ORIGINAL RESEARCH

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Effects of vascularization when different alloplastic implant materials are used in adjacently with acellular dermal matrix

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Abstract

Objective: Autologous tissue transplantation is the best way to repair tissue defects. Autologous graft materials can cause in the formation of scars and, in some cases, a reduction in the functionality of the donor site. This study aimed to ascertain how often revascularization in the acellular dermal matrix (ADM) is formed when different types of alloplastic implant materials are used in reconstructions.

Method: The Wistar albino rats were assigned to three groups (n=7): various alloplastic materials (porous polyethylene, titanium, tricalcium phosphate, silicone), coated with ADM, were placed in distinct subcutaneous pockets on the thoracodorsal region of the rats, at 7, 14, and 21 days post-procedure, the rats were sacrificed for sampling. Sections were stained with hematoxylin-eosin. The degree of revascularization was assessed through the use of immunohistochemical labelling (anti-CD105 antibody).

Results: The results indicated that minimal revascularization was observed on day 7, while significantly increased revascularization was evident on days 14 and 21. The use of alloplastic materials showed a significant increase in the number of CD105-positive vessels on days 7, 14 and 21. There was an increase in the number of CD105-positive vessels on day 21 compared to day 7. There was no significant difference in the number of CD105-positive vessels between days 7 and 14 in the tricalcium phosphate and silicone groups.

Conclusion: The study concluded that distinct alloplastic implants used adjacent to ADM have no negative impact on revascularization rates. This is the most sought-after objective in the field of soft tissue reconstruction.

Keywords: Acellular dermal matrix, alloplastic material, vascularization, immunohistochemistry

INTRODUCTION

Biomaterials have been widely used for tissue augmentation in plastic, reconstructive and aesthetic surgery practice (1). The soft tissue covering over the inserted implant must be well vascularized and preferably thick (2). Well-vascularized and thick coverage prevents implant extrusion, visibility, and palpation especially when placed in pockets with thin or insufficient soft tissue coverage (1-4). Well-vascularized tissue coverage also helps prevent infection and perfusion problems. Finding sufficient tissue to cover the implant is sometimes a challenge, such as unreliable and/or inadequate soft tissue or skin due to previous surgery or radiation (4-7).

The concept of covering an alloplastic material with another avascular layer may decrease or prevent revascularization, thus creating a dead space and increasing the risk of infection, which is generally chronic and resistant to antimicrobial treatment. The acellular dermal matrix (ADM) is used for supporting the envelope covering the implant for reconstruction after mastectomy (7-9). ADM can also be used for reconstruction of calvarial bone defects in order to prevent extrusion of the implant (10-12). These instances can be expanded according to many other clinical

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scenarios (13-15). Although this type of dual use, "adjacent to alloplastic material" has proven to be successful in the clinical scenario, experimental studies are needed to evaluate the neovascularization behavior of the biological matrix when used adjacent to an alloplastic material (dual use) (12,14).

In this study, it was aimed to determine the vascularization rate/amount of ADM when used adjacent to different kind of alloplastic material [dual use such as; silicone (dimethylsiloxane), ceramic (calcium triphosphate), metal (titanium), polymer (porouspolyethylene)]. It was thought that the revascularization rate/amount over time is an important measure for a complication-free application of dual use of ADM adjacent to alloplastic material.

METHOD

The present study was conducted in accordance with the approval of the Ankara University Animal Experimentations Local Ethics Committee, as evidenced by its decision dated May 22, 2013 and numbered 11/78. Twenty-one male Wistar albino rats weighing between 250-280 g were used in this study. The animals were kept under standard light/dark cycle and temperature and provided with water and standard dry rat food ad libitum.

Surgical procedures

All animals were administered by single intramuscular injection of ketamine HCL (Ketalar, Pfizer Warner Lambert, NY, USA) 1 mg/kg and xylazine (Alfazyne %2, Alfasan, Woerden, Holland) 0.2 mg/kg prior to surgery. After anesthesia, the dorsal region of the rats was shaved and scrubbed with povidone iodine solution.

