased cellular permeability
2. Stimulation of microcirculation (blood, lymph)
3. Release of substance P and CGRP with dilution
4. Reduction of unmyelinated nerve fibers
5. Release of nitric oxide (no) causing vasodilation
6. Increased metabolic activity: angiogenesis, vasculogenesis lymphangiogenesis (anti-inflammatory effect)
7. Release of growth hormones (blood vessels, epithelium, bones, and collagen)
8. Stimulation of stem cells
9. Stimulation of neurons and regeneration
10. Production of progenitor cells and exosomes
11. Decreased viscosity and increased production of hyaluronic acid
Summary: Proliferation, migration, growth, and cellular differentiation

Extracorporeal Shock Waves

ESWT is a therapeutic approach that can be classified into two main modalities, depending on how the acoustic energy is generated and propagated. Focused ESWT is developed using technologies such as electrohydraulic, electromagnetic, and piezoelectric methods, producing high-energy pulses that concentrate on specific areas of the body. In contrast, Radial Pressure Waves (rESWTs) are created through pneumatic and electromagnetic methods, providing a gradual increase in pressure, resulting in a broader distribution of energy in a fan-like shape. Both modalities provide relevant mechanical effects, generating pressure and tension forces through mechanotransduction, as well as inducing the formation of cavitation bubbles in fluids. The collapse of these bubbles creates localized shear forces and generates jet streams [38] (Fig. 1).

ESWT and its Effects on Chronic Inflammation: ESWT has proven effective in modulating chronic inflammation by utilizing acoustic pulsations that trigger mechanotransduction and cavitation. These effects transform mechanical stimuli into biochemical signals that facilitate tissue repair. The technique is employed in various medical conditions, including musculoskeletal, vascular, and urological disorders, and is well tolerated by patients due to its low risk of complications. In addition to being a cost-effective option, the therapy may be helpful in decreasing inflammation, stimulating cellular proliferation, and improving blood circulation [38, 39].

Research suggests that ESWT may benefit skin health by increasing microbial diversity in burn scars, regulating bacterial composition, and strengthening skin protection. This approach not only improves the appearance of scars but also may positively influence the dynamics of the microbiome, resulting in balanced and functional microbial communities that are essential for preventing skin complications and promoting recovery [40].

Extracorporeal shock waves assist in revascularization and promote or reactivate the healing mechanisms of connective tissue and bone, alleviating pain and improving functions. Furthermore, these waves can enhance muscle strength through appropriate motor stimulation of muscles and tendons. At present, ESWT is used to treat musculoskeletal system diseases; however, it is not yet widely recognized for peripheral nerve injuries and central nervous system diseases, representing an intervention that requires scientific validation [41, 42].

The use of ESWT for the treatment of tendinopathies has shown positive results in promoting healing and tissue regeneration. Several

studies have explored the biological effects of ESWT at the molecular level. Membrane hyperpolarization and the formation of free radicals may stimulate cell proliferation, mimicking the effects of capsaicin and modulating cytokine release and collagen fiber synthesis [43].

Moreover, these actions are associated with the activation of local stimulatory factors such as TGF-β1, vascular endothelial growth factor (VEGF-A), and proliferating cell nuclear antigen. The activation of mitogen-activated protein kinases (MAPKs), which are essential parts of cellular signaling, regulates various physiological processes, including cell growth, differentiation, and stress response, potentially increasing nitric oxide (NO) production, especially in endothelial cells, thereby facilitating angiogenesis and tissue healing [43, 44].

ESWT also induces activation of TLR3/TLR4, PI-3K/AKT, and NF-κB pathways, which play a crucial role in controlling the inflammatory response, the expression of inflammation-related genes, and cellular survival through adenosine triphosphate release and the activation of kinases such as Erk1/2 and p38 MAPK. Furthermore, shock waves increase the production of ROS, which are important in healing and inflammation. This includes the modulation of inducible NO synthase expression and the expression of pro-inflammatory cytokines and growth factors such as IL-6, IL-8, TNF-α, and MCP-1 [42-49] (Table 1).

In a study evaluating skin laxity in obese patients after weight loss, the effectiveness of Radial Pressure Wave Therapy was validated in women with grade II obesity who had lost 10% of their weight before bariatric surgery. These women underwent seven treatment sessions in the abdominal region, with the opposite side serving as a control [36].

