

# Biological effects of extracorporeal shockwave therapy in tendons: A systematic review

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## Overview

The document is a systematic review of the biological effects of extracorporeal shockwave therapy (ESWT) on tendons, discussing its mechanisms, optimal dosing, and clinical applications.

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## What are the two types of ESWT mentioned?

The two types of extracorporeal shockwave therapy (ESWT) mentioned are:

1. **Focused ESWT:** This type comprises high-energy pressure pulses that converge to a focal point, where maximal pressure is reached. It is extensively used in clinical practice.
2. **Radial ESWT:** This type is characterized by a diverging pressure field, with maximal pressure at the source. Some researchers suggest that radial ESWT should be described as radial pressure wave therapy due to its different physical features compared to focused ESWT.

## What is focused ESWT used for?

Focused ESWT is used extensively in clinical practice for treating various tendon disorders. Initially, it was used for kidney stone disintegration and later applied to treat calcific tendinitis. Its therapeutic applications have expanded to include numerous types of tendinopathies, such as those affecting the shoulder and plantar fascia.

## What tendon disorders can ESWT treat?

ESWT can treat a variety of tendon disorders, including:

1. **Calcific tendinitis**
2. **Shoulder tendinopathies**
3. **Plantar fasciitis**

Additionally, it has been used to address other types of tendinopathies in different parts of the body.

## What are the clinical benefits of ESWT?

The clinical benefits of ESWT include:

1. **Pain Relief:** ESWT has been shown to reduce pain in various tendinopathies.
2. **Improved Function:** It enhances the functional abilities of the affected tendons.
3. **Neovascularization:** Promotes the formation of new blood vessels, aiding in the healing process.
4. **Cellular and Extracellular Matrix Changes:** Stimulates cellular activity and extracellular matrix remodeling, which contributes to tendon repair.
5. **Modulation of Metalloproteases and Cytokines:** Helps in regulating enzymes and cytokines involved in tendon healing.
6. **Lubricin Production:** Increases the production of lubricin, which enhances tendon gliding and reduces friction.

These benefits collectively lead to improved biomechanical properties of the treated tendons, making them more resistant to stress.

## Explain the changes in cellularity after ESWT

After ESWT, several changes in cellularity occur:

1. **Tenocyte Proliferation:** ESWT promotes the proliferation of tenocytes, which are the cells responsible for maintaining and repairing the tendon matrix.
2. **Increased Metabolism:** Tenocytes show increased metabolic activity, producing more growth factors like TGF- $\beta$ 1 and IGF-1, which are crucial for extracellular matrix (ECM) biosynthesis.
3. **Blast-like Forms:** There is an increase in blast-like forms of tenocytes, which are more active in protein synthesis and contribute to tendon healing.
4. **Enhanced Mobility:** ESWT induces a migratory phenotype in tenocytes, particularly in cells derived from ruptured tendons, enhancing their mobility and aiding in tissue repair.
5. **Prevention of Phenotype Drift:** ESWT helps maintain the normal phenotype of tenocytes, preventing them from shifting to an ovoid shape, which is associated with altered protein synthesis and tendon pathologies.

These cellular changes contribute to the overall healing and regeneration of the tendon tissue.

## How do cytokines influence the healing process in tendons?

Cytokines play a significant role in the healing process of tendons by influencing various cellular activities:

1. **Promotion of Inflammation and Healing:** Cytokines like IL-1 $\beta$ , IL-6, and IL-10 are involved in the inflammatory response. IL-1 $\beta$  induces the release of IL-6,

which in turn promotes the increase of IL-10, an anti-inflammatory cytokine that helps limit the inflammation process and promote healing.

