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REVIEW

Tendon Healing and Repair: A Review of Current Approaches

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Summary

The treatment of tendon diseases increasing as the result of longer life expectancy and further taking place of re-creative activities in life maintains its importance in orthopedic surgery. Significant data's have been obtained with numerous conducted studies and many developed surgical methods in this field, however the ongoing challenges and some complications are still lasting today. Therefore, a number of studies were conducted in order to obtain the ideal tendon repair method and are still conducted. For reaching the desired goal of all of these studies, to have a good knowledge about the biological and biomechanical structure of the tendon, the healing stages, and the factors affecting the repair mechanisms and healing has an undeniable place. In this review it has been aimed to help the researchers by reviewing the studies about tendon repair and healing in the literature.

Keywords: *Tendon healing, Tendon repair, Tendon surgery, bFGF, PRP, Hyaluronic acid, Growth factors, Gliding mechanism, Suture techniques*

Tendon İyileşmesi ve Tamirinde Güncel Yaklaşımların Gözden Geçirilmesi

Özet

Yaşam süresinin uzaması ve rekreatif aktivitelerin yaşamda daha fazla yer alması sonucunda artan tendon hastalıklarının tedavisi ortopedik cerrahideki önemini korumaktadır. Bu alanda yapılan çok sayıda çalışmalar ve geliştirilen birçok cerrahi metotlarla önemli kazanımlar elde edilmiş olmasına karşın öteden beri devam eden zorluklar ve komplikasyonların bir kısmı günümüzde de hala devam etmektedir. Dolayısı ile ideal tendon tamir metodu elde etmek için çok sayıda çalışma yapılmış ve yapılmaktadır. Bütün bu çalışmaların istenen hedefe ulaşabilmesinde, tendonun biyolojik ve biyomekanik yapısının, iyileşme evrelerinin, tamir mekanizmaları ve iyileşmesini etkileyen faktörlerin iyi bilinmesi yadsınamaz bir gerçektir. Bu çalışma, tendon tamiri ve iyileşmesi konusunda son yıllarda yapılan çalışmalar ve klasik bilgilerin harmanlanarak güncel yaklaşımların aktarılması amacıyla rapor edilmiştir.

Anahtar sözcükler: *Tendon iyileşmesi, Tendon tamiri, Tendon cerrahisi, bFGF, PRP, Hyaluronik asit, Büyüme faktörü, Kayma mekanizması, Sütür*

INTRODUCTION

Tendon is one of the most important part of musculo-skeletal system. It provides mobilization of the skeletal system by transfer of the forces obtained from the muscles to the bone. For this reason, the disorders occurred in the structure of tendon may directly affect the mobility of the organism. Tendon injury may occur as a result of acute direct injury or by chronic process which some of inflammatory diseases accompanied or ongoing with excessive use. According to their function and anatomical locations, tendon disorders have characteristic features in their selves. Increased life expectancy and recreational activities, lead to an increase in the incidence of tendon disorders. As a result of tendon injuries, appropriate treatment and the good management of recovery process, has a great importance in re-obtaining of the functions.

Tendon healing is a very slow process. Surgical and conservative treatment methods have many challenges and complications. Some of them are re-ruptures, adhesions, loss or reduction of function in related extremity as a result of disorder at tendon slip mechanism. Today, all these challenges continue to be one of the most important issues

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that the orthopedic surgery is trying to manage. Thus, the innovations about the management of tendon healing and repair never ends. This review aimed to present these innovations at the field [1-3].

TENDON BIOLOGY and FUNCTIONS

Normal tendon is composed of the organization of soft fibrous connective tissues [4].

Tendon forms as the result of composition of collagen fiber bundles packaged by connective tissues. Fiber bundles show a parallel arrangement to the tendon axis. These tendon bundles are surrounded by the tendon sheath including also the extracellular matrix components (ECM) *(Fig. 1)* [5,6].

