



## RESEARCH

# BIOMECHANICAL AND HISTOLOGICAL FEATURES OF COSTAL CARTILAGE GRAFT IN A RABBIT MODEL: COMPARATIVE RESULTS WITH THREE MONTHS OF FOLLOW-UP

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### SUMMARY

**Objective:** In this study, histological and biomechanical characteristics of rabbit rib cartilage used as a nasal dorsal graft were investigated.

**Material and Method:** This prospective animal study included 8 male New Zealand rabbits. After harvesting rib cartilage, the graft was placed in the subperiosteal pocket made on the nasal dorsum. Contralateral 7th costal cartilages were also harvested as controls. On the third month after the procedure, the cartilage grafts and contralateral controls were removed and subjected to 3-point bending test. Hematoxylin-eosin stained sections were also used to evaluate chondrocyte viability and the status of the chondroid tissue.

**Results:** There was no statistical difference between the dimensions (thickness and width) of nasal dorsal graft and 7th costal cartilage. The flexural strength of the contralateral 7th costal cartilage and the number of viable chondrocyte cells were found to be significantly higher compared to nasal dorsal grafts (p=0.028, p=0.027, respectively)

**Conclusion:** Although we did not determine any significant reduction with time in the dimensions of costal cartilage grafts used in nasal surgery, it seems that biomechanical characteristics are altered as identified by the reduction in viable chondrocyte count and flexural strength.

**Keywords:** Costal cartilage, nasal dorsal graft, rabbit model

### BİR TAVŞAN MODELİNDE KOSTAL KIKIRDAK GREFTİNİN BİYOMEKANİK VE HİSTOLOJİK ÖZELLİKLERİ: ÜÇ AYLIK TAKİP İLE KARŞILAŞTIRMALI SONUÇLAR

#### ÖZET

**Amaç:** Bu çalışmada nazal dorsal greft olarak kullanılan tavşan kaburga kırırdağının histolojik ve biyomekanik özellikleri araştırıldı.

**Gereç ve Yöntem:** Bu prospektif hayvan çalışmasına 8 erkek Yeni Zelanda tavşanı dahil edildi. Kaburga kırırdağı alındıktan sonra greft, nazal dorsum üzerine yapılan subperiosteal cebe yerleştirildi. Karşı taraf 7. kostal kırırdağlar da kontrol olarak alındı. İşlemden sonraki üçüncü ayda kırırdağ greftleri ve karşı taraf kontroller çıkarıldı ve 3-nokta bükme testine tabi tutuldu. Hematoksilin-eozin boyalı kesitler, kondrosit canlılığını ve kondroid dokusunun durumunu değerlendirmek için de kullanıldı.

**Bulgular:** Nazal dorsal greft ile 7. kostal kırırdağın boyutları (kalınlık ve genişlik) arasında istatistiksel olarak fark yoktu. Karşı taraf 7. kostal kırırdağın bükülme dayanıklılığı ve canlı kondrosit hücre sayısı nazal dorsal greftlere göre anlamlı olarak yüksek bulundu (sırasıyla p = 0,028, p = 0,027).

**Sonuç:** Nazal cerrahide kullanılan kostal kırırdağ greftlerinin boyutlarında zamanla önemli bir azalma tespit etmemiş olsak da, canlı kondrosit sayısındaki ve bükülme dayanıklılığındaki azalma ile tespit edildiği üzere biyomekanik özelliklerinin değiştiği görülmektedir.

**Anahtar Sözcükler:** Kostal kırırdağ, nazal dorsal greft, tavşan modeli

## INTRODUCTION

Cartilage grafts in nasal surgery, especially in rhinoplasty, are frequently required for both structural and aesthetic purposes. Autogenous cartilage grafts are preferred due to

viral load of homografts and immune reactions frequent in alloplastic materials. An ideal cartilage graft material for nasal surgery must be biocompatible, easy to obtain, and should demonstrate strength while having sufficient elasticity<sup>1,2</sup>.

Although the main source of autogenous cartilage grafts is the nasal septum, in various conditions, including revision surgery, traumatic cases with reduced nasal tip projection, caudal septal weakness and/or saddle nose deformity, grafts are obtained from auricular or costal cartilage<sup>3,4</sup>.