2. **Stimulation of Growth Factors:** Cytokines can stimulate the production of growth factors such as TGF- $\beta$  and VEGF. TGF- $\beta$  is involved in ECM biosynthesis, while VEGF promotes neovascularization, both of which are crucial for tendon repair.
3. **Regulation of Metalloproteases:** Cytokines influence the levels of metalloproteases (MMPs), which are enzymes that break down ECM components. In diseased tendons, increased levels of MMPs can lead to ECM degradation. ESWT has been shown to reduce the elevated levels of MMP-1, MMP-13, and IL-6 in diseased tenocytes, contributing to a more balanced ECM remodeling and healing process.
4. **Enhancement of Cell Viability and Proliferation:** Certain cytokines released after ESWT can enhance cell viability and proliferation, aiding in the regeneration of tendon tissue.

Overall, cytokines orchestrate a complex interplay of inflammatory and reparative processes that are essential for effective tendon healing.

### **Which cytokines are involved in the inflammatory response?**

The cytokines involved in the inflammatory response in tendons include:

1. **Interleukin-1 $\beta$  (IL-1 $\beta$ ):** This cytokine plays a key role in initiating the inflammatory response and can induce the release of other cytokines like IL-6.
2. **Interleukin-6 (IL-6):** IL-6 is involved in promoting inflammation and is also crucial for the subsequent healing process. It stimulates the production of VEGF, which aids in neovascularization.
3. **Interleukin-10 (IL-10):** IL-10 is an anti-inflammatory cytokine that helps limit the inflammation process and promotes healing by reducing the inflammatory response.

These cytokines work together to regulate the balance between inflammation and healing, which is essential for effective tendon repair.

### **What is the significance of TGF- $\beta$ in tendon healing?**

Transforming Growth Factor-Beta (TGF- $\beta$ ) plays a crucial role in tendon healing due to its involvement in several key processes:

1. **Extracellular Matrix (ECM) Biosynthesis:** TGF- $\beta$  stimulates the production of ECM components, including collagen, which is essential for the structural integrity and repair of tendons.
2. **Cell Proliferation and Differentiation:** TGF- $\beta$  promotes the proliferation and differentiation of tenocytes, the cells responsible for maintaining and repairing tendon tissue.

3. **Regulation of Inflammation:** TGF- $\beta$  helps modulate the inflammatory response, ensuring that it is controlled and does not become chronic, which can impede healing.
4. **Promotion of Collagen Maturation:** TGF- $\beta$  is involved in the maturation process of collagen from type III to type I, which provides the tendon with greater tensile strength and durability.

Overall, TGF- $\beta$  is significant in tendon healing as it enhances the repair and regeneration of tendon tissue, contributing to improved biomechanical properties and functional recovery.

### **What role do tenocytes play in tendon healing?**

Tenocytes play a vital role in tendon healing through several key functions:

1. **Matrix Maintenance and Repair:** Tenocytes are responsible for maintaining and repairing the extracellular matrix (ECM) of tendons, which is primarily composed of collagen. They produce and organize collagen fibers, crucial for tendon strength and flexibility.
2. **Mechanical Signal Transduction:** Tenocytes can convert mechanical stimulation into biochemical responses, a process known as mechanotransduction. This leads to the release of growth factors and other signaling molecules that promote tissue repair and adaptation.
3. **Cell Proliferation and Differentiation:** During tendon healing, tenocytes proliferate and differentiate to replace damaged cells and restore the normal cellular structure of the tendon.
4. **Production of Growth Factors:** Tenocytes produce growth factors such as TGF- $\beta$  and IGF-1, which are essential for ECM biosynthesis and the overall healing process.
5. **Regulation of Inflammation:** Tenocytes can modulate the inflammatory response by producing cytokines and other signaling molecules, ensuring that inflammation is controlled and does not hinder the healing process.

Overall, tenocytes are crucial for the structural and functional recovery of tendons following injury, contributing to the regeneration and remodeling of tendon tissue.

**Today**

### **What growth factors are released by tenocytes?**

Tenocytes release growth factors such as transforming growth factor-beta 1 (TGF- $\beta$ 1) and insulin-like growth factor 1 (IGF-1). These growth factors are involved in extracellular matrix (ECM) biosynthesis and contribute to tendon healing.

