

# Effect of Sodium selenite administration on the process of tendon healing in Wistar male rats

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Received August 11, 2022; Accepted February 17, 2023

DOI: 10.3892/etm.2023.11880

**Abstract.** Tendon lesions have a great effect on the quality of life and medical spending. Thus is important to investigate the mechanisms responsible for tendon healing and to identify novel treatment options. The aim of the present study was to evaluate the effect of Selenium on the healing processes of injured tendons. A total of 20 Wistar male rats were used and were split into two groups with two different treatment methods. The first group received a normal food administration, while the second group received Na<sub>2</sub>SeO<sub>3</sub>. The animals were kept for 28 days. During the eighth day, all animals underwent surgical experimental Achilles tendon lesion and a Kessler-type suture. After three weeks, the animals were sacrificed and the tendon was extracted for histological evaluation in order to do a comparison according to the Movin scale (modified by Bonar). The histological evaluation revealed an even orientation of the collagen fibers in the case of the experimental group (Se) compared with the second group. The Bonar score was 1.62 for the Se group, while the control group had a Bonar score of 1.98. The average number of tenocytes in the Se group was lower which is demonstrated by a lower Bonar score (1.22), compared with the second group (Bonar Score 1.85). In addition, a slightly higher number of tenocytes compared with the intact tendon areas was recorded. In vascularization, a decreased amount of blood vessels in the experimental group (Se) was observed (Bonar Score 1.70), compared with the control group (Bonar score 1.96). The present study demonstrated that Selenium administration on murine models could be beneficial for tendon healing. Further clinical research is required in order for this to be confidently recommended.

## Introduction

The incidence of tendinopathy is >30% in patients with musculoskeletal disorders (1). The tendon lesions are multifactorial and could be split into two main categories: Tendinitis, characterized by inflammation, and tendinosis, characterized by degenerative modifications of tendon structures. The extrinsic factors, such as physical activity, are usually linked with tendon lesions. A series of predisposing factors, such as age, sex, diabetes, rheumatoid arthritis and hereditary factors could also be responsible (2).

Tendon lesions have great effect on the quality of life and medical spending. Thus is important to investigate the mechanisms responsible for tendon healing and to identify new treatment options.

Data from the literature indicates the fact that after tendon injuries, a strong inflammatory response takes place (2-4). During this process, one of the main mechanisms responsible is based on Reactive Oxygen Species (ROS) (3). These appear in the inflammation area and have an essential role during the inflammatory stage. Studies demonstrate that these hyperreactive molecules decrease the synthesis and polymerization of collagen (4). This effect also slows the regeneration of soft tissues and may be linked to the development of tendinopathies (4,5). Thus the regulation of oxidative stress is important. Some studies demonstrated that vitamin C, vitamin D or quercetin are beneficial for tendon healing, regeneration of its structure and reducing the risk of tendon adhesion (6-8).

The importance of selenium (Se) as an essential element is well established in the literature and it is considered an important element of antioxidant enzymes such as glutathione peroxidase (GPx), thioredoxin reductase (TrxR) or deiodinase iodothyronine (IDD) (9,10). The deficit of this element has significant negative effects, such as Keshan disease, Kashin-Beck disease, hypothyroidism, recurrent miscarriage or cognitive impairment (11,12). It is well known the fact that Selenium deficiency slows the development and growth of bone and cartilage (13,14).

It should be noted that selenium is a microelement that, administered in high dosages, can be toxic. Vinceti *et al* mention that human intake of ≥260 µg/day for organic selenium and 16 µg/day for inorganic selenium is toxic. An intake

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*Key words:* Achilles tendon, selenium

of <13-19  $\mu\text{g/day}$  of inorganic selenium seems to be a risk factor for Keshan disease or cardiomyopathy (15). Thus, every attempt in order to use selenium for a therapeutic purpose should take into account its toxic potential.

Another parameter that has been noted in the literature is bone turnover. It is well known that the bone turnover markers are lower following Se administration. However, it seems that this effect is noticeable only in short-term (16).

By taking into account the aforementioned data, the aim of the present study was to evaluate the effect of selenium as an essential promoter of antioxidant effects on the healing processes of injured tendons.

## Materials and methods

**Biologic material.** A total of 20 Wistar male rats (200-250 g), aged between 6 and 12 months, brought from the Experimental Medicine Center of the Faculty of Veterinary Medicine of Bucharest were used. The animals were held in polypropylene cages with a temperature of 22°C, 40% humidity and a 12-h light/dark cycle. All rats received a commercial standard chow (18% protein; Global 2018; Harlam Tekland). The food and water was administered *ad libitum*. All the animals were examined and treated according to the national legislation regarding animal caretaking and all the ethical norms were taken into account. All the experimental procedures were approved by the ethics committee of USAMV Cluj-Napoca, Romania (approval no. 24692/2021).