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The nose, despite being located in an area open to external traumatic forces, has a unique elastic cartilage structure that can compensate against such forces. Therefore, correct cartilage graft selection is critical for the adequate reconstruction of this biomechanical structure in order to ensure long term success.

Previous cross-sectional studies showed that the 6th and 7th costal cartilages have similar biomechanical properties with the nasal septum<sup>5,6</sup>. Although several experimental histopathological studies have demonstrated long term cartilage viability with the use of autogenous costal cartilage<sup>7-9</sup>, long term biomechanical results of such reconstructions have not been shown yet. It is also interesting that while some literature shows cellular loss of cartilage tissue that leads to recurrent deformation in the long term, other authors have stated that there was no significant cartilage resorption in long term follow up<sup>7,10,11</sup>.

In this study, the histological and biomechanical characteristics of rabbit rib cartilage used as a nasal dorsal graft were investigated.

## MATERIAL and METHODS

The study included 8 male (3200-3800 gram) New Zealand rabbits (*Oryctolagus cuniculus*). The Ethical Committee of xxxxxxxxxxxxxxxx approved the study (Date:10/11/2011, No:2011/155). Animals were received from the local laboratory of animal experiments and were housed in appropriately-sized pens in two groups (according to weight) during the 1-week habituation period during which they received scattered feeding with greens and hay, and standard pellet food. They were then transferred to single-animal cages inside the same room with water, scattered greens and standard pellet food. The light/dark cycle was 12/12 hours; temperature was 20-22 °C with 45% humidity.

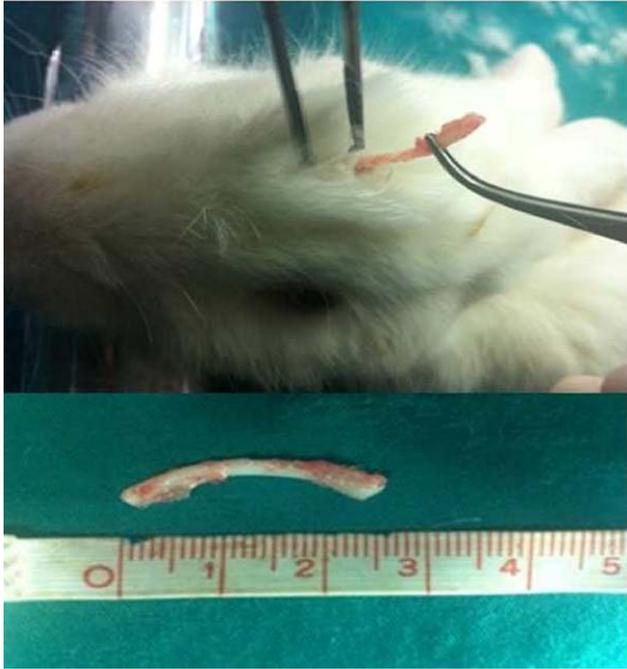
**Animal Care and Procedures** Under general anesthesia with 50 mg/kg ketamine hydrochloride and 10 mg/kg xylazine, the left thoracal region of each animal was shaved and sterilized. Rib cartilage harvesting method was performed as described previously by Coult et

al.<sup>12</sup>. A 2-cm horizontal incision was performed to the left inferior costal region and an approximately 2 cm section of the medial cartilaginous part of the 7th costal cartilage was resected with meticulous dissection, cleared from the surrounding soft tissue and perichondrium, and washed with isotonic sodium chloride (Figure 1). The width and thickness of all graft materials were measured by a digital caliper (Mitutoyo, Japan). The chest was closed with 4/0 polyglactin for muscular and dermis closure, and 4/0 silk for epidermal suture.



**Figure 1:** Harvesting of costal cartilage graft. 2cm horizontal 271 incision was performed to the left inferior costal region and approximately 2 cm long medial cartilaginous part of the 7th costal cartilage resected.