Seventy five percent of the dry weight of the tendon is formed by type I collagen. Type I collagen is the component which has the most important function in transmission of the force along axis of the tendon tissue. Tendon structure has been well organized to provide the transport of force, which is resulting from the muscle contractions, to the bone tissue [4-6].

Muscle-tendon units are composed of collagen fibers and rod or spindle-like fibroblasts embedded in the ECM [5-7].

Collagen is synthesized by 'tenocyte' and the most basic building block. Tenocytes have the ability to respond to mechanical loads. Collagen polypeptides, formed by cross-linking of the collagen fibrils in themselves, are triple helix structure. The parallel placement of these fibrils, which are triple helix structure, in fibers, is the most important feature which provides tensile strength of the tendon. Collagen fibrils which are at helix structure are synthesized within the cell and secreted into the ECM and formed collagen fibers by connecting to each other in the micro-fibril unit. Type I collagen is the major component forming tendon. However, there is a small amount of type III collagen. Type III collagen mostly involved in the structure endotenon and epitenon. Diameter of the collagen fibers is important for the durability of tendon. Due to bundles of collagen fibers is very thin at diameter in the early stages of repair, tensile strength is low in the early stage of healing. At this stage, the synthesis of type III collagen increases [7]. Type V collagen provides to regulate other collagen types in fibriller structure of tendon by cross-linking [6,8].

ECM also includes other regulatory proteoglycans such as agregant and decorin. It has been thought that, water consists approximately 55% of the ECM and proteoglycans have a friction-reducing effect in ECM. Also the proteins with the structure of elastin and glycopeptide in ECM play a role in collagen fibril stability [9,10].

Collagen fibrils tied in bundles in wide fibers with 100-500 nm in diameter. When they were investigated under light microscopy, according to their lengths, they were observed to elongated in 1-3%. It has been thought that, this state of elongation inhibited tendon damage with sudden loads [11].

Spindle - shaped tendon fibroblasts are the responsible cells for the secretion and the continuity of the contents in the ECM. Collagen fibers are wrapped by endotenon and formed fascicles [6,12,13]. Endotenon a thin layer of connective tissue that containing the vascular, lymphatic, and neural structures [14]. Tendons are wrapped by tendon sheath and pulleys which are located close to the regions of joints that tendons pass through. The tendon sheath called paratenon surrounds the tendon across all regions. Paratenon composed of loose tissue supplying the entry of blood vessels to epitenon and endotenon. These sheaths includes also synovial cells, thus provide lubrication and

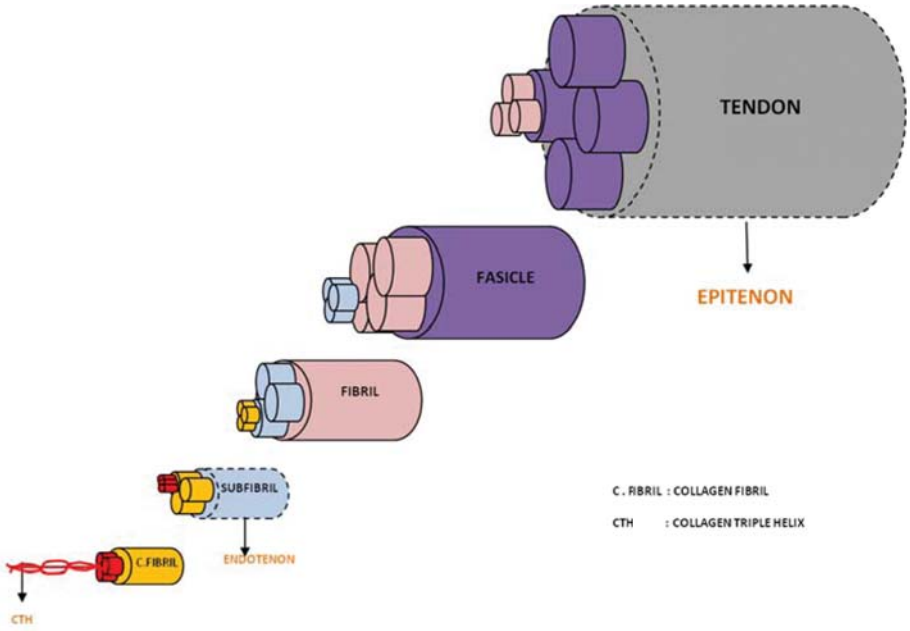

Fig 1. Structural schema of the tendon

Şekil 1. Tendonun yapısal şeması

help to tendon for sliding in the sheath [12-14].