The results showed a significant increase in fibroblast cells and collagen fiber types I and II on the treated side. Radial pressure wave therapy promoted neocollagenesis and neoelastogenesis, improving the firmness and elasticity of the skin where laxity was present. This technique provided a positive physiological response in preventing laxity in obese individuals, reinforcing its efficacy in treating dermatological complications related to obesity [36, 47, 48].

However, in patients with MS, there may be factors that influence the response to shock wave treatment, potentially affecting the outcomes negatively [1].

Impact of Metabolic Syndrome on Shock Wave Treatment Outcomes

MS can significantly influence the outcomes of shock wave therapy, primarily due to three interrelated factors.

First, systemic inflammation is a common characteristic among patients with this condition, who often exhibit a state of low-grade chronic inflammation. This inflammatory scenario can interfere with the healing response of tissues since tissue regeneration relies on a well-coordinated process of inflammation, regeneration, and remodeling. The presence of chronic inflammation may, therefore, delay or hinder this process, resulting in slower or even incomplete recovery.

Second, insulin resistance, frequently observed in patients with MS, can negatively affect cellular function and tissue repair capacity. Insulin plays a crucial anabolic role in promoting protein synthesis and tissue regeneration. When insulin resistance is present, healing processes tend to be compromised, directly impacting the effectiveness of shock waves in treating musculoskeletal injuries [5, 49].

Finally, MS is also associated with vascular problems such as atherosclerosis and reduced endothelial function, leading to poor blood circulation. This compromised circulation can affect the delivery of nutrients and oxygen to tendons, hindering the healing process induced by shock waves. Given that the effectiveness of this treatment relies on promoting regeneration and angiogenesis, circulatory inefficiency may impair the expected outcomes. Thus, the interaction between the components of MS and shock wave therapy underscores the need for a careful and individualized approach to maximize therapeutic benefits [49, 50] (Fig. 2 and 3).

Discussion

Patients with MS commonly present with comorbidities such as diabetes, hypertension, and obesity, which can compromise connective tissue health and negatively affect treatment responses. To maximize treatment benefits, it is essential to control the risk factors associated with MS. Therefore, patients should aim to improve insulin sensitivity, reduce systemic inflammation, and optimize blood circulation. An accompanying treatment plan is equally important, as a multidisciplinary approach involving lifestyle changes, dietary control, targeted medications, and physical therapy can significantly enhance the response to shock wave therapy [44, 50-52].

However, it is vital to recognize that although shockwave therapy is generally safe and well tolerated, the presence of systemic inflammation and compromised vascularity, often seen in patients with MS, may present additional risks. When these factors are not managed appropriately, ineffective or slower healing, recurrence of musculoskeletal injury, and poor response to treatment may occur, resulting in minimal benefit to the patient. Therefore, a careful and personalized approach is essential to ensure the efficacy of the therapy and promote patient recovery [41, 50].

A recent study discussed the dermatological complications associated with obesity, focusing on the deterioration of the integumentary tissue resulting from changes in collagen and elastin fibers. These changes can lead to skin laxity and an increased susceptibility to infections. The importance of considering skin health in obese individuals during obesity treatment is often underestimated. ESWT emerges as a promising approach in addressing cutaneous complications associated with obesity, creating a favorable environment for tissue regeneration and improving skin health, especially during the weight loss process. Attention to dermatological treatment in obese individuals is essential, as skin health is critical for maintaining physiological homeostasis and ensuring successful obesity management [36, 50, 51].

The results indicated that ESWT not only activated inflammatory cells but also stimulated neoangiogenesis. This activation was evidenced by increased markers of Cyclooxygenase-2 and VEGF, which play crucial roles in tissue regeneration. The therapy demonstrated the ability to induce subclinical inflammation, resulting in increased vascularization and local nourishment, both fundamental for skin healing and regeneration [39-41, 50].

Histological analysis revealed an increase in immune cell expression, such as T lymphocytes and macrophages, which are essential in the inflammatory response. In addition, ESWT promoted collagen

production and neoangiogenesis, facilitating recovery of affected areas and improving the viscoelastic properties of the skin [36, 50, 51].

The study also highlighted an increase in natural killer cells and the expression of markers related to angiogenesis, supporting ESWT's potential to enhance tissue conditions in obese patients. Moreover, the effectiveness and safety of ESWT in obese individuals were evident, with minimal adverse responses recorded [36, 41, 50].