To prepare the recipient site, as previously described by Maas et al.<sup>13</sup>, A 1-cm anterior incision through skin and subcutaneous tissues was made on the dorsum of the nose. A subcutaneous pocket extending 3 cm in the cranial direction was formed directly over the bony dorsum superficial to the periosteum. The cartilage graft was placed in this pocket and the incision was closed in one layer with 4/0 silk suture (Figure 2).



**Figure 2:** *Placing of costal cartilage graft into the subcutaneous pocket over the nasal dorsum.*

Pain control that may occur in animals was provided by subcutaneous administration of 0.05 mg/kg buprenorphine hydrochloride before and after the operation every 12 hours for 3 days. Postoperatively, each rabbit was examined daily for signs of wound infection, seroma, hematoma, wound dehiscence, flap necrosis or pneumothorax until all wounds were healed. Subsequently, the animals were examined twice a week for 3 months. It has been previously shown that a 3-month follow up period in rabbits roughly corresponds to a 1-year follow-up in humans<sup>14</sup>. At the end of this period, the rabbits underwent anesthesia in a manner similar to the already described and then were sacrificed with intravenous administration of pentobarbital sodium (200 mg/kg). A midline incision was made along the nasal dorsum and cartilage grafts were removed, washed, dried and measured (width and thickness). Moreover, previous horizontal costal incision was extended through the contralateral side for harvesting contralateral 7th costal cartilages as controls. For histological examination, 0.5 cm-long specimens were harvested from both nasal dorsal graft and contralateral costal cartilages. The grafts were wrapped in saline impregnated gauze.

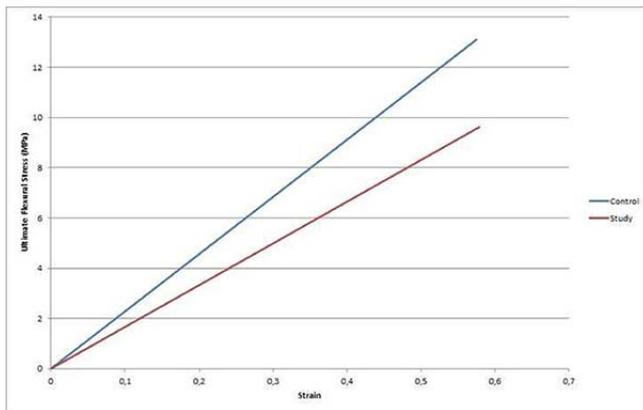
## Mechanical Testing

Three-point bending was carried out on a rectangular cross-section resting freely on two supports by means of the load acting on the specimen midway between the supports. The test specimen is deflected in this way at a constant rate until rupture occurs at the opposite (inferior) surface of the specimen (Figure 3). During this procedure, the force applied to the specimen and the resulting midspan deflection of the specimen was measured. The fracture formation was directly observed in all experiments and the force-deflection curve (mm) was automatically plotted. Flexural strength and elastic modulus were determined (Figure 4). Flexural strength can be defined as the ability of a material to withstand deformation under loading without failure. Elastic modulus, or Young's modulus, which was calculated from the force-deflection curve, describes tensile elasticity or the tendency of an object to deform along an axis when opposing forces are applied along that axis.

All of the cartilage strips were subjected to the 3-point bending test. The strips were placed freely on supports that were 10 mm apart and the load applicator was located above the center of the strips. Deflection was imposed at a rate of 1 mm/s and the load was measured at a resolution of 0,001 N.



**Figure 3:** *The test specimen is deflected in this way at a constant rate until rupture occurs at the other surface of the specimen.*