Despite tendon has so unique and strong structure. As of its structure, does not have a large security area [15]. Sometimes, in the transfer of the force generated by the muscles, the maximum resistance level for tendons can be exceeded. In this case, tendon can rupture and sometimes tears and degeneration can occur in the structure of tendon [16]. Although, tensile forces are within the borders of resistance of tendon, in repetitive overuse, as a result of deterioration of function of gliding mechanism and sheath defined as a functional medium of tendon, damage may occur [15,16].

Among other things, tendon injury may occur direct penetrating and cutting factors. The rate of loss of function resulting from tendon injury and clinical findings are the factors that determine the need and method for treatment [17].

TENDON HEALING PROCESS

Tendon does not rupture with the normal borders of physiological loads. However, tendon which has a deterioration of in its structure particularly as a result of aging and external injuries, can rupture without sudden and extreme loads [12]. Beside the ruptures, the exposure of tendon to the degenerative process sometimes may result in malfunction which can need medical treatment [18].

For the returning of tendon to its normal function after injury, the integration of tendon fibers parallel to the tendon axis and re-obtaining the gliding relationship between tendon and its environment are very important [13,19].

As in other tissues, with tendon injury, a repair cascade begins that cellular and biochemical events play a role. Tendon healing process consists of three main phases. In the first section, known as the inflammatory phase, hematoma caused by the injury, provides the release of many chemo-active factors. The pro-inflammatory agents and vaso-dilators, play an important role for providing the building blocks of repair. The fibroblasts collecting in the region, provide the synthesis of many components in ECM [20]. The angiogenic agents stimulate the formation of new blood vessels in the region [21].

With the proliferation of fibroblasts collected in the region and beginning of synthesis of ECM, proliferative phase begins. In this phase, abundant synthesis of collagen is performed. However, in general, the type of collagen synthesized in the inflammatory and proliferative phase is Type III collagen.

In the process which begins evolve towards the scar phase. Dense network of blood vessels formation is remarkable in scar phases [22,23].

At this stage, the density of type III collagen and water in the ECM is quite high. In the scar phase, the complete connection between ruptured end of tendon is established literally. Approximately in 6-8 weeks after the injury, scar begins to fall in. The ECM in the cell density decreases significantly, Type I collagen the rate of water and collagen type III begins to decrease. The cell density in ECM decreases significantly, Type I collagen begins to appear [24].

Then, Type I collagen begins to settle in parallel with the tendon axis. With the organization of type I collagen and resorbtion of scar tissue, it has been thought that, mechanical stimuli played a role in the initiation of transforming of tendon to its anatomic structure [25].

Biomechanics of Tendon in Healing Process

Tendons have more stronger structure than muscles, in terms of the resistance that they show against to tensile forces, are equal to bone tissue but more flexible and more extensible than the bone [26].

The biomechanical properties of tendons in healing process, have been the subject of extensive studies and the data obtained were compared with the normal tendon.