Four types of implants were prepared prior to surgery;

1) Silicone sheets were prepared from smooth rectangle 15×8 cm expandable implant (Mentor®, Santa Barbara, California, USA) cut with scissors for implantation (1×1 cm flat in size).

2) Titanium plates (Trimed®/Electron Medical, Ankara, Türkiye) were prepared 1×1 cm flat in size.

3) Tricalcium phosphate cement sheets (Arex Bone®, Kasios, France) were prepared 1×1 cm flat in size.

4) Porous polyethylenes (Medpor®/Howmedica Osteonics Corp., Newnan, USA) were prepared 1×1 cm flat in size.

After following step, ADMs, 4×12 cm 0.7-1.7 cm thick (Belladerm/MTF®, Edison, NJ, USA) and rehydrated state, were taken from its package for use and were cut with scissors and sterilely prepared for implantation (1×1 cm flat in size). 1×1 cm in diameter were made on the surface of rat's thoracodorsal region two of them on the left side and three of them on the right side in all groups. Five subcutaneous pockets were created just above the panniculus carnosus. In all groups, dorsal pockets were prepared and implants were inserted adjacent to ADM in four dorsal subcutaneous pockets for the next step. The implants and ADM were not attached or wrapped, they were only inserted adjacently. They were fixed in because of the dorsal pockets's size appropriate. No deformation was observed. The fifth pocket was used as a control and only ADM was inserted. Finally, the incisions were closed with 4/0 polypropylene suture (Prolene®, Ethicon, Pomezia, Italy) (Figure 1). The rats were taken into separate cages to prevent them harming each other. Animals were examined daily by the investigator for wound infection, tissue reaction, haematoma, implant exposure, and bulging. All animals survived after the procedures without complications were related to the implantation sites. Days 7, 14, and 21 were sacrificed by decapitation and the implants and surrounding tissues were removed. Biopsies were harvested by rectangular full thickness way of surrounding and totally integrated tissue around the implants. Implants were removed before sampling. Histological specimens were obtained from ADM located at the anterior surface of the implants inserted subcutaneous tissue below skin.

Histopathological evaluation

Specimens were fixed in 10% neutral buffered formalin solution for 48 hours and prepared for routine histological investigation. Afterwards, the biopsies embedded in paraffin, 4µm thick vertical sections were taken with the help of microtome (Leica ® RM2125RT, Leica Austria-Vienna). The sections were stained with hematoxylin-eosin and they were examined by light microscopy.

Immunohistochemical staining protocol

Tissues were held in 10%-neutral formalin solution (pH:7.4) for 48 hours. Routine light microscopic tissue analysis was carried out for fixed tissues and then they were stored in paraffin-embedded blocks. In order to evaluate the vascularization in the tissues, the sections taken from the blocks were properly stained with anti-CD105 antibody in accordance with the protocol mentioned below. Sections with a thickness of 4 µm were placed over adhesive slides. In order to get rid of fixation and antigen masking caused by embedding in paraffin, they were treated with trypsin (pH:7.6) at 37 °C for 30 minutes (antigen retrieval). They were then washed with phosphate-buffered saline (PBS) 3× for 5 minutes. To block the endogenous peroxidase activity, they were incubated with 12.5% hydrogen peroxide (H2O2) in distilled water for 10 minutes and washed with PBS 3× for 5 minutes. To prevent non-specific antibody binding, they