MS is characterized by a complex interplay of multiple inflammatory and oxidative factors. The condition leads to an increase in multiple detrimental biological processes. One of the main changes is the increase in ROS, which contribute significantly to oxidative stress and damage to cellular structures. This is accompanied by an elevation in M1 macrophages, the pro-inflammatory variant of macrophages, which secrete inflammatory cytokines such as TNF-α, IL-6, and IL-8, all hallmarks of systemic inflammation seen in MS. These cytokines amplify insulin resistance, further aggravating metabolic dysfunction [36, 50].

In addition, TGF-β, an important mediator of fibrosis and tissue remodeling, is also elevated in MS. This is concerning as it leads to thickening and fibrosis of tissues, potentially impairing normal organ function, particularly in the liver and heart. Elevated levels of MCP-1 also indicate a continuous recruitment of inflammatory cells to adipose tissues, perpetuating a cycle of low-grade chronic inflammation known as meta-inflammation [21, 27, 50, 52].

Another significant factor in MS is the increase in leptin, an adipokine that normally regulates energy balance and appetite. In MS, leptin levels rise but become ineffective due to leptin resistance, contributing to persistent obesity and inflammatory signaling. Similarly, C-reactive protein, a widely used marker for systemic inflammation, is elevated in MS and correlates with cardiovascular risk. Resistin, an adipokine linked to insulin resistance, and uric acid, which predisposes patients to gout, are also elevated, further complicating the clinical picture [1, 2, 20].

Intestinal dysbiosis is strongly associated with increased systemic inflammation. The imbalance in gut flora not only increases intestinal permeability but also leads to the leak of bacterial endotoxins into circulation, exacerbating the systemic inflammatory state [20, 34].

One of the significant effects of ESWT is the stimulation of microcirculation (both blood and lymphatic). Improved blood flow brings essential nutrients and oxygen to inflamed or damaged tissues, while enhanced lymphatic drainage removes inflammatory byproducts. The release of NO in response to ESWT contributes to vasodilation, further improving blood flow and reducing inflammation [42-44, 50].

Furthermore, ESWT reduces the activity of unmyelinated nerve fibers, helping alleviate pain and discomfort associated with chronic inflammation. Biochemically, ESWT promotes the release of growth hormones, which stimulate tissue regeneration, including blood vessels, epithelium, bone, and collagen. This release of growth factors is essential for healing damaged tissues and mitigating fibrotic processes exacerbated by MS [40, 41, 50, 52].

In addition, the stimulation of stem cells by ESWT is one of the most intriguing effects, offering potential for regeneration of tissues damaged by chronic inflammation. ESWT also stimulates the production of progenitor cells and exosomes, which play a critical role in tissue repair and immune response modulation [50].

In conclusion, ESWT promotes cellular proliferation, migration, and differentiation, essential processes in tissue repair. This means that ESWT can counterbalance the negative effects of chronic inflammation, including fibrosis and tissue stiffness commonly observed in patients with MS [41, 44, 50-52].

Conclusion

ESWT offers a promising intervention in the context of MS, particularly regarding its anti-inflammatory and tissue regeneration properties. At the cellular level, shock waves increase cellular permeability, enhancing nutrient uptake and the removal of waste products. This process is vital in tissues compromised by oxidative stress and poor circulation, as seen in patients with MS [1, 50].

MS elevates various pro-inflammatory and oxidative factors, severely compromising tissue function and health. ESWT, with its ability to reduce inflammation, promote regeneration, and stimulate circulation, provides a therapeutic approach to mitigate these harmful processes. However, the interaction between MS and the efficacy of ESWT requires further exploration, as the chronic inflammatory state in MS may potentially interfere with healing processes induced by shock wave therapy. Therefore, a comprehensive approach that addresses both metabolic dysfunction and localized inflammation is essential to optimize clinical outcomes for patients [1, 2, 3, 20, 36].

While shock wave therapy shows promising results in patients with musculoskeletal disorders, MS presents challenges that may affect treatment efficacy. Implementing interventions aimed at modifying behaviors, improving metabolic health, and reducing inflammation is crucial. Effectively addressing the triad of restful sleep, proper diet, and daily physical exercise represents the best strategy for correcting the metabolic disturbances that lead to chronic low-grade inflammation, thereby optimizing clinical outcomes for shock wave therapy in musculoskeletal diseases and promoting patient recovery [44, 49-51].

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the Journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Conflicts of Interest: Nil. **Source of Support:** None.

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Conflict of Interest: NIL
Source of Support: NIL

How to Cite this Article

Simplício CL, Rodrigues IJ, De Barros GAM | Extracorporeal Shock Waves in Metabolic Inflammation | Journal of Regenerative Science | Jul-Dec 2024; 4(2): 18-25.