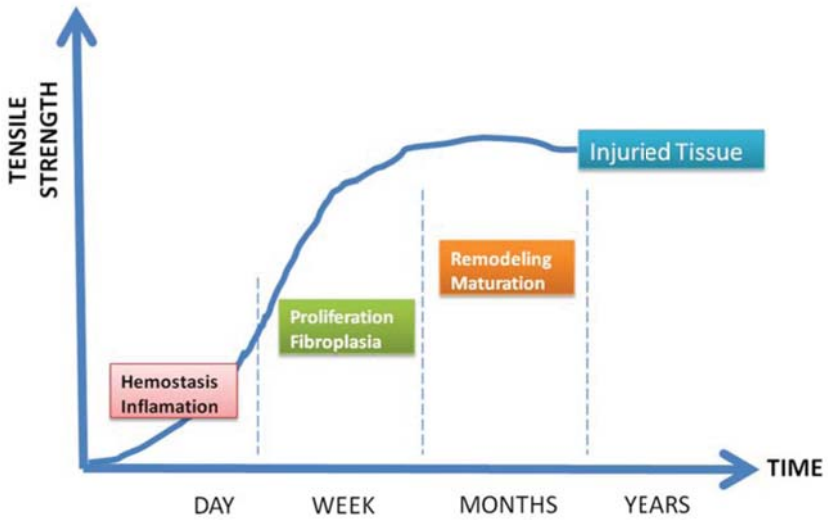

Fig 2. Biomechanic process of tendon healing [27]
Şekil 2. Tendon iyileşmesinin biyomekanik süreci [27]

It has been seen that in these studies, repaired or healed tendon tissue never reached the normal biomechanical properties of the tendon *(Fig. 2)* [27].

Taking into consideration of biomechanical properties of tendon in the healing process is critical for the management of tendon repair and healing. The scar tissue in the first stages of the repair process is in insufficient state for stretching. For this reason, immobilization of the joints related to tendon in the process of repair and recovery is necessary for recovery. It has been mentioned that, in tendon healing process, the mechanical stimuli play an important role in the formation of scar tissue and collagen fibrils [28]. To achieve this depends on the strength of the repaired or healing tendon tissue. Therefore, to obtain the strength of healing tissue was considered as main part in the development of tendon repair methods [29].

SURGICAL REPAIR APPROACHES OF THE TENDON

In orthopedic surgery, tendon repair plays an important role. Spontaneous recovery after the tendon injuries is possible in extensor tendons and partial tendon injuries. However, in the events that tendon is injured directly and resulted in complete rupture of the tendon, surgery is almost the only option.

In surgical repair of the tendon, many tendon repair methods, which are able to show resistance against the tension occuring in the repair region and is able to show resistance against the 'gap' formation, were developed [28,30,31].

Double core suture stands technique and the early methods such as Kessler, Bunnel, Tajiama etc. which tendon ends matched mutually were applied together with post-operative immobilization. Many subsequent studies on these techniques have showed that, tendon tissue has failed to reach the baseline values biomechanically in tendon repair region even after 3-4 weeks [32]. For this reason, the multi-stand techniques were developed and thus more resistant tissue was obtained in the early period and the continuity of this resistance could be maintained and thus the opportunity of early mobilization was obtained despite it was a limited situation. Winters method was obtained with the eight-strand loop shaped modification of double parallel Kessler suture technique and superior values were obtained than the modified Kessler method applying as four-strand suture. Double loop techniques, without increasing the number of knots, by providing the passage of more number of suture, provides more resistant repair mechanically [32-34].

All of these methodological improvements have not provided exactly becoming secure of repaired tendon in the level of desirable active exercise [35]. Therefore, as well as the development of surgical methods, many researches were needed for the materials used in repair [35]. Barie et al.[37] compared in cadaveric digitorum profundus tendons repaired with USP 4/0 dacron with the tendons repaired with USP 3/0 dacron, they seen that, with USP 4/0 dacron, they obtained more durable repair.

Taras et al.[36] obtained 167%, 391% more durable repaired human cadaveric digitorum profundus tendons in with the modified Kessler technique which they applied USP 2/0 diameters of suture instead of USP 5/0 and with double grasping method, respectively.

On the other hand, it has been proposed that, the location and number of knot points of core sutures increased the endurance [39].

The distance of the knots of core sutures from the the repair area increases durability. Adding peripheral sutures to the core sutures is also contributes to a stronger repair [40].