were incubated with protein block for 8 minutes. The protein block over the tissues was removed away and, without any washing, anti-CD105 rabbit polyclonal primary antibody (Abcam, ab107595), which was diluted 1/200 with 0.5% bovine serum albumin (BSA)was instilled. The sections were incubated overnight at +4 °C. After application of primary antibody, they were washed with PBS 3× for 5 minutes. The polyvalent secondary antibody, which is conjugated with biotin (Abcam, ab93697) was instilled. They were kept at room temperature for 10 minutes and then washed with PBS 3× for 5 minutes. They were incubated with streptavidin peroxidase enzyme solution for 10 minutes and washed with PBS 3× for 5 minutes. Diaminobenzidine, a substrate of peroxidase, was instilled. Counterstaining was carried out with hematoxylin. For negative control, 0.5% PBS-BSA containing no primary antibody was instilled to the sections. Then the protocol was followed in the same way. After the sections were stained, CD105-positive vessels were counted in each of 10 different areas at 400× magnification and the mean density was reported. Sections were photographed with an integrated digital camera of the Olympus BX50 light microscope.

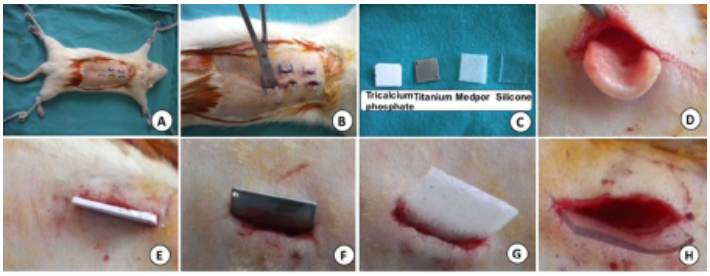

Figure 1. (A, B) Different skin pouches created on thoracodorsal region of the rats. (C) Used different alloplastic implant materials. (D) The ADM, (E) the tricalcium phosphate, (F) the titanium, (G) the metpor, and (H) the silicone was inserted into skin pouche created on the right thoracodorsal region.

Table 1. The number of the CD105-positive vessels in ADM and alloplastic implants on days 7, 14, and 21

Variable	Day 7	Day 14	Day 21	p-value
ADM	410.14±143.62‡	642.14±98.03*,II	787.00±92.95*,‡,§,II	p^b<0.001
Titanium	287.28±83.91	1006.28±118.82*	1198.28±66.73*	
Medpor	448.14±97.99	693.42±187.96*	960.14±161.04*	
TP	715.28±79.61†	876.00±162.81†	1353.42±180.26	
Silicone	577.42±192.59†	782.71±215,06†	1497.57±240.74	
p -value	p^a<0.001			
p-value	p^c <0.0001	p^d =0.002	p^e<0.001	

Data are presented as mean ± SD values. ADM: The acellular dermal matrix. TP: Tricalcium phosphate. p^a: Repeated measures ANOVA's p values to compare main effects of time p^b: Repeated measures ANOVA's p values to compare interaction effects of time and groups $p^{c,d,e}$: p values for One-Way ANOVA test. Statistically significant pair wise comparisons for time after Bonferroni post hoc test. *: Compared to Day 7, †: Compared to Day 21. Statistically significant pair wise comparisons for groups on days after Bonferroni post hoc test; ‡: Compared to Tricalcium phosphate, §: Compared to Silicone; II: Compared to Titanium

Statistical analysis

SPSS v.27 software package was used for all statistical analysis of the data. The Shapiro-Wilk test was used to check the assumption of normality. Numeric variables were summarized with the mean and standard deviation. The CD105-positive vessel numbers of means on different days (7, 14, and 21 days) at implant groups were compared by two-factor ANOVA with repeated measures. Also one-way ANOVA was used to compare between implant groups. For pairwise group comparisons according on the ANOVA results, we used the post hoc Bonferroni test. Error-bar graphs were drawn for numerical variables according to different days and groups. For all analyses, $p<0.05$ was considered as statistically significant.

RESULTS

Histopathological findings

Histopathological examination showed minimal revascularization on day 7, increased revascularization on day 14, and increased vessel proliferation on day 21 (Figure 2). Considering the ADM and alloplastic implants used, the number of vessels was found to be higher on day 21 compared to on days 7 and 14 .

