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Glucosamine-chondroitin sulphate accelerates tendon-to-bone healing in rabbits

Glukozamin kondroitin sülfat tavşanlarda tendon-kemik iyileşmesini hızlandırır

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ABSTRACT

Objectives: This study aims to investigate the contribution of glucosamine-chondroitin sulphate (GlcN-CS) to the healing of tendons within the bone tunnel.

Materials and methods: Tendon-to-bone healing was investigated in 28 New Zealand rabbits by re-attaching the extensor digitorum longus tendon into bone tunnel which was created in the proximal tibia. Rabbits were separated into two groups as treatment and control groups. Treatment group (n=14) received 210-250 mg/kg/day glucosamine sulphate and 170-200 mg/kg/day chondroitin sulphate, whereas control group (n=14) received equivalent dose of vehicle. Treatment and control groups were compared at sixth and 12th week after the procedure according to histological and biomechanical analysis. Yamakado scoring system was used to evaluate the histological changes.

Results: According to histological analysis, scores were significantly higher at both sixth and 12th week evaluations in the treatment group (p=0.029). Although not statistically significant, the ultimate pullout strength was higher in the treatment group at the 12th week evaluation (35.3 N/mm^2 vs. 24.3 N/mm^2) (p>0.05). However, stripping occurred at the muscle-tendon junction in the treatment group whereas tendons stripped from the bone tunnels in the control group. While no tendons in the treatment group stripped from the bone tunnels, we observed at sixth and 12th week evaluations that tendons in the control group stripped from the tunnels.

Conclusion: Glucosamine-chondroitin sulphate treatment enhances tendon-to-bone healing by increasing hyaline cartilage formation and decreasing formation of capillary vessels.

Keywords: Chondroitin sulphate; glucosamine sulphate; tendon-to-bone healing.

ÖZ

Amaç: Bu çalışmada glukozamin kondroitin sülfatın (GlcN-CS) kemik tünel içindeki tendonların iyileşmesine katkısı araştırıldı.

Gereç ve yöntemler: Tendon-kemik iyileşmesi 28 Yeni Zelanda tavşanının proksimal tibialarında oluşturulan kemik tünel içine ekstansör digitorum longus tendonu yeniden yerleştirilerek araştırıldı. Tavşanlar tedavi ve kontrol grubu olmak üzere iki gruba ayrıldı. Tedavi grubuna (n=14) 210-250 mg/kg/gün glukozamin sülfat ve 170-200 mg/kg/gün kondroitin sülfat verilirken kontrol grubuna (n=14) aynı dozda yem verildi. Tedavi ve kontrol grupları işlem sonrası altıncı ve 12. haftada histolojik ve biyomekanik analize göre karşılaştırıldı. Histolojik değişiklikleri değerlendirmek için Yamakado puanlama sistemi kullanıldı.

Bulgular: Histolojik analize göre, tedavi grubunda hem altıncı hem 12. hafta değerlendirmesinde puanlar anlamlı olarak daha yüksek idi (p=0.029). İstatistiksel olarak anlamlı olmasa da 12. hafta değerlendirmesinde tepe çekim gücü tedavi grubunda daha yüksekti (35.3 N/mm^2'ye kıyasla 24.3 N/mm^2) (p>0.05). Öte yandan, tedavi grubunda kas-tendon bileşkesinde sıyrılma meydana gelirken kontrol grubunda tendonlar kemik tünellerden sıyrıldı. Tedavi grubundaki hiçbir tendon kemik tünellerden sıyrılmazken altıncı ve 12. hafta değerlendirmelerinde kontrol grubundaki tendonların tünellerden sıyrıldığı görüldü.

Sonuç: Glukozamin kondroitin sülfat tedavisi hiyalen kıkırdak oluşumunu artırıp kapiller damar oluşumunu azaltarak tendon-kemik iyileşmesini güçlendirir.

Anahtar sözcükler: Kondroitin sülfat; glukozamin sülfat; tendon-kemik iyileşmesi.