### **How do tenocytes respond to mechanical stimulation?**

Tenocytes respond to mechanical stimulation by converting it into a biochemical response, a process known as mechanotransduction. This leads to the release of

growth factors and cellular adaptation, which can result in the maintenance, remodeling, or degeneration of the tendon through the regulation of anabolic and catabolic genes.

### **How does ESWT influence extracellular matrix changes?**

Extracorporeal shockwave therapy (ESWT) influences extracellular matrix (ECM) changes in several ways:

1. **Collagen Synthesis:** ESWT promotes collagen synthesis, initially increasing type III collagen, which later matures into type I collagen. This process enhances the structural integrity and tensile strength of the tendon.
2. **Collagen Turnover:** ESWT accelerates collagen turnover, leading to an increase in degraded collagen shortly after treatment, followed by a decrease as mature collagen replaces the damaged collagen over time.
3. **Hydroxyproline and Pyridinoline Levels:** ESWT increases the levels of hydroxyproline and pyridinoline, which are indicators of collagen synthesis and maturation, respectively.
4. **Matrix Turnover:** In normal tendons, ESWT stimulates matrix turnover, increasing enzymatic cleavage of collagen initially and promoting the replacement of damaged collagen with mature collagen in the long term.
5. **Glycosaminoglycans (GAG):** ESWT can influence the levels of GAG, which are components of the ECM, although the specific effects may vary depending on the timing and dosage of the treatment.

Overall, ESWT contributes to the remodeling of the tendon ECM, improving its biomechanical properties and aiding in the healing process.

### **What are the effects of ESWT on collagen synthesis?**

The effects of extracorporeal shockwave therapy (ESWT) on collagen synthesis include:

1. **Increased Collagen Production:** ESWT promotes the synthesis of collagen, particularly type I collagen, which is essential for tendon strength and integrity. This is observed in both in vivo and in vitro studies.
2. **Enhanced Collagen Turnover:** ESWT accelerates the turnover of collagen, initially increasing the levels of degraded collagen, which is then replaced by newly synthesized, mature collagen over time.
3. **Hydroxyproline Content:** ESWT increases the hydroxyproline content in tendons, indicating enhanced collagen synthesis. Hydroxyproline is a major component of collagen and serves as a reliable marker for new collagen formation.
4. **Pyridinoline Levels:** ESWT elevates pyridinoline levels, which are crosslink residues of collagen, reflecting increased collagen maturation and stability.
5. **Collagen Fibril Diameter and Adhesion:** ESWT can increase the diameter of collagen fibrils and improve their adhesion, contributing to the overall strength and resilience of the tendon.

These effects collectively contribute to the improved structural and functional properties of tendons treated with ESWT.

### **Describe the role of ECM in tendon healing**

The extracellular matrix (ECM) plays a crucial role in tendon healing through the following mechanisms:

1. **Structural Support:** The ECM provides a scaffold that maintains the structural integrity of the tendon. It consists mainly of collagen fibers, which give the tendon its tensile strength and elasticity.
2. **Cellular Environment:** The ECM creates a conducive environment for tenocytes (tendon cells) to function. It supports cell attachment, proliferation, and migration, which are essential for tissue repair and regeneration.
3. **Collagen Synthesis and Remodeling:** During tendon healing, the ECM undergoes significant remodeling. Initially, type III collagen is synthesized, which is later replaced by type I collagen, the primary structural component of tendons. This process ensures the restoration of the tendon's mechanical properties.
4. **Biochemical Signaling:** The ECM contains various signaling molecules, such as growth factors and cytokines, that regulate cellular activities. These signals are crucial for coordinating the healing process, including inflammation, cell proliferation, and tissue remodeling.
5. **Mechanical Properties:** The ECM's composition and organization determine the tendon's mechanical properties, such as strength and flexibility. Proper ECM remodeling during healing restores these properties, allowing the tendon to withstand mechanical loads.
6. **Matrix Turnover:** The ECM undergoes continuous turnover, involving the degradation of damaged components and the synthesis of new ones. This dynamic process is essential for removing damaged tissue and replacing it with healthy, functional tissue.