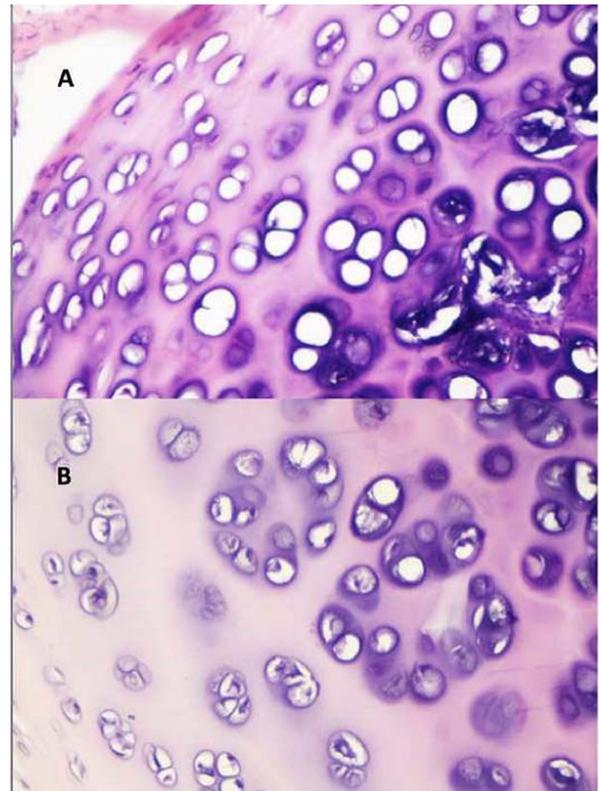
**Figure 4:** Fracture formation was observed in experiments. During this procedure force deflection curve (mm) was automatically plotted.

### Histological examination

Hematoxylin-eosin stained sections were used to evaluate chondrocyte viability and the status of the chondroid tissue. The pathologist was blinded to the specimens. The specimens were fixed in 10% formaldehyde and then embedded in paraffin. Five micrometer thick horizontal 3 serial sections were performed from each specimen. The absence of chondrocyte nuclei was considered to indicate non-viable chondroid tissue. Viable cartilage cells were counted in 3 serial sections at 10 high-power field and the average of these results were calculated (Figure 5). Inflammation, osteogenesis, calcification, necrosis and fibrosis were evaluated and reported as present or absent.

### Statistical Analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). For the normality check, the Shapiro Wilk test and Q-Q plots were used. Data are given as mean  $\pm$  standard deviation for continuous variables. Continuous variables were analyzed with the Mann Whitney U test.  $p < 0.05$  values accepted as statistically significant results.



**Figure 5:** A) Loss of viable chondrocytes with nuclei at high-power field and calcification in study group material B) Viable chondrocytes with nuclei at high-power field in control group material

### RESULTS

Eight animals were included in the study. Two subjects died on the 4th and 9th week of the follow-up period due to unknown reasons. Therefore, the 3 month follow up period was completed by 6 animals. The width, thickness, flexural strength, elastic modulus, and strain of nasal dorsal grafts and contralateral 7th costal cartilage are shown in Table 1. Mean thickness of nasal dorsal graft and contralateral 7th costal cartilage were  $2.02 \pm 0.39$  mm and  $2.05 \pm 0.34$  mm, respectively. Mean width of nasal dorsal graft and contralateral 7th costal cartilage were  $2.4 \pm 0.24$  mm and  $2.27 \pm 0.3$  mm, respectively. There was no statistical difference between the dimensions (thickness and width) of nasal dorsal graft and contralateral 7th costal cartilage ( $p=0.498$ ,  $p=0.249$ , respectively) (Table 1). The flexural strength of the nasal dorsal graft and contralateral 7th costal cartilage were measured as  $9.4 \pm 3.6$  MPa and  $12.8 \pm 3.47$  MPa,



respectively. We found that the flexural strength of the contralateral 7th costal cartilage was significantly higher compared to the nasal dorsal graft ( $p=0.028$ ). Mean Elastic modulus obtained from the load deflection curve was  $0.57 \pm 0.1$  N/m<sup>2</sup> in nasal dorsal grafts and  $0.58 \pm 0.05$  N/m<sup>2</sup> in contralateral 7th costal cartilage ( $p=0.917$ ) (Table 2).

There were no materials with histological calcification, osteogenesis and/or necrosis. However, nasal dorsal grafts of 3 subjects showed inflammatory reaction. In addition to

this, the nasal dorsal grafts of 4 subjects had fibrosis around the grafted materials. Viable chondrocyte counting results revealed that nasal dorsal grafts had  $25.1 \pm 2.63$  mean viable cells, while the contralateral 7th costal cartilages had  $32.6 \pm 3.01$  mean viable cells. The number of viable chondrocyte cells in contralateral 7th costal cartilage were found to be significantly higher than that of nasal dorsal grafts ( $p=0.027$ ) (Table 2).