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Tendon injuries are common and pose great challenges to treating surgeons due to the healing problems of the enthesis which exists between the soft tendon and hard bone and may lead to undesired disabilities.[1] This problem seems to be related to the high level of stress at this interface, which in turn may deteriorate the healing process. Also, tendon-to-bone healing is a complex and slow process, including inflammation, proliferation, matrix synthesis, and matrix remodeling. Maturation of healing tissue, mineralization and osseous ingrowth directly affect the strength of tendon-to-bone interface. Satisfactory tendon-to-bone healing is imperative for full functional recovery after surgical repair of such injuries. Both collagen and fibrocartilage reorganization are highly critical to enable mechanical optimization of the tendon-to-bone healing after the injury.[2,3] The healing of the connection between bone and tendon is dependent on the correct restructuring of the fibro-vascular interface and later attachment of the bone to this interface.[4]

Healing problems at the recovery zone may originate from bone resorption, failure of enthesis formation, or collagen deficiency between the tendon and the bone.[5-7] Many modalities have been tried to obtain good results at the recovery zone, including electroshock wave therapy, allogeneic chondrocyte implantation, or platelet derived growth factor, bone marrow stem cell and bone morphogenetic protein applications.[8-10] Recently, platelet rich plasma has gained popularity, affecting healing by increasing tenocyte proliferation and stimulating collagen production.[11,12] Using growth factors with coverage of tendon with the periosteum as a shield have been also used to improve healing.[13,14] In contrast to platelet rich plasma, a topical hemostatic agent (Ankaferd Blood Stopper®; Ankaferd Ilac Kozmetik AS, Istanbul, Turkey) was shown to negatively affect tendon healing.[15] Despite all these tested methods, there is no consensus on any technique which enables and expedites perfect bone-tendon healing.

Glucosamine chondroitin sulphate (GlcN-CS) is frequently preferred for a great number of indications in daily usage.[16,17] It is reported to reduce chondromalacia by increasing matrix proteoglycans and inhibit inflammation by blockage of the cyclo-oxigenase-2 pathway.[17-19] At the same time, GlcN-CS has been shown to stimulate collagen production in tendons and fibrous tissue.[20] To our knowledge, any positive effect of these actions on enthesis healing has not been demonstrated. Therefore, in this study, we aimed to investigate the contribution of GlcN-CS to the healing of tendons within the bone tunnel. Our main objective was to determine whether GlcN-CS has a constructive action on the biomechanical and histological properties of tendon-to-bone enthesis. We hypothesized that GlcN-CS would cause a strong healing tissue by expediting the healing in the injured enthesis.

MATERIALS AND METHODS

This experimental study was conducted between April 2010 and July 2010 in the Experimental Research Laboratory of Medical Faculty of Gazi University, Biomechanics Laboratory of Engineering Faculty of Gazi University and Histology Laboratory of Medical Faculty of Kırıkkale University; following approval by the ethical committee of Medical Faculty of Gazi University (08/01/2010 and B.30.2.0.05.06.00/5-448).

Twenty-eight New Zealand rabbits were divided into two groups as the treatment group (n=14) which was planned to receive a preparation of GlcN-CS and the control group (n=14). In all rabbits, the extensor digitorum longus tendon was extracted from the insertion point at the right extremity and then attached to the bone tunnel of tibia (Figure 1a, b). The control group was fed with the routine diet protocol without any drugs, whereas the treatment group was given 750 mg/day glucosamine sulphate, 600 mg/day chondroitin sulphate, 20 mg/day manganese, and 300 mg/day methil-sulphonil methane (Kondromin-S MSM effervescent tablet, ASSOS İlaç, Türkiye) in addition to routine diet protocol. Daily dosage usage was calculated according to body weight (3-3.5 kg) as 210-250 mg/kg/day glucosamine sulphate and 170-200 mg/kg/day chondroitin sulphate. The administered doses were adjusted with regard to the minimum toxic dosage.

To evaluate the healing time of tendons, seven rabbits from each group were sacrificed at the postoperative sixth and 12th week and samples were taken. The surgical procedure involved extraction of tibia and extensor digitorum longus tendon. From each group, three samples were selected for biomechanical examination and four samples for histological examination. Histological samples were kept in 10% formaldehyde solution and specimens for biomechanical testing were wrapped in saline-soaked gauze and stored at -80 °C until evaluation. Before evaluation, all specimens were thawed overnight at 4 °C.