Overall, the ECM is integral to tendon healing, providing both the structural framework and the biochemical signals necessary for effective tissue repair and regeneration.

### **What is the significance of collagen in tendon structure?**

Collagen is highly significant in tendon structure due to the following reasons:

1. **Tensile Strength:** Collagen, particularly type I collagen, provides the primary tensile strength to tendons, enabling them to withstand the high mechanical loads and stresses encountered during movement and physical activity.
2. **Structural Integrity:** Collagen fibers are organized in a parallel, longitudinal arrangement, which contributes to the tendon's structural integrity and ability to transmit forces from muscle to bone efficiently.

3. **Elasticity and Flexibility:** Collagen's unique triple-helix structure allows tendons to be both strong and flexible, accommodating stretching and recoiling without damage.
4. **Repair and Regeneration:** During tendon healing, collagen synthesis is crucial. Initially, type III collagen is produced, which is later replaced by type I collagen, restoring the tendon's original strength and functionality.
5. **Matrix Composition:** Collagen is a major component of the extracellular matrix (ECM) in tendons, providing a scaffold that supports cellular activities such as proliferation, migration, and differentiation, which are essential for tissue maintenance and repair.
6. **Biochemical Signaling:** Collagen interacts with various signaling molecules and receptors, influencing cellular behavior and contributing to the regulation of tendon homeostasis and healing processes.

In summary, collagen is fundamental to the structural and functional properties of tendons, playing a key role in their strength, flexibility, and ability to repair and regenerate after injury.

### **What is the relationship between collagen and tendon strength?**

The relationship between collagen and tendon strength is intrinsic and multifaceted:

1. **Primary Structural Component:** Collagen, especially type I collagen, is the main structural protein in tendons. It forms strong, parallel fibers that provide the primary tensile strength necessary for tendons to withstand mechanical loads and transmit forces from muscles to bones.
2. **Fiber Organization:** The highly organized, parallel arrangement of collagen fibers in tendons contributes to their ability to resist stretching and tearing. This organization ensures that tendons can handle high tensile forces without compromising their structural integrity.
3. **Collagen Cross-Linking:** Collagen molecules form cross-links with each other, which enhances the overall strength and stability of the collagen fibers. These cross-links are crucial for maintaining the tendon's mechanical properties and resistance to deformation under stress.
4. **Healing and Remodeling:** During tendon healing, collagen synthesis and remodeling are critical processes. Initially, type III collagen is produced, which is then replaced by type I collagen. This transition is essential for restoring the tendon's original strength and functionality after injury.
5. **Biochemical Properties:** Collagen's biochemical properties, such as its triple-helix structure, contribute to the tendon's elasticity and ability to absorb and dissipate energy. This elasticity is vital for the tendon's ability to return to its original shape after being stretched.
6. **Extracellular Matrix (ECM) Composition:** Collagen is a major component of the ECM in tendons, providing a scaffold that supports cellular activities and contributes to the overall mechanical properties of the tendon. The ECM's composition and organization, largely determined by collagen, are key factors in the tendon's strength and resilience.

In summary, collagen is fundamental to tendon strength due to its structural role, fiber organization, cross-linking, and involvement in the healing and remodeling processes. The presence and quality of collagen directly influence the tendon's ability to withstand mechanical forces and maintain its functional integrity.