**Table 1.** Measurements of each nasal dorsal graft and each contralateral 7th costal cartilage

Subject	Width (mm)	Thickness (mm)	$\sigma_f$ (MPa)	$\epsilon_f$ (N/m <sup>2</sup> )	Strain (mm)
<b>Study group</b>					
1	2.88	2.08	5.43	0.54	2.82
2	2.33	1.38	5.97	0.71	3.47
3	2.40	1.81	14.97	0.52	3.10
4	2.26	2.56	12.11	0.72	3.03
5	2.21	2.17	9.61	0.37	1.82
6	2.34	2.12	8.78	0.57	2.00
<b>Control group</b>					
1	2.32	2.05	13.57	0.52	2.75
2	2.24	1.99	10.60	0.64	3.46
3	1.77	1.63	19.39	0.54	3.54
4	2.31	2.38	12.14	0.62	2.82
5	2.73	2.17	9.83	0.52	2.60
6	2.28	2.08	11.32	0.63	3.25

$\sigma_f$ : Flexural strength,  $\epsilon_f$ : Elastic modulus



**Table 2.** Measurements of nasal dorsal grafts and contralateral 7th costal cartilages

	Nasal dorsal graft	Contralateral 7th costal cartilage	p
Thickness (mm)	2.02 ± 0.39	2.05 ± 0.34	0.498
Width (mm)	2.40 ± 0.24	2.27 ± 0.30	0.249
σf (MPa)	9.40 ± 3.60	12.80 ± 3.47	<b>0.028</b>
εf (N/m <sup>2</sup> )	0.57 ± 0.10	0.58 ± 0.05	0.917
Viable chondrocyte cells	25.10 ± 2.63	32.60 ± 3.01	<b>0.027</b>

σf: Flexural strength, εf: Elastic modulus

Data are given as mean ± standard deviation

## DISCUSSION

Exposure to various kinds of external forces, such as compression, tension, bending and/or combinations, are frequent in the nose. The nasal septum has a pivotal role in the resistance to these mechanisms<sup>6</sup>. Costal cartilage is mostly required in patients with inadequate nasal septum or severe septal deformations and/or patients who need more cartilage graft material for sufficient reconstruction. The primary aim is the creation of a stabilized nasal framework that is both aesthetically accurate and functional<sup>15,16</sup>. In this study, it was determined that there was no statistically significant difference in the dimensions of the costal cartilage used in nasal surgery over time. On the other hand, the elastic modulus and the number of viable chondrocyte cells decreased significantly over time when compared to the control group.

Costal cartilage grafts can be used for both structural and aesthetic purposes in nasal dorsal otografts for the augmentation of the nasal dorsum and/or in L strut-shaped costal cartilages for structural support<sup>15,16</sup>. Long term results of

costal cartilage grafts are often contradictory in the literature. Lattyak et al., in an animal model, reported a resorption rate of septal, auricular and costal cartilage with a frequency of 30.8%, 12.6% and 7.6%, respectively<sup>7</sup>. However, Wiseman et al. stated no resorption with viable chondrocytes in long term costal cartilage otografts<sup>17</sup>. Although, there are studies which show increased cartilage resorption rate in diced and crushed groups, some studies showed no difference in these groups<sup>18,19</sup>. Despite these conflicting results, histological examinations are utilized to assess viability and/or resorption rate in the majority of publications. In our study, we used both histological and mechanical bending parameters for the first time in the literature. Microcaliper results showed that there was no significant dimension change after 90 days in nasal dorsal cartilage grafts and contralateral controls. In addition, elastic modulus, a parameter that is usually substance-specific, was also determined to be unchanged in nasal dorsal grafts after 90 days. However, mechanical bending test revealed an average 26.56% reduction in the resistance of nasal dorsal cartilage graft deformation against applied load-compared to controls. Parallel to this,



histological examination revealed an average 23% reduction in viable chondrocyte count in nasal dorsal cartilage grafts compared to controls.

