Hallucis longus and Digitorum longus Double Tendon allograft as a safe and effective candidate for orthopedic surgery

Abstract

Background/objective: Tendon allografts are valuable tools for reconstructing tendon tissues in several anatomical sites, when autograft or tendon transfer is not available or feasible. For the aim of introducing an ideal tendon graft, in the following investigation, a specific allograft tendon was processed and characterized.

Methods: Tendon allograft obtained from hallucis longus and digitorum longus tendon named Double Tendon (DT) was evaluated regarding its structural stability as well as in-vitro biological compatibility. On this basis, a clinical trial including 20 male patients aged between 30-40 years was performed via designing a questionnaire and asking the surgeons to evaluate the predefined qualifications (such as stabilization, repairability, handling, sizing, etc.) of DT during and post-surgery in a 1-year follow-up on a 4-stage ranking (excellent, very good, good, and fail).

Results and discussion: According to performed evaluations, this product was capable of tensile load bearing to the ultimate extent of 7.33 ± 0.87 MPa, which is acceptable for a tendon substitute concerning the literature. Regarding the cytocompatibility results, the cellular viability on DT (Double Tendon) with 98.13 ± 0.18 % was not significantly lower than the cell viability of the control sample. Also, based on the statistical analysis, the surgeons reported satisfaction with DT's structural attributes and clinical effectiveness since no "failure" was observed in any parameters. Additionally, there were no instances of inflammation, infection, or rejection reported following DT transplantation.

Conclusion: Herein, the DT was introduced as safe and efficient substitute for the aim of tendon tissue repair.

Keywords: Allografts, Clinical Trial, Tendons, Orthopedic Procedures.

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Introduction

Tendon injuries, account for 30% of all musculoskeletal complaints[1]. There are an estimated 30 million tendon/ligament procedures carried out every year, costing over EUR 150 billion in both America and Europe[2]. Tendons are prone to acute or chronic injury despite having high tensile strength and the capacity to withstand the tremendous pressures produced by skeletal muscle contractions[3]. Tendon damage has several biological reasons, including trauma, persistent overuse, aging, inflammation, and genetic factors[4]. The healing process of the tendon as a connective tissue is slow and precarious due to its sparse vascular network and low metabolic rate. limiting regeneration potential after an injury[5]. Complications can often linger after a long recovery period, with tendon adhesions being the leading factor[6]. Restrictive adhesions within the synovial sheath of the tendon can lead to impaired function, increased re-rupture risk, and an extended recovery time[7].

Several investigations have been performed to introduce the ideal graft capable of overcoming the above difficulties. Currently, different types of tissue grafting are used to repair tendon injuries[8]. Autologous tissue is the most common type and considered as the gold standard, but it has been challenged by significant difficulties such as donor site morbidity and insufficient availability. Tendon allograft has the advantages of reduced surgical time, more flexible surgical incisions, a lack of donor site morbidity, and reduced risk of arthrofibrosis[8,9]. Feature of the native tendon which could also be mimicked by allograft tendon is

Fig 1. The prepared DT (Double Tendons) product of ITP.co (Iranian Tissue Product), are placed longitudinally next to each other to be sutured at two endpoints.

piezoelectricity due to the presence of collagen fibers. Piezoelectricity is described as transducing mechanical stress to electric signals that are capable of accelerating the healing process through improving cellular growth, ECM production, and tissue repair[10]. Safety of allograft is an important remaining concern[11]. Tendon allografts may be used for repairing different injured areas such as: repairing of anterior cruciate ligament (ACL), posterior cruciate ligament (PCL), complex ligament injuries in the knee, patellofemoral tendon instability, chronic patellar tendon rupture, chronic damage of extensor ton don in total knee replacement, lateral ligament of ankle, pectoralis major tendon rupture, biceps tendon rupture, chronic triceps deficiency, etc. with mechanical strength similar to the native tissue[8]. Accordingly, for approving the clinical efficiency of DT on an evidence-based approach, it is critical to evaluate its performance within a predesigned clinical trial.

Despite the significant efficiency of allografting in the reconstruction of tendon injuries, there are still serious challenges. The probability of immuno-incompatibility as well as the potential for bacterial, fungal, viral and prion disease transmission, notwithstanding the risk of disease transmission associated with using allografts, antigenicity, which may pose an immunologic reaction and rejection issue[8,12] are some of the challenges. Efficient donor screening, aseptic preparation and terminal sterilization methods and cryopreserving can reduce the untoward effects of allograft tissue[8,13,14].