**Experimental protocol.** The animal models were split into two groups with two different treatment methods. The first group received a normal food administration, while the second group received 1.2 mg/kg/food of  $\text{Na}_2\text{SeO}_3$  (MilliporeSigma). According to Woth *et al* (17), inorganic selenium possesses a stronger antioxidant effect. Thus, this form of the element was used in the experimental protocol. By taking into account the potential toxicity of  $\text{Na}_2\text{SeO}_3$ , a certain dosage was used in order to not harm the rats (18,19). The dosage was calculated according to Jacevic *et al* (20). The experiment had a duration of 28 days. On the eighth day, all animals underwent surgical experimental Achilles tendon lesions. The animals were monitored for 21 days following the surgery for their recovery. Their behavior was analyzed and also a short clinical exam was performed. None of the animals succumbed during the experiment. All were sacrificed at the end of the experiment.

**Surgical procedure.** In order to minimize the suffering induced by the experiment, the animals were anesthetized during the surgical procedure using ketamine (80 mg/kg) and xylazine (12 mg/kg) as an anesthetic. A 0.5 cm longitudinal incision was developed right over the Achilles tendon. Proximal to the calcaneal insertion (5 mm) a tendon section was created and a Kessler tendon suture was developed. After that, the wound was closed using a 4.0 monofilament separate suture. The whole surgical procedure respected asepsis measures. After the treatment, the animals were kept in the cages aforementioned. No movement restrictions or immobilization were applied. The animals were supervised for 2 h after the surgery by checking their vital signs.

**Preparation and histological examination of tendon tissue.** After 3 weeks, the animals were sacrificed according to approved experimental protocol and legal procedures. It consisted of a rich  $\text{CO}_2$  atmosphere exposure of the rat cage. The death of animals following sacrifice was verified by checking the vital signs, pupil dilation and also by checking the pupilar reflex. The Achilles tendon was extracted for histological evaluation in order to do a comparison according to the Movin scale (modified by Bonar) (7). The tendons were dissected and then immersed in paraformaldehyde 4% at room temperature for 12 h. Then, the tendons were washed with phosphate-buffered saline 0.1 M, pH 7.4 and cryoprotected by using sequential immersion in different concentrations of sucrose (10, 20 and 30%). Longitudinal sections (20  $\mu\text{m}$ ) were stained using hematoxylin-eosin technique (HE) which consisted of 5 min of hematoxylin staining and minutes of eosin staining at room temperature. Images were captured using a light microscope at 10x and 20x magnification.

**Histologic evaluation.** The histological analysis consisted of 5 histological examinations of each sample evaluated using the Movin scale (modified by Bonar) measures the following (7): i) The form, alignment and orientation of collagen fibers; ii) the cellular aspect and concentration; iii) the number of glycosaminoglycans and iv) vascularization. These assessments are recorded on a scale between 0 and 4 (7).

The average result tends to be towards 0 while total points rarely exceed 1.9, according to Maffulli *et al* (21) study on rotator cuff diseases. This tendon health evaluation method was used because of its wide usage in the literature despite the fact that some authors suggest a revision of this scale (22). According to Fearon *et al* (22), the tendon may present a disorganized area that may not be secondary to trauma. The present study compared the results between two homogenous experimental groups which followed the same treatment. Thus, the presence of nontraumatic disorganized collagen fibers may be identified in both groups in equal proportions which may not influence the assessment and results of the present study.

**Statistical analysis.** The data were analyzed using SPSS 22.0 (IBM Corp.). The mean and standard deviations were calculated. Unpaired Student t-test was used in order to evaluate the statistical significance between groups.  $P < 0.05$  was considered to indicate a statistically significant difference.

## Results

There were no infections or mortality during the experiment. The following histological criteria were taken into account to evaluate the tendon healing process: The morphological aspects of the tenocytes, the shape and direction of the collagen fibers, the amount of angiogenetic processes and intracellular matrix composition.