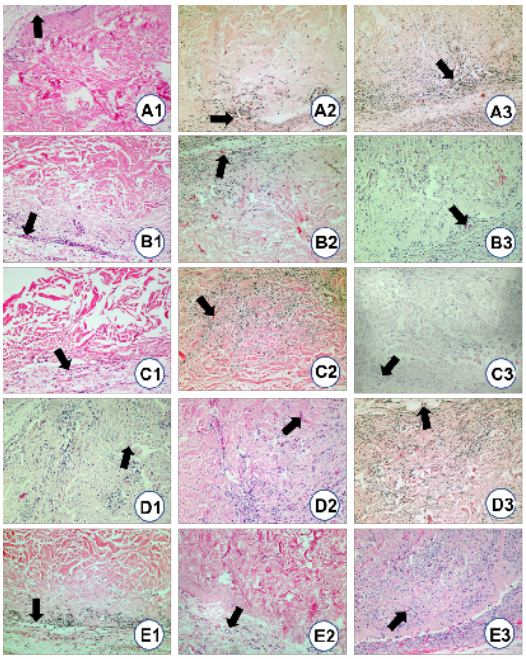

Figure 2. Histological evaluation of the tissue sections. Revascularization is shown on (A1) day 7 ADM, (A2) day 14 ADM, (A3) day 21 ADM, (B1) day 7 silicone, (B2) day 14 silicone, (B3) day 21 silicone, (C1) day 7 medpor, (C2) day 14 medpor, (C3) day 21 medpor, (D1) day 7 tricalcium phosphate, (D2) day 14 tricalcium phosphate, (D3) day 21 tricalcium phosphate, (E1) day 7 titanium, (E2) day 14 titanium, (E3) day 21 titanium. Arrows show blood vessels (H&E stain, All photos magnification 100X).

Immunohistochemical findings

When the evaluation was made without considering the ADM and alloplastic implants used, a statistically significant increase was found in the number of CD105-positive vessels on days 7, 14, and 21 ($p^a<0.001$) (Figures 3, 4, Table 1). Considering the ADM and alloplastic implants used, the number of CD105-positive vessels on days 7th, 14th, and 21st was statistically evaluated. Different alloplastic implants and time were found to affect the vascularization rate ($p^b<0.001$) (Figures 3, 5, Table 1).

The number of CD105-positive vessels in ADM and alloplastic implants was evaluated on days 7, 14, and 21 (respectively; $p^c<0.001$; $p^d=0.002$; $p^c<0.001$) (Figures 3, 5). When compared to ADM on day 7, the number of CD105-positive vessels in the tricalcium phosphate group increased statistically ($p = 0.03$), but there was no significant difference between the other groups ($p > 0.05$) (Figure 5, Table 1). When compared to ADM on day 14, the number of CD105-positive vessels was found to be statistically increased in the titanium group ($p<0.001$) but there was no significant difference between the other groups ($p < 0.05$) (Figure 5, Table 1). When compared to ADM on day 21, the number of CD105-positive vessels was found to be statistically increased in the titanium, tricalcium phosphate and silicone groups, but no significant difference was found with the medpor group (for all groups $p<0.001$ except medpor) (Figure 5, Table 1).