Histological evaluation

Five pieces of 5-6 mm thick sections were taken from the paraffin blocks with the help of rotary microtome to 3-aminopropyltriethoxysilane adhesive

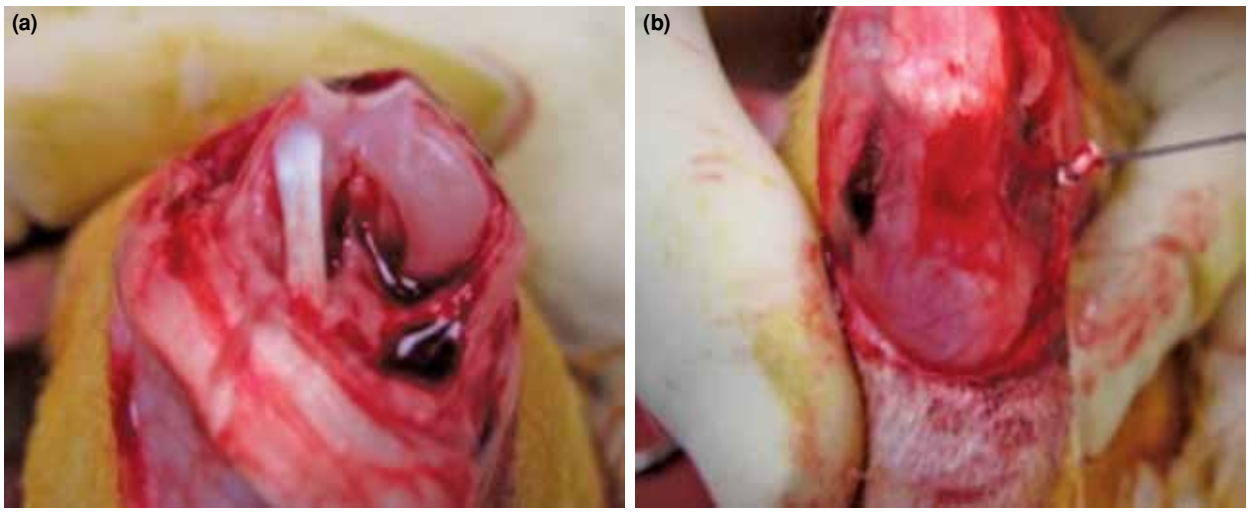

Figure 1. (a) Extensor digitorum longus tendon was taken from insertion point at right extremity. **(b)** Extensor digitorum longus was attached to bone tunnel of tibia.

coated slides. After staining with routine hematoxylin and eosin, Masson's trichrome staining (Bio-Optica, Milano, Italy) was applied to evaluate connective tissue proliferation and also Tolouidin blue staining (Sigma Aldrich, St. Louis, Missouri, USA) was performed to evaluate hyaline cartilage formation. All histopathological examinations were performed via a binocular research microscope Olympus BX51 (Olympus, Tokyo, japan) and microphotographs were taken with Olympus DP25 digital microscope camera (Olympus, Tokyo, Japan). Histologic changes for each case was scored semi quantitatively in respect to Yamakado et al.[21] scoring criteria and evaluated according to a range from 0 to 3 points depending on the severity and extent of changes.

Biomechanical evaluation

Biomechanical evaluation was made with Shimadzu AG-I/50N-10kN device (Shimadzu Corporation., Kyoto, Japan) in the biomechanics laboratory of Gazi University Engineering Faculty by 10 mm/minute breakout force. The parts of the bone material, which had been removed from the rabbits, were mounted on the fixed holder of the clamping device. Muscle components with muscle tendon junction were attached to the supernatant moving holder. Muscle tendon junction region was also included to the holder so as to provide a second weak point (Figure 2).

After thoroughly ensuring that the material was held by the device, the tendon was stretched manually to create minimal tension in the tendon and system settings were calibrated at 0 level. System parameters were determined as the amount of force and strain amount per mm^2 for each sample to clear off variation of results even in case of millimeter differentiations in dimensions of the tendon diameter. The force unit per mm^2 was calculated in newton. The tension was initiated after device settings were calibrated at the 0 level. Tensile tests were continued until elusion from the holder, separation through the bone tunnels or rupture of the tendons. Tests were repeated for eluted material.

Figure 2. Muscle components with muscle tendon junction were attached to supernatant moving holder.

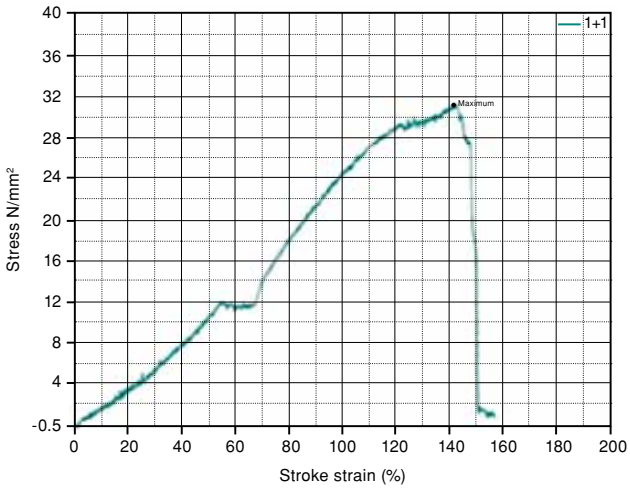

Figure 3. Graphic with x/y axis showing amount of stretch/force unit per mm².