In this study, for the aim of introducing an ideal tendon graft, in the following investigation, a specific allograft tendon from cadaveric specimens of hallucis longus and digitorum longus tendons was processed via antibiotic treatment and cryopreservation in aseptic criteria. Then, in the first step of evaluation, the prepared graft was characterized regarding its structural stability as well as *in-vitro* biological compatibility. Finally, its clinical performance was investigated by designing a clinical trial.

Mate23rials and Methods

2.1 Graft preparation

A tendon allograft called (double tendon) was prepared by Iranian Tissue Product (ITP) company, harvested from cadaveric flexor halluces, extensor halluces longus, flexor or extensor digitorum longus. Donners of 15-65 years of age were chosen after fully checking for bioburdens of bacteria, yeast, mold, and HIV[1], HCV[2], HTLV-1[3]. The tendon grafts were treated with antibiotic and cryopreservation in aseptic environment. The tendon would be laid longitudinally and end point of two of the four tendons were sutured (fig 1).

2.2 Mechanical properties of DT allograft

Mechanical properties of the DT scaffold were evaluated using a tensile testing machine (H10KS; H. ounsfield). Briefly, the dimensions (width, length, and thickness) of the dried sample were measured using a micrometer. Tensile testing was performed at a load cell of 25 N and a pulling rate of 1 $mm.min^{-1}$, similar to previous report by Wangz, et al[15].

1. HIV: Human immunodeficiency virus.
2 HCV: Hepatitis C virus.
3 HTLV-1: Human T-lymphotropic virus 1.

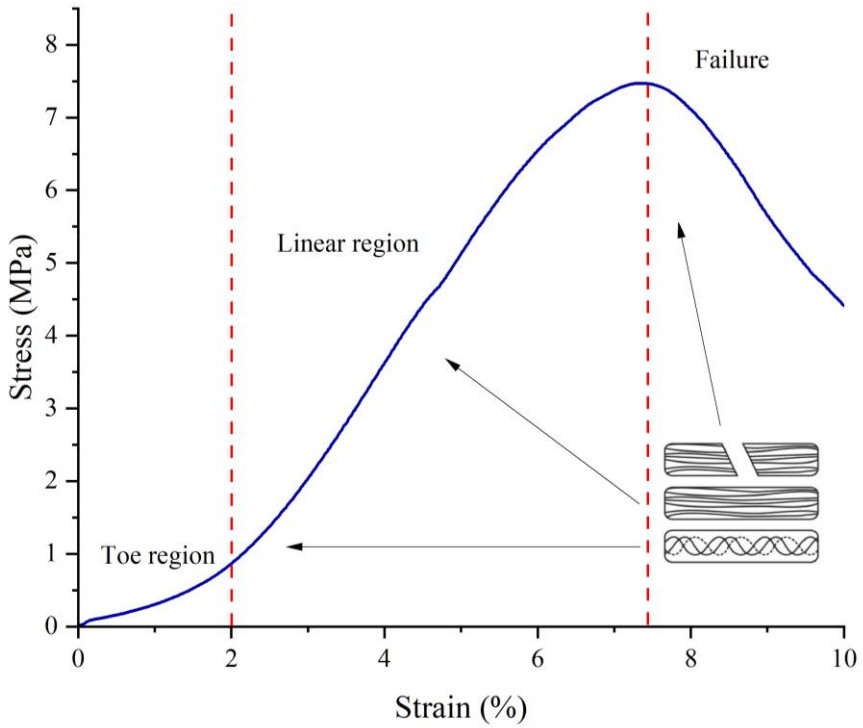

Fig 2. The stress-strain curve of the DT (Double Tendon) product of ITP.co (Iranian Tissue Product) was measured using the uniaxial tensile test until failure with a 25 kN load cell and a 1 mm/min tensile loading rate.

2.3 Biological evaluation

2.3.1 Endotoxin testing

Before initiating the clinical application, the DT products were tested for endotoxin contamination using the Gel-Clot Limulus Amebocyte Lysate (LAL) kit with a sensitivity of 0.125 EU/mL[16].