### **What role does type I collagen play in tendon strength?**

Type I collagen plays a crucial role in tendon strength through the following mechanisms:

1. **Primary Structural Component:** Type I collagen is the most abundant collagen type in tendons, forming the primary structural framework. Its fibers are densely packed and aligned in parallel, providing the necessary tensile strength to withstand mechanical loads.
2. **High Tensile Strength:** The molecular structure of type I collagen, with its triple-helix configuration, contributes to its high tensile strength. This allows tendons to resist stretching and tearing when subjected to the forces generated by muscle contractions.
3. **Fiber Organization:** The organized, parallel arrangement of type I collagen fibers ensures that tendons can efficiently transmit forces from muscles to bones. This organization is critical for maintaining the tendon's structural integrity and functional performance.
4. **Cross-Linking:** Type I collagen fibers form cross-links with each other, which enhances the overall strength and stability of the tendon. These cross-links are essential for maintaining the tendon's mechanical properties and resistance to deformation under stress.
5. **Healing and Remodeling:** During tendon repair, type I collagen is synthesized to replace the initially produced type III collagen. This transition is vital for restoring the tendon's original strength and functionality after injury, as type I collagen provides greater tensile strength and durability.
6. **Extracellular Matrix (ECM) Composition:** Type I collagen is a major component of the ECM in tendons, providing a scaffold that supports cellular activities such as proliferation, migration, and differentiation. The ECM's composition and organization, largely determined by type I collagen, are key factors in the tendon's strength and resilience.

In summary, type I collagen is fundamental to tendon strength due to its structural role, high tensile strength, organized fiber arrangement, cross-linking, and involvement in the healing and remodeling processes. Its presence and quality directly influence the tendon's ability to withstand mechanical forces and maintain its functional integrity.

### **How does type III collagen differ from type I collagen?**

Type III collagen differs from type I collagen in several key aspects:

1. **Structure and Composition:**

- **Type I Collagen:** It is composed of two alpha-1 chains and one alpha-2 chain, forming a triple-helix structure. It is the most abundant collagen type in the body and provides high tensile strength.
  - **Type III Collagen:** It consists of three identical alpha-1 chains, also forming a triple-helix structure. It is less abundant than type I collagen and is typically found alongside type I collagen in various tissues.
2. **Function and Mechanical Properties:**
    - **Type I Collagen:** Known for its high tensile strength, type I collagen is crucial for the structural integrity and mechanical strength of tendons, bones, skin, and other connective tissues.
    - **Type III Collagen:** It provides structural support but is more flexible and less tensile than type I collagen. It is often found in tissues that require elasticity, such as blood vessels, skin, and the gastrointestinal tract.
  3. **Role in Tendon Healing:**
    - **Type I Collagen:** During tendon healing, type I collagen is synthesized to replace the initially produced type III collagen. This transition is essential for restoring the tendon's original strength and functionality.
    - **Type III Collagen:** It is produced early in the healing process and provides a temporary scaffold that supports tissue repair. Over time, it is replaced by type I collagen to enhance the tensile strength of the healing tissue.
  4. **Tissue Distribution:**
    - **Type I Collagen:** Predominantly found in tendons, ligaments, skin, bone, and other connective tissues that require high tensile strength.
    - **Type III Collagen:** Commonly found in tissues that require flexibility and support, such as blood vessels, skin, and internal organs.
  5. **Pathological Conditions:**
    - **Type I Collagen:** Mutations or defects in type I collagen can lead to conditions such as osteogenesis imperfecta, characterized by brittle bones.
    - **Type III Collagen:** Mutations or defects in type III collagen can result in conditions like Ehlers-Danlos syndrome type IV, which affects the vascular system and skin elasticity.

In summary, type I collagen is primarily responsible for providing tensile strength and structural integrity, while type III collagen offers flexibility and support, particularly in tissues that require elasticity. During tendon healing, type III collagen is initially produced and later replaced by type I collagen to restore the tendon's strength.

### **What role does collagen play in tendon healing?**

Collagen plays a crucial role in tendon healing through the following mechanisms:

1. **Initial Scaffold Formation:**
  - **Type III Collagen:** During the early stages of tendon healing, type III collagen is produced to form a temporary scaffold. This scaffold provides structural support and helps to stabilize the injured area, facilitating the initial repair process.