At three weeks after the experimental tenotomy, the histological evaluation revealed an even orientation of the collagen fibers in the case of the experimental group (Se) compared with the second group. The Bonar score was 1.62 for the Se group, while the control group had a Bonar score of 1.98. Those differences were significant in the proximal area but in

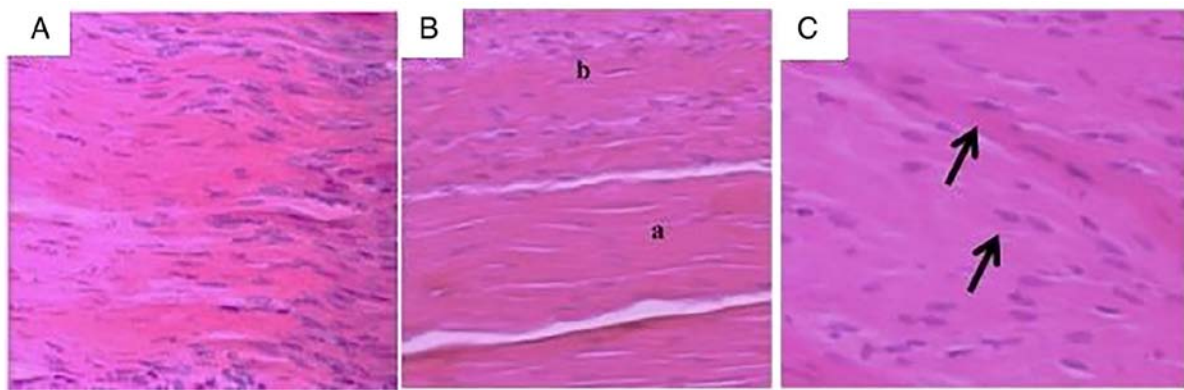


Figure 1. Experimental group (Se), three weeks after tenotomy. (A) Image of advanced healing. The longitudinal orientation of collagen fibers is noticeable (H&E stain; magnification, x20). (B) Healthy tendon area (a) and in a fully healing process (b) (H&E stain; magnification, x10). (C) Advanced healing site, with oblong shaped nuclei (arrows; H&E stain; magnification, x20). H&E, hematoxylin and eosin.

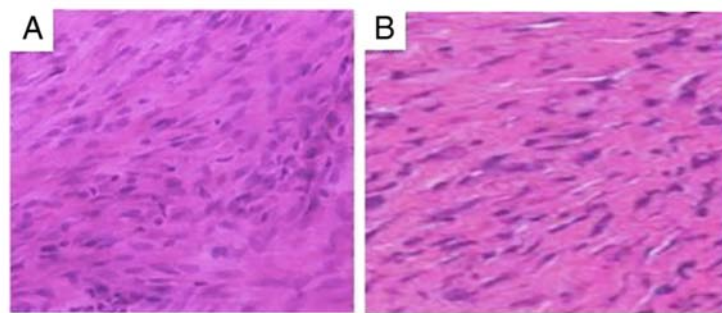


Figure 2. Control group at 3 weeks after the experimental tenotomy. (A) An increased number of tenocytes with oval nuclei (H&E stain; magnification, x20). (B) An increased number of tenocytes with a mild undulation of collagen fibers (H&E stain; magnification, x20). H&E, hematoxylin and eosin.