2.3.2 Cytocompatibility assay

The samples of DT were placed in Dulbecco's modified eagle medium F12 (DMEMF12; Invitrogen) with 10% fetal bovine serum (FBS; Gibco), and 1% antibiotic penicillin/streptomycin (Sigma-Aldrich) for 72 hours to produce extraction media as previously described[17]. This was done to assess the cytocompatibility. Human tenocytes were seeded 1 × 10^4 per well, simultaneously. A microplate reader (ELISA reader; ELX808, BioTek) evaluated the optical absorbance of the samples at 540 nm. In this assay, the cells cultured on the tissue culture plate (TCP) were the control group.

2.3 DT clinical trial

In order to assess clinical performance of this product, the tendon underwent a clinical trial was designed. A questionnaire was designed considering the key structural as well as biological factors of the tendon including repairability, stabilization after defrosting, handling, suitable sizing, suture-ability, biomechanical performance, and macroscopic consistency. The surgeons were asked to examine the parameters before and after the surgery and up to a 1-year follow-up on a 4-stage ranking (excellent, very good, good, and fail). They were also required to report any sign of infection, inflammation, or rejection. Statistical population was selected to be 20 males aged between 30-40 years with no history record of previous orthopedic and cardiac surgery whom underwent ACL and PCL replacement surgery caused by sport injuries. Eventually, the qualitative output was analyzed statistically.

2.4 Statistical analysis

GraphPad Prism 8 was employed for the statistical analysis. The data were presented as the mean ± standard deviation (SD). To discern variations among the study groups, a one-way analysis of variance (ANOVA) followed by Bonferroni's post hoc test was utilized. A significance level was set at a P-value ≤ 0.05.

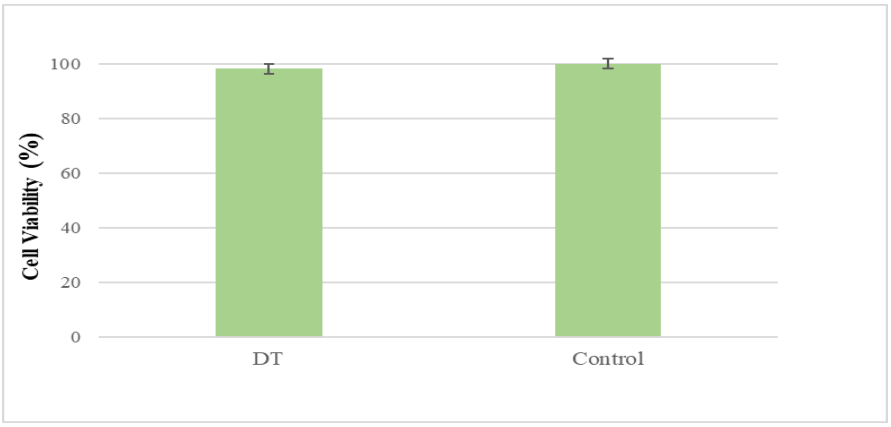

Fig 3. Cell viability evaluation of MTT* assay. Tenocyte cells were cultured for 24h with extraction media from DT (Double Tendon), and negative control represents the incubation of cells with fresh medium.

*. The MTT colorimetric assay is used to determine the cellular viability or metabolic activity in microcapsules.

Results

3.1 Mechanical properties of DT allograft

The mechanical characteristics of the tendon was acquired through the process of uniaxial tensile testing. The stress-strain curve of DT is represented in Fig 2. The elastic modulus based on the slope of the linear region of the plot was 135.02 ± 4.15 MPa. Also, the ultimate tensile strength was 7.33 ± 0.87 MPa.

3.2 Biological evaluation

3.2.1 Endotoxin testing

The existence of endotoxins could impact the assessment of biomaterial bioactivity by triggering substantial inflammatory responses. The Gel-clot test yielded a negative outcome, signifying that the endotoxin concentration is below 0.5 EU/ml. This measurement fell beneath the endotoxin threshold (0.5 EU/mL or 20 EU/device) established by the FDA for medical devices[18].

3.2.2 Cytocompatibility assay

In order to assess the potential cytotoxicity of DTSs arising from any remaining processing reagents, MTT[4] testing was conducted to evaluate cell viability and predict biocompatibility. Regarding the bar chart as shown in Fig 3, although the cellular viability on DT with 98.13 ± 0.18 % was not significantly lower than the cell viability of TCP, it was acceptable for approving DT cytocompatibility.