## 2. Transition to Type I Collagen:

- As healing progresses, type III collagen is gradually replaced by type I collagen. This transition is essential because type I collagen has higher tensile strength and is better suited to withstand the mechanical loads that tendons experience.

## 3. Extracellular Matrix (ECM) Remodeling:

- Collagen is a major component of the ECM in tendons. During healing, the ECM undergoes remodeling, where old or damaged collagen fibers are broken down and new collagen fibers are synthesized. This process helps restore the structural integrity and functionality of the tendon.

## 4. Collagen Synthesis and Cross-Linking:

- New collagen fibers are synthesized and cross-linked to form a strong and resilient network. Cross-linking enhances the mechanical properties of the tendon, making it more resistant to stretching and tearing.

## 5. Cellular Activities:

- Collagen provides a scaffold that supports cellular activities such as proliferation, migration, and differentiation of tenocytes (tendon cells). These cells are responsible for producing and organizing collagen fibers, contributing to the repair and regeneration of the tendon.

## 6. Mechanical Strength Restoration:

- The synthesis of type I collagen and its organization into parallel fibers restore the tendon's tensile strength. This is crucial for the tendon to regain its ability to transmit forces from muscles to bones effectively.

## 7. Reduction of Adhesions:

- Proper collagen organization during healing helps minimize the formation of adhesions (scar tissue) that can restrict tendon movement and function. Well-organized collagen fibers ensure that the tendon remains flexible and functional.

In summary, collagen plays a vital role in tendon healing by providing structural support, facilitating ECM remodeling, supporting cellular activities, restoring mechanical strength, and minimizing adhesions. The transition from type III to type I collagen is particularly important for achieving a fully functional and strong tendon after injury.

## Explain the process of collagen maturation in tendons

The process of collagen maturation in tendons involves several key steps that transform newly synthesized collagen into a mature, organized structure capable of withstanding mechanical stress. Here is an overview of the process:

### 1. Collagen Synthesis:

- **Procollagen Production:** Tendon cells, primarily tenocytes, synthesize procollagen, which is the precursor of collagen. Procollagen molecules are composed of three polypeptide chains that form a triple-helix structure.

- **Secretion and Cleavage:** Procollagen is secreted into the extracellular matrix (ECM), where specific enzymes cleave the terminal propeptides, converting procollagen into mature collagen molecules.
2. **Collagen Fibril Formation:**
    - **Self-Assembly:** The mature collagen molecules spontaneously self-assemble into fibrils. This process is driven by the alignment and interaction of collagen molecules, forming a staggered array that provides tensile strength.
    - **Cross-Linking:** Enzymes such as lysyl oxidase facilitate the formation of covalent cross-links between collagen molecules within the fibrils. These cross-links enhance the mechanical stability and strength of the collagen fibrils.
  3. **Fibril Organization:**
    - **Parallel Alignment:** In tendons, collagen fibrils are organized into parallel bundles aligned along the direction of mechanical load. This alignment is crucial for the tendon's ability to transmit forces efficiently.
    - **Formation of Collagen Fibers:** Collagen fibrils aggregate to form larger collagen fibers. These fibers are further organized into fascicles, which are bundles of collagen fibers surrounded by a sheath of connective tissue.
  4. **Type III to Type I Collagen Transition:**
    - **Initial Healing Phase:** During the early stages of tendon healing, type III collagen is predominantly synthesized. Type III collagen provides a temporary scaffold that supports the initial repair process.
    - **Maturation Phase:** As healing progresses, type III collagen is gradually replaced by type I collagen. Type I collagen has a higher tensile strength and is better suited to withstand the mechanical demands placed on tendons.
  5. **Extracellular Matrix Remodeling:**
    - **Degradation and Synthesis:** The ECM undergoes continuous remodeling, where old or damaged collagen fibers are degraded by matrix metalloproteinases (MMPs), and new collagen fibers are synthesized. This dynamic process ensures the maintenance and adaptation of the tendon structure.
    - **Collagen Fiber Realignment:** Mechanical loading and physical therapy can influence the realignment and organization of collagen fibers, promoting the formation of a more functional and resilient tendon.
  6. **Final Maturation:**
    - **Increased Cross-Linking:** Over time, the degree of cross-linking within collagen fibers increases, further enhancing the mechanical properties of the tendon.
    - **Formation of Mature Collagen:** The collagen fibers become more densely packed and well-organized, resulting in a mature tendon with optimal tensile strength and functionality.