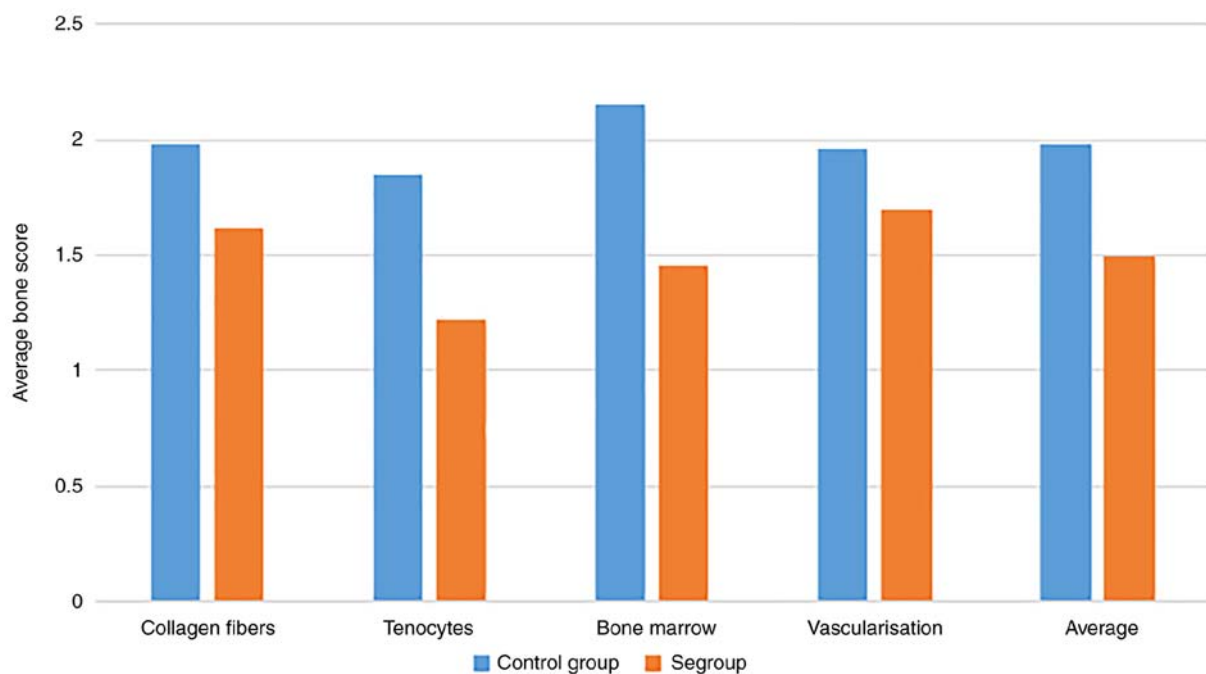


Figure 3. Average Bonar score detailed in all four parameters included in the study (Control group, blue; Se group, orange).

the distal portion of the tendons as well. The healing process was faster at the muscle-tendon junction, compared with the midportion or distal portion of the tendon.

In the Se group, primary collagen fibers synthesis was identified, which consists of longitudinal and undulated fibers. By contrast, in the control group, the collagen fibers were

Table I. Average and standard deviation of Bonar score, detailed on all four parameters included in the present study.

	Average Bonar score				
	Collagen fibers	Tenocytes	Bone marrow	Vascularization	Average
Control group (n=10)	1.98±0.1	1.85±0.2	2.15±0.12	1.96±0.13	1.985±0.11
Se group (n=10)	1.62 <sup>a</sup> ±0.15	1.22 <sup>a</sup> ±1.75	1.45 <sup>a</sup> ±0.11	1.70 <sup>a</sup> ±0.21	1.4975 <sup>a</sup> ±0.13

<sup>a</sup>P<0.01.

much less organized, with abnormal orientation and departed from the natural orientation.

The average number of tenocytes in the Se group was lower which is demonstrated by a lower Bonar score (1.22), compared with the second group (Bonar Score 1.85).

In case of the Se group, the microscopy sections of the tenotomy site, demonstrated advanced healing after 3 weeks with longitudinal orientation of collagen fibers (Fig. 1A). A slightly higher number of tenocytes compared with the intact tendon areas was also noticed (Fig. 1B). Those cells were oval-shaped and with an increased size of the nucleus. (Fig. 1C). Cells were correctly positioned and followed the collagen fiber's direction. The tenocyte cytoplasm was not visible under the microscope. The tendinous regions had a similar aspect to the healthy tendons. Those regions presented sporadic, oblong and darker nuclei.

The control group possessed a significantly greater amount of cells (Fig. 2A and B). The fibroblasts showed bigger, oval or round-shaped nuclei (Fig. 2A). Those cells were unevenly distributed under the microscopic field and occasionally the cytoplasm was noticeable.

In regard to vascularization, there was a decreased number of blood vessels in the experimental group (Se; Bonar Score 1.70), compared with the control group (Bonar score 1.96). In the case of Se group, a decreased amount of blood vessels was identified, especially at the tenotomy level, compared with the control group, which showed a significantly increased amount of blood vessels. The Bonar score regarding bone marrow evaluation was significantly lower in the Se group compared with the control group. (1.45 and 2.15 respectively).

The differences between those two groups are shown in Table I and Fig. 3. The average Bonar score, for all parameters, was 1.985 for the control group and 1.4975 for the Se group. The difference in average Bonar score between groups was 0.488. Thus, the score for the control group was 24.5% higher than the Se group which was statistically significant. Moreover, the total points for the control group were 7.94±0.94, but 5.99±0.61 (P<0.01) for the Se group. The maximum differences were recorded regarding the tenocytes, while the vascularization showed the lowest differences.

The experiment demonstrated histological modifications which were more significant after three weeks in the control group, while the Se group demonstrated a higher healing rate. This result is supported by the lower Bonar score for the Se group, especially regarding the number of tenocytes and the mucopolysaccharides in the extracellular matrix.

The present study also evaluated the toxicity of sodium selenite treatment. The heart, liver, lung and kidneys were

investigated using HE staining. No significant changes were found.

## Discussion

After injury, the tendon healing process begins with an acute inflammatory reaction, which is followed by proliferation and tissue remodeling (23). These separate histological events represent the main reason for using murine models to evaluate tendon tissue regeneration.