At the conclusion of the tests, a graphic with x/y axes showing the stretching amount versus force per mm² for each test was generated (Figure 3).

Statistical analysis

Statistical analysis was performed using SPSS version 15.0 software for Windows (SPPS Inc., Chicago, IL, USA). The Mann-Whitney U test was used to evaluate histological and biomechanical results. A *p* value of <0.05 was considered statistically significant.

RESULTS

Histological results

All samples were scored according to the scoring system described by Yamakado et al.[21] (Table I). The histological scores of the group sacrificed in the sixth week showed no significant differences between the two groups in terms of the amount of collagen formation and maturation at the enthesis (p>0.05). However, hyaline cartilage formation and reduction in formation of capillary vessels were significantly higher in the treatment group at the sixth week (p<0.05). Although evaluation at 12th week demonstrated no significant difference between the treatment and the control groups in terms of connective tissue continuity, collagen formation, fibroblasts maturation, hyaline cartilage formation, and formation of blood vessels, total scores were significantly higher in the treatment group at both sixth and 12th week evaluations (p=0.029) (Table II).

Biomechanical results

An analysis of the samples revealed no statistically significant difference between the treatment and the control groups at the sixth week and 12th week (Mann-Whitney U test, p>0.05) (Table III). However, tendons stripped through bone tunnels in the control group. Biomechanical test data obtained from the stretch tests indicate the peeling force of the tendons

TABLE I

Histological scoring according to Yamakado et al.[21]

Sample no	Group	Connective tissue continuity	Intercellular matrix/collagen	Fibroblast maturation	Hyaline cartilage	Capillary formation	*Total*
1.	C 6th week	1	1	1	0	1	4
2.		1	0	1	0	1	3
3.		2	1	0	0	1	4
4.		1	1	1	0	1	4
5.	C 12th week	2	2	3	1	2	9
6.		3	2	2	0	2	9
7.		2	3	2	2	3	12
8.		1	1	3	1	3	9
9.	T 6th week	2	2	1	1	2	8
10.		2	1	3	2	3	11
11.		1	2	2	2	2	9
12.		2	2	2	2	3	11
13.	T 12th week	2	3	3	3	3	14
14.		3	3	3	2	3	14
15.		3	2	3	2	3	13
16.		3	3	3	3	2	14

C: Control group; T: Treatment group.

TABLE II

Histological evaluation in detail

	Connective tissue continuity	Collagen connections	Fibroblast maturation	Chondral metaplasia	Capillary formation
C 6th week	Cellular and loose	Weak	Elliptic nucleuses and wide cytoplasma	None	Rich capillary formation
C 12th week	Less cellularity and increased continuity	Interruption sites at repair areas	Small and long nucleuses and fusiform cytoplasma	2-3 layers of hyaline metaplasia in multifocal areas	Small vessels that included small numbers of erythrocytes
T 6th week	Longitudinal cells compact continuity at narrow areas	Interrupted collagen formations	Fibroblasts with elliptic nucleuses and mature fibroblasts	Hyaline metaplasia in limited areas	Small capillary formations in limited areas
T 12th week	Full continuity at bone-tendon junction	Dense collagen fibers	Mature fibrocytes	Clusters of hyaline metaplasia	Poor capillary formations

C: Control group; T: Treatment group.

within the bone tunnel. As opposed to this, no tendons in the treatment group stripped from the bone tunnel at the sixth or 12th week. At the ultimate tensile strength, all tendons detached from the tendon body or the muscle-tendon connection in the treatment group.

DISCUSSION

This study investigates the hypothesis that GlcN-CS would cause a strong healing tissue by expediting the healing in the injured bone-tendon enthesis. We demonstrated that the GlcN-CS preparation has increased collagen synthesis in rabbits. As Lippiello[20] have shown the *in vitro* stimulatory effect of low dose combinations of GlcN and CS on collagen and noncollagenous protein synthesis by ligament cells, tenocytes and chondrocytes, we also ascertained that GlcN-CS complex increased the maturation of fibroblasts in the bone tendon interface and stimulated collagen synthesis in the direction of the fibroblasts. As the time needed for collagen fibers to reach sufficient functional strength is quite long, additional treatment options to accelerate healing will be greatly useful.