In summary, collagen maturation in tendons involves the synthesis of collagen molecules, their assembly into fibrils and fibers, the transition from type III to type I

collagen, and the continuous remodeling and organization of the ECM. This process is essential for restoring the structural integrity and mechanical strength of tendons after injury.

### **How does ESWT affect collagen synthesis in tendons?**

Extracorporeal shockwave therapy (ESWT) affects collagen synthesis in tendons through several mechanisms that promote tendon healing and regeneration. Here is an overview of how ESWT influences collagen synthesis:

#### **1. Stimulation of Collagen Production:**

- **Increased Type I Collagen:** ESWT has been shown to increase the synthesis of type I collagen, which is the primary collagen type in healthy tendons and provides high tensile strength. This helps in the maturation and strengthening of the tendon.
- **Enhanced Collagen Turnover:** ESWT accelerates collagen turnover, promoting the removal of damaged collagen and the synthesis of new collagen fibers. This process is crucial for the repair and regeneration of the tendon.

#### **2. Upregulation of Growth Factors:**

- **Transforming Growth Factor-Beta (TGF- $\beta$ 1):** ESWT stimulates the release of TGF- $\beta$ 1, a growth factor that plays a key role in collagen synthesis and ECM remodeling. TGF- $\beta$ 1 promotes the production of collagen by tenocytes and enhances the overall healing process.
- **Insulin-Like Growth Factor 1 (IGF-1):** ESWT also increases the levels of IGF-1, which supports collagen synthesis and tenocyte proliferation. IGF-1 contributes to the anabolic response in the tendon, facilitating tissue repair.

#### **3. Modulation of Cellular Activity:**

- **Tenocyte Proliferation and Activation:** ESWT promotes the proliferation and activation of tenocytes, the cells responsible for collagen production in tendons. Activated tenocytes increase their metabolic activity and produce more collagen, aiding in tendon healing.
- **Prevention of Phenotypic Drift:** ESWT helps maintain the normal phenotype of tenocytes, preventing them from shifting to a less functional state. This ensures that tenocytes continue to produce and organize collagen effectively.

#### **4. Reduction of Inflammatory Mediators:**

- **Anti-Inflammatory Effects:** ESWT reduces the levels of pro-inflammatory cytokines and matrix metalloproteinases (MMPs) that can degrade collagen and damage the ECM. By decreasing inflammation, ESWT creates a more favorable environment for collagen synthesis and tendon repair.

#### **5. Enhanced Collagen Fiber Organization:**

- **Improved Collagen Alignment:** ESWT promotes the alignment and organization of collagen fibers in a parallel arrangement, which is essential for the tendon's mechanical strength and functionality. Properly

aligned collagen fibers enhance the tendon's ability to withstand tensile forces.

**6. Increased Expression of Collagen-Related Genes:**

- **Scleraxis (Scx) and Type I Collagen Genes:** ESWT increases the expression of genes related to collagen synthesis, such as scleraxis (Scx) and type I collagen. This genetic upregulation supports the production and maturation of collagen fibers in the tendon.

In summary, ESWT positively affects collagen synthesis in tendons by stimulating collagen production, upregulating growth factors, promoting tenocyte activity, reducing inflammation, enhancing collagen fiber organization, and increasing the expression of collagen-related genes. These effects contribute to the overall healing and strengthening of tendons treated with ESWT.