The inflammatory reaction aforementioned is modulated by cytokines which regulate the processes following this healing phase (23,24). During this period, an overproduction of reactive oxygen species (ROS) and cellular phagocytosis takes place, which eventually leads to a reduction of the inflammatory process. ROS are partly reduced oxygen metabolites that have a high oxidative potential. They have a high oxidative effect on cellular protein and lipids, but also on DNA. Through this mechanism, they also inhibit the synthesis and polymerization of tendons that suffer lesions (6,24,25).

According to these data, oxidative stress could be harmful to the tendon healing process by increasing the amount of extracellular matrix and proliferation of interstitial fibroblasts. It also seems to be linked with the development of pathological fibrosis (26).

The present study gathered tendon samples to evaluate collagen fibers, tenocytes, bone marrow and vascularization according to the Bonar score. All four parameters demonstrated significantly improved results following Se administration. This result could be linked to decrease of oxidative stress and this hypothesis is supported by Murrell (27) and Moraes *et al* (28), who demonstrated that decreased oxidative stress helps to provide a much more potent tissue regeneration. Thus, the present study complimented the aforementioned data. The Se group demonstrated a slightly higher number of tenocytes but cells were correctly positioned and followed the direction of collagen fibers. On the other hand, the control group had fibroblasts with bigger, oval, or round-shaped nuclei. Those cells were unevenly distributed without following the fiber direction. This could be caused by an increased oxidative stress which eventually increases the extracellular matrix components and proliferates interstitial fibroblasts. Some studies also note that, among the markers of oxidative stress, malondialdehyde is strongly linked with pathological fibrosis (26,29).

Referring to the selenium mechanism, it is well known the fact the effects of selenium are achieved mainly through selenoproteins. These enzymes, such as GPx and TrxR are responsible for protection against oxidative stress. The

literature underlines the role of selenoproteins against ROS (30,31).

Due to the fact that the mitochondrial electron transport is also a source of ROS, the loss of mitochondrial integrity could be a source of oxygenation and inflammation which may eventually lead to cellular apoptosis Kaushal *et al* (32). Selenium has a protective potential that directly targets mitochondria and upregulates mitochondrial transcription factors (33).

Moreover, the relations between cellular redox status and cyclooxygenase (COX) and lipoxygenase activation are well known. Those enzymes are involved in a process responsible for the synthetization of prostaglandins (PG), thromboxanes and prostacyclins (PGI<sub>2</sub>), which are inflammatory biomarkers that are released as a response to potential pathogen events (such as stress, free radicals and infections). It was discovered that a selenium deficit leads to a lower GPx activity, which may reduce the control of COX and LOC (33-36). Thus, selenium is highly efficient in suppressing the aforementioned elements (32). Selenium deficit is also proved to be linked with increased production of reactive nitrogen species and C reactive proteins (32,34,35).

Selenium administration proved to be beneficial for tendon healing. The present study showed the availability and the efficiency of studying tendon healing processes in murine models. No significant adverse reactions were noted regarding wound healing. The results indicated the positive effects on tendon healing, although the results provided by other randomized controlled trials demonstrate that in certain conditions selenium has no effect on musculoskeletal health and bone turnover (16,37). According to Perri *et al* (16), these results could be due to the fact that the test participants had a physiological level of selenium at the moment of evaluation, concluding that the study would need to be extended to populations with selenium deficit.

The present study also investigated the potential toxicity of low-dosage selenium and histological analysis demonstrated no adverse reactions on major organs.

The results of the present study underlined the necessity of additional research to clarify the mechanisms responsible for the tendon healing process under selenium treatment and the long-term results, which is also the main weakness of the present study. Additional research is required regarding the effect of treatment on major organs.

The present study demonstrated that selenium administration on murine models could be beneficial for tendon healing. Further clinical research is required in order to warrant recommendation.

## Acknowledgements

Not applicable.

## Funding

No funding was received.

## Availability of data and materials

All data generated or analyzed during this study are included in this published article.

## Authors' contributions

DC planned the clinical study and contributed to the conception and design of the study, as well as the acquisition, analysis, and interpretation of the data. SD contributed to the conception and design of the study, the translation and critical revision for important intellectual content. AI planned the clinical study and contributed to the conception and design of the study. GZ contributed to the analysis and data interpretation. AD contributed to the analysis and interpretation of the data and the critical revision for important intellectual content. All authors read and approved the final manuscript. DC and AD confirm the authenticity of all the raw data.

## Ethics approval and consent to participate

All procedures performed in studies involving animal participants were in accordance with the national ethical standards. The present study was approved by the Ethics Committee of the University of Agricultural Sciences and Veterinary Medicine, 011464, Bucharest, Romania (approval no. 1153/2021; date of approval 10 March 2021).

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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