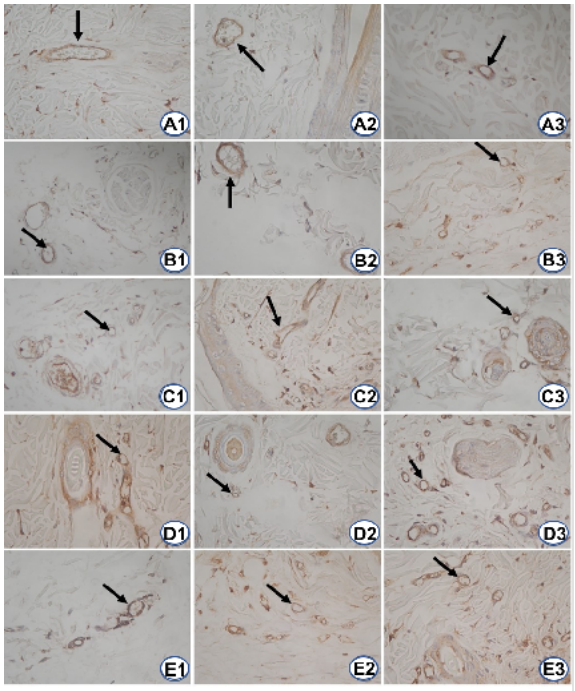

Figure 3. CD105 immunolabeling. Revascularization is shown on (A1) day 7 ADM, (A2) day 14 ADM, (A3) day 21 ADM, (B1) day 7 silicone, (B2) day 14 silicone, (B3) day 21 silicone, (C1) day 7 medpor, (C2) day 14 medpor, (C3) day 21 medpor, (D1) day 7 tricalcium phosphate, (D2) day 14 tricalcium phosphate, (D3) day 21 tricalcium phosphate, (E1) day 7 titanium, (E2) day 14 titanium, (E3) day 21 titanium. Arrows show CD105-positive vessels (All photos magnification 400X).

The mean number of CD105-positive vessels between days in the ADM group showed a statistically significant difference (Figure 5, Table 1). The increase in the number of CD105-positive vessels on days 14, and 21 was statistically significant compared to day 7 in the ADM group (respectively, $p= 0.04$; $p<0.001$) (Figure 4, Table 1). However, when comparing the mean number of CD105 positive vessels on day 14 and day 21 in the ADM group, no statistically significant difference was found ($p > 0.05$) (Figure 5, Table 1). The mean number of CD105-positive vessels between days in all alloplastic implant groups showed a statistically significant difference (Figure 5, Table 1). The increase in the number of CD105-positive vessels on days 14 and 21 was statistically significant compared to day 7 in the titanium and medpor groups (respectively, $p < 0.001$; $p < 0.001$) (Table 1). The increase in the number of CD105-positive vessels on day 21 was statistically significant compared to days 7 and 14 in the tricalcium phosphate and silicone groups (respectively, $p<0.001$; $p<0.001$) (Figure 5, Table 1). However, when the number of CD105 positive vessels was compared between days 7 and 14, no statistically significant difference was found ($p>0.05$) (Table 1).

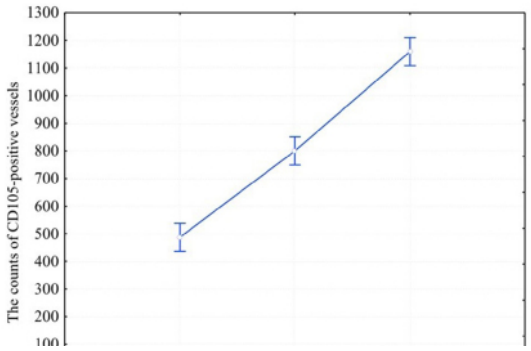

Figure 4. Graphical comparison of CD105-positive vessels counts at days 7, 14 and 21. For Day 7 vs. Day 14 and Day 21, p<0,001; for Day 14 and Day 21, p<0,001 (all p values are for Bonferroni post hoc test after repeated measures ANOVA)

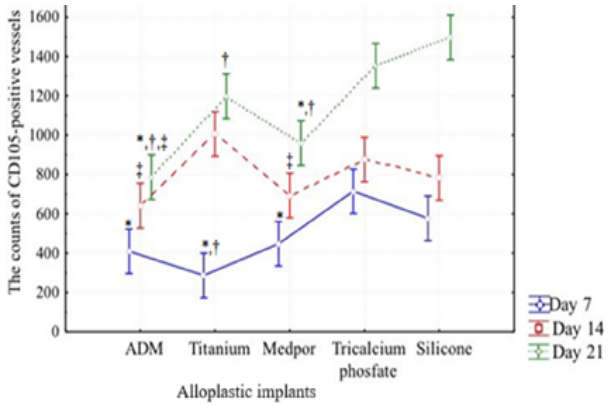

Figure 5. Graphical comparison of the CD105-positive vessels counts of ADM and alloplastic implants (silicone, metpor, tricalcium phosphate, titanium) on days 7, 14 and 21. ADM: The acellular dermal matrix.*: Compared to Tricalcium phosphate; †: Compared to Silicone; ‡: Compared to Titanium. The p-value for the Bonferroni test for all signed pairwise comparisons is <0.05.