The decrease in the modulus of elasticity may cause complications such as bending, displacement/extrusion and graft fracture and may have negative effects on clinical results. Many studies have reported these complications at various frequencies. In a systematic review of 21 different studies examining autologous costal cartilage procedures in rhinoplasty, Varadharajan et al. reported the following frequencies of complications: 5.2% warping, 0.6% displacement/extrusion, and 0.2% graft fracture at long-term<sup>20</sup>. In a meta-analysis examining the results of the use of autologous rib cartilage in rhinoplasty, Wee et al. found warping in 3.08% and displacement in 0.39%, while 14.07% of the patients required revision surgery in the long term. Consistent with our study, the authors reported that there were no dimensional differences in the graft after a follow-up of more than 1 year<sup>21</sup>. The long-term modulus of elasticity results of the graft could not be evaluated because previous studies were performed on humans. The fact that our study is an animal study is an important advantage that allows the graft to be removed and re-evaluated. In the current study, although no significant difference was found in the modulus of elasticity in the time interval examined, we thought that the results of the research, where longer term investigations will be conducted, may be a guide in determining the pathophysiology of the related complications.

It is remarkable that in the current study, the number of viable cartilage cells was statistically significantly lower in the nasal dorsal graft group compared to the control group. Although the lack of a similar study in the literature restricts any meaningful comparison, it was thought that a significant decrease in the count of viable cartilage cells may manifest itself clinically with a decrease in the strength of the graft, possibly leading to resorption or nasal fracture. As a matter of fact, these complications have been reported at various frequencies in various studies<sup>20-23</sup>. On the other hand, two

surgical operations on the grettes in the nasal dorsal graft group may have affected the results. Because cartilage grafts, although they are immunologically privileged, have a high risk of resorption over time has been the biggest concern<sup>24</sup>. Experts try to solve this problem by choosing some modifications in graft preparation. In previous studies, it has been reported that mild to moderately crushed cartilage grafts give better results in terms of viability, flexibility, stability and proliferation rate compared to highly crushed grafts<sup>25,26</sup>. In addition, it has been reported that diced cartilage grafts with less stress applied to cartilage compared to crushed, fragmented cartilage grafts perform better with a higher number of living cells<sup>27,28</sup>. In this context, it was thought that higher exposure to trauma in grafts that underwent two surgical operations may increase apoptosis in the grafts and decrease the number of viable cells. Additionally, the results of homologous and autologous grafts were evaluated in other studies. In a meta-analysis comparing the results of rhinoplasty using autologous and homologous costal cartilage graft, Vila et al. reported that complications due to the modulus of elasticity of the graft and the count of viable chondrocytes were at similar frequencies in both groups<sup>22</sup>. Saadi et al. reported the same results in a similar study<sup>23</sup>. Although these studies suggest that autologous and homologous costal cartilages are not superior to each other, more studies are needed in this regard.

According to the results of this study, especially in structural reconstructive surgery, nasal septal grafts and/or columellar struts prepared from costal cartilages, alar cartilages and/or nasal dorsal onlay grafts may have a considerable risk for deformation due to the reduction of flexural strength by time. Therefore, increased bending moment of the costal cartilage grafts may improve long term results when relatively larger dimensions are used.

The most important limitation of our study is the small number of cases per group which was compounded by the fact that two animals were lost prior to final analyses. Secondly, although no subjects had graft



necrosis in our study, 4 subjects had nasal dorsal grafts surrounded by fibrous tissue. We also did not determine the effect of fibrous tissue formation on chondrocyte viability and its role in providing additional mechanical support. Another limitation of the study is that the deflation rate limit (1 mm/sn) we used is higher (0.02 mm/sn) compared to other similar studies<sup>29</sup>. It is possible that this situation has reduced the sensitivity of the measurement. Finally, anatomical structures such as perichondrium, intercartilaginous ligaments, and surgical interventions such as transeptal and/or intercartilaginous sutures enabling a reduction on graft load were not assessed or applied in the current study.

In conclusion, although the dimensions of grafts remained similar at the end of follow-up, the chondrocyte loss identified via histological analysis may demonstrate underlying alterations in structural integrity. This possibility is supported by the decrease in flexural strength. New clinical studies are needed to determine the properties of the ideal costal cartilage graft required to minimize possible complications.

### Conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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