Accelerating the healing at the enthesis will improve clinical outcomes and functional activity level. Previously, many animal studies have been made to shorten the healing time of bone tendon junction and contribute to the healing power.[7,9-11,22] Although promising results were achieved, these studies are still in the experimental stage. It is important to ensure proper healing of tendon-to-bone transition with normal morphology, instead of fixing the actual tendon to its original localization. Soft tissue attachment to the bone was shown as non-specific hypercellular structure and hypervascular granulation tissue in animal experiments. This granulation tissue is composed of disorganized short collagen fibers.[23,24] In an animal study, Liu et al.[23] demonstrated that type 3 collagen proliferates at sixth week. In course of time, a progressive integration occurs between the two tissues and collagen bridges would be formed.[25,26]

TABLE III

Ultimate tensile strength of each tendon

	Control group		Treatment group	
Sample no	6th week	12th week	6th week	12th week
1	13 N/mm^2	24 N/mm^2	19 N/mm^2	34 N/mm^2
2	16 N/mm^2	28 N/mm^2	22 N/mm^2	41 N/mm^2
3	15 N/mm^2	21 N/mm^2	21 N/mm^2	31 N/mm^2
Mean	14.7 N/mm^2	24.3 N/mm^2	20.7 N/mm^2	35.3 N/mm^2

The increased stress level at the enthesis deteriorates healing. Rodeo et al.[14] showed in their study that tendon strain-resistant force might depend on collagen continuity in the bone tunnel. They also underlined that tendon surgery should be protected for at least eight weeks until the tendon reaches sufficient strength at the 12th week. In their study concerning protection of repair area, Chen et al.[27] wrapped the tendon graft with the periosteum to evaluate tendon healing in the bone tunnel. In this study, it was shown that a fibrous tissue appeared first in tendons covered with periosteum, then a progressive fibrotic tissue grew advancing into the bone, thus organized collagen fibers extended between bone and tendon. Finally, the group covered with periosteum had more successful stretching test properties.

There are many studies in the literature that overcame this problem, which can be defined as the weakest link in tendon healing.[8-14] Still, in addition to the physiological difficulties, which may be experienced in the healing process, implementation materials may also affect the recovery phase negatively. Tsukada et al.[28] histologically and biomechanically investigated the effect of the remaining sutures placed on the tendon in the tunnel by a study conducted on 60 rabbits. This study concluded that the sutures left in the tunnel had adverse effect on healing. However, using autogenous materials with the metallic materials would have a positive effect on healing. Kyung et al.[29] found that the periosteum interface on tendon in the bone tunnel would provide a better connection for all time periods. Similarly, Karaoğlu et al.[13] showed that bone marrow and periosteum would contribute positively to tendon healing in the bone tunnel by the help of pluripotent stem cells.

In our study, we hypothesized that glucosamine and chondroitin sulfate might strengthen the healing structure of the tendon-to-bone interface. This is a preferred compound for patients with cartilage problems to decrease symptoms. Regression of symptoms is provided by the effect of the drug, by means of stimulating collagen synthesis on the cartilage cells and with anti-inflammatory properties.[30] This drug is not only specific to cartilage cells, but also affects the cells such as the ones in the ligament and tenocytes.[20] Although it was shown that GlcN-CS did not have a positive effect on rehabilitation of the athletes with anterior cruciate ligament repair, Özer et al.[30] and Eraslan and Ulkar[31] showed that GlcN-CS complex increased the synthesis of collagen and also that collagen type is more organized.

Our study has some limitations including the small sample size, lack of comparison of different molecules, lack of differentiation of collagen subtypes and extra-articular investigation of the samples. First, this investigation included a relatively insufficient number of animals. Secondly, comparing the effects of GlcN-CS with those of other agents that accelerates tendon healing in the bone tunnel would be useful in obtaining data concerning the efficiency of GlcN-CS. Also, identifying the collagen in the healing tissue might provide important information concerning the quality of the healing tissue. Finally, further investigations of intra-articular tendon healing should be performed; hence, many sports related injuries involve intra-articular component of tendons or ligaments. It is generally accepted that synovial leakage may alter tendon-to-bone healing.

In conclusion to this experimental study, GlcN-CS combination showed a positive effect on the recovery time and recovery quality of the tendon inserted into the bone tunnel. The use of this molecule, which is advantageous with low cost and high patient compliance, may have positive effects in post-surgical rehabilitation and the repair process in sports surgeries.

Declaration of conflicting interests

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