4. The MTT colorimetric assay is used to determine the cellular viability or metabolic activity in microcapsules.

3.3 DT clinical trial

The clinical trial was designed qualitatively to evaluate the performance of DT in orthopedic surgeries. The gathered information from the performed survey is presented in Fig 4. As can be observed, there was no report of any kind of failure in any aspect (biomechanical properties, sizing, handling, and operational performance). According to the results, the tendons have gained an "excellent" ability to be sutured as well as macroscopic consistency and strength by 90% confirmation of the surgeons. The stabilization after defrosting, capability of handling, and size for procedure were reported to be "good" by only 10% of the surgeons, the others believed that they were "excellent" or "very good" regarding the mentioned factors. Biomechanical performance during surgery was 60% "excellent"- 40% "very good" and repairability of the defect site has gained the statistics on the contrary. Furthermore, there was no report regarding the observation of any type of inflammation, infection, or rejection after the DT transplantation.

Discussion

Obviously, an appropriate mechanical strength is desirable for a tendon graft to facilitate the healing process. As Pien et al[19]. have revealed, the minimum required tensile strength of a flexor tendon regenerative substitute should be approximately 4 MPa. Hence, it may be stated that the prepared DTs are suitable substitutes for tendon healing. According to the literature, the toe region,

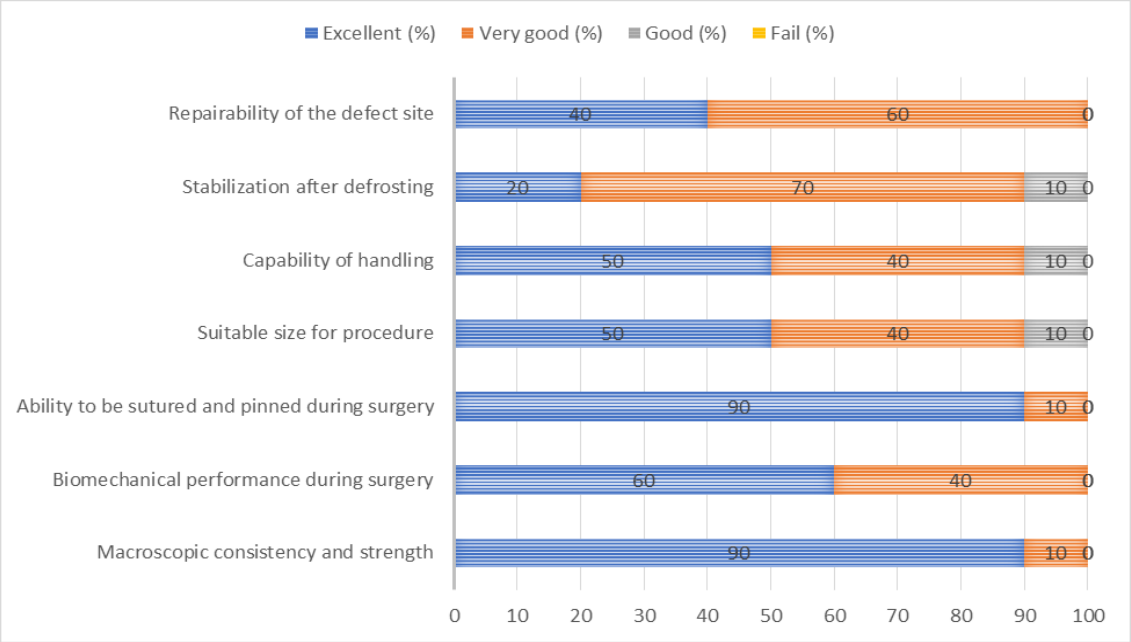

Fig 4. Performance evaluation of DT (Double Tendon), reported as percent frequency.