Despite the modification of tendon repair techniques and improvement of the properties of materials used, complications were not fully eliminated. These complications may be listed as re-rupture, scar tissue hypertrophy, suture pullout, and adhesions [15,41,42]. Because, extrinsic and intrinsic biological repair mechanisms of tissues play a role with surgical applications in wound healing. These mechanisms allow for the healing of tendon, but on the other hand, by causing complications such as scar tissue hypertrophy and adhesion, may also result in deterioration of the gliding mechanism [15].

BIOLOGICAL MODIFICATIONS OF THE TENDON

Researchers, in order to shorten the duration of repair, achieve more resistant repair tissue and gliding ability, continue to perform the studies which may ensure to modify the repair mechanisms [41]. These studies aimed at biological modifications and revived a different approach for the repair. Some studies conducted for this purpose, showed that the use of hyaluronic acid (HA) had an effect on tendon healing [43-45].

Mora-oka et al.[46] reported that, they reduced the adhesion with the combination of HA and phosphatidylcolin.

Moreover, in another study, lubricin was used with the aim of improving tendon gliding mechanism and it was found successful [47].

In addition to all of these developments, it has been thought that, the growth factors whose effects in tendon healing were known, may be used in order to modification of the biological environment, and many studies have been conducted [48-51].

These studies seems to offer significant opportunities

for accelerating the repair event, decreasing the duration of immobilization and obtaining more durable repair tissue. For this purpose, in the studies the agents such as bFGF (fibroblast growth factor beta), TGF-beta (transforming growth factor beta), PDGF (platelet derived growth factor) and PRP (platelet rich plasma) are used, usually good results have been reported. All of these factors increase mitotic activity of fibroblasts and collagen synthesis, in specific experimental conditions [52-55].

However, in practice, the problems such as to reach sufficient concentration of these agents in repair area and maintenance the concentration, have not been resolved [56,57].

The huge advances in genetic engineering and the complications and deficiencies which still continue in tendon repair, pointed the researches to this direction. Tang et al. cloned bFGF (basic fibroblast growth factor) gene by transferring adeno associated virus-2 vector to tendon fibroblasts [58]. In this study, the obtained genes were incorporated the ends of the cut tendon, expression of local bFGF was increased and thereby, it has been shown that, the strength of tendon repair tissue was higher in 2nd and 4th weeks.

On the other hand, BMP-12 was used for tenogenesis and found to be effective. In the patients undergoing BMP-12, the resistance of repaired tendon was higher than control group [58-61].

Despite the developments in all of these exogenous modification methods, surgical techniques and the materials used, today, the basic inability and complications affecting the success of the repair of the tendon were not fully resolved. Maybe in the future the use of the combination of all of these developments in the tendon repair, a new era can be opened.

Some researchers thought the use of the implant in order to overcome the failure caused by tendon repair and complications. So, putting an extra support next to the suture materials, they aimed to overcome the problems developing due to both early active exercise and the limp use and immobilization-induced adhesion and gliding [62].

Aygün et al.[15] in their study implanted flexible polyethylene (PE) material for rabbit ruptured achilles tendons. In this way, through the use of plate, instead of putting the suture parallel to the tendon axis, they provided the facility for positioning les number of suture vertically to the tendon axis. In addition, by ensuring the transfer of the tendon tensile forces to the implant instead of repaired ends and suture materials, they made use of early active possible [15]. However, in order to able to take the place of these and similar studies in the practical application, production of implants which are able to resorb and have biological compatibility and able to adapt to the tendon functions and development of these implants with extensive researches are required.

CONCLUSION

Tendon injuries and repair are the main topics of orthopedic surgery and the complications and deficiencies which have continued since the beginning since are not fully resolved yet. Despite the development of surgical techniques and suture qualifications which are the main materials in surgery and the use of many exogenous biological modifiers, for the ideal method of tendon repair, there is still long way to be taken. In the future, these studies will progress rapidly, seems to be effective in the improvement and recovery of function of the injured tendon in the shortest time.

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