the linear region, and the yield and failure zone are three separate sections of the stress/strain curve[20]. The majority of tendons are found in the toe and partly in the linear region during normal activity. Since the slope of the toe area is not linear, it is this region that causes the nonlinear stress-strain curve depicted in Fig 2. The toe area indicates the "un-crimping" of collagen fibrils. This area of the stress-strain curve displays a comparatively low stiffness compared to the linear component because it is easier to stretch out the crimp of the collagen fibrils. When all crimped fibers straighten, the toe area terminates at about 2 percent strain. The collagen fibers stretch until all of the collagen fibrils loosen up. The sliding of collagen triple helices between molecules causes the tendon to deform linearly. When the strain is less than 4%, this part of the tissue reverts to its original length upon unloading and as a consequence, it has elasticity and flexibility. The slope of the curve indicates an elastic modulus. Some fibrils start to fail when tendons are stretched beyond physiological limits. Microscopic failures gradually accumulate, leading to a reduction in stiffness and initiating the failure of the tendon. This is due to the failure of intramolecular crosslinks between collagen fibers. Hence, the tendon undergoes irreversible harm due to plastic deformation. When tendons are stretched 8-10% of their original length, gross failure occurs[20,21].

This research demonstrated that the level of endotoxin load within DT scaffolds is minimal, aligning with the standards set by the US Food and Drug Administration (FDA) for permissible endotoxin contamination in medical devices[18].

The output complied with previous research; as Zhou et al[22], reported the results of the MTT colorimetric assays suggest that there is no cell growth inhibition in tendon allograft. The tenocyte cells cultured in the media extracted from DT scaffolds exhibited viability exceeding 90%, indicating the presence of metabolically active cells and affirming the non-toxic characteristics of the residual reagents released during the DT processing procedure. Hence, the biocompatibility of DT and their cellular safety in case of implantation in the tendon defect area were observed.

In case of the clinical performance, there are still controversial debates about the graft type selection; autograft versus allograft since both sources would result in desirably recovering the patients' level of activity while struggling with notable limitations[23-26]. A clinical trial was performed using the allograft flexor hallucis longus for chronic insertional Achilles tendonitis in North Carolina, United States (identified as NCT00950053). The improved clinical and functional outcomes as measured by ankle Plantar flexion strength and American Orthopedic Foot and Ankle Society score were observed in this trial[27]. Moreover, in a study by Bistolfi et al, autograft and allograft gracilis and semitendinosus tendon were utilized for reconstruction of ACL in a 10-year follow-up. 94

middle-aged patients (mean 40 years) were divided into 2 groups and received the tendons. The evaluations were based on using the International Knee Documentation Committee (IKDC) and Lysholm score (10-point scoring systems regarding function and observed symptoms). Also, the complaints of mechanical instability, infection, intolerance, swelling, etc. were recorded. According to the results, no significant differences were observed and no critical complications were reported. Furthermore, the rate of minor complications such as wound, hematoma and deep venous thrombosis was 5% and 6% for the allograft and autograft group, respectively. On this basis, the authors indicated the allograft tendon as an optimal alternative for autograft since it is not challenged by the donor site morbidity drawbacks (mild to severe pain, tendon shortening, and patellofemoral osteoarthritis)[28]. On the other hand, it was revealed in a meta-analysis study by Rai et al that concerning the remarkable pain decrease of allografting compared to autografting, the patients who obtained allografts, would tend to resume their physical activity relatively earlier in spite of the slightly longer engraftment time[29]. Therefore, as Singhal et al has reported, allograft tendon is more suitable for the middle-aged patients who are not involved in tense physical activities and could manage the rehabilitation procedure[30].

Conclusion

Herein, allograft tendons were introduced as safe and efficient substitutes for the aim of tendon tissue repair. Specifically, a tendon graft called “Double Tendon” was presented which is produced by ITP in Iran. According to the mechanical evaluation, this graft comprised the required load-bearing ability for the tendon healing procedure. Based on the biological evaluations, the biocompatibility of DT and their cellular safety in case of implantation in the tendon defect area were observed. Moreover, regarding the performed clinical trial follow-up which was performed qualitatively through orthopedic surgeons’ evaluations, this product had remarkable structural properties as well as operational performance and it could be considered an efficient tendon regenerative graft.

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Ethics Approval

All human rights were concerned in this research. All the tissues (as the raw material) were utilized after obtaining the written consent of the next of kin. Also, this project was approved by research ethics committee of Imam Khomeini Hospital Complex – Tehran University of Medical Sciences with the approval ID of IR.TUMS.IKHC.REC.1399.354.

Conflicts of interest

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report.

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