DISCUSSION

Allogeneic dermal grafts are used for skin transplantation between genetically disparate individuals of the same species (4,5,16). Acellular allogeneic dermal grafts are derived from human skin of genetically disparate individuals in tissue banks. Donors are evaluated in terms of medical and social aspects in accordance with the United States Food and Drug Administration regulations. All patients undergo serological tests including rapid plasma reagin, venereal disease research laboratory, hepatitis B antigen, human immunodeficiency virus antibody, anti-hepatitis C virus 2 antibody, and anti-human T-lymphotropic virus type 1. Dermal and epidermal cells of the skin grafts are removed to prevent cellular rejection (4). Acellular dermal grafts constitute a suitable ground for the migration, repopulation, and revascularization of the fibroblasts and the endothelial cells of the recipient, thereby, stimulating an improved integration of the ADM with the tissue (6-10,16,17). In addition, ADM has been widely adopted by reconstructive and aesthetic surgeons thanks to its dermal content and biochemical features with low scar contraction in the surgical site. In recent years, these grafts have been used as an additional layer between the prosthesis and the skin to support silicone breast prosthesis in breast reconstruction surgeries (6-10,16-18). Therefore, insertion of these grafts to the adjacent to the alloplastic biomaterials, which can be vascularized, is highly reasonable to prevent extrusion, palpation, or unusual appearance (8,9,16,17). In this study, it was investigated the revascularization pattern of the ADM with implant materials (metpor, tricalcium phosphate, titanium) other than silicone, in which its biological behavior has been well-established to shed light on the scar healing process in different regions of the body.

With the introduction of alloplastic implants in several types of procedures in recent years, studies aiming to prevent material-related complications have been carried out (19,20). In addition, alloplastic implants have been increasingly utilized in the reconstruction of soft tissues and bone defects (21,22). A number of approaches including synthetic, biosynthetic materials, non-absorbable implants, allografts, and cross-linked biological materials have been defined for tissue defect repair. Based on the chemical compositions, implant materials can be classified into four groups including metal alloy implants, ceramic alloy implants, polymers, and biological implants (1-3,23). The main merits of these implants, as an alternative to the autogenous tissue grafts, include shorter surgery time, absence of donor site-related morbidity, and low exposure to resorption (4,5,7). Review of the literature also revealed several studies reporting the use of ADM in the prevention of implant exposure during breast reconstruction with silicone implants (5-9,16,17). In addition, several biomaterials including biological meshes can be used in other regions of the body.

Since there is no published material with comparative data related to the vascularization pattern of the ADM combined with titanium, calcium triphosphate, or porous polyethylene implants in the literature, in the present study, the revascularization process of the ADM was evaluated with implant materials other than silicone, including titanium, calcium triphosphate, and porous polyethylene. One of the early experimental studies on revascularization of ADM was conducted by Eppley (24). In the aforementioned study, the author placed sheet and rolled ADM configurations subcutaneously and evaluated the revascularization pattern. He reported that vascular ingrowth along the implants was slower in the rolled configurations, while revascularization of single-layer acellular human dermis was completed by 14 days following surgery (4). The aim of the present study was to determine the incidence of revascularization in ADM when different types of alloplastic implant materials (porous polyethylene, titanium, tricalcium phosphate, silicone) were used for reconstruction. When the evaluation was made without taking into account the ADM and alloplastic implants used, we found that the number of vessels increased on days 7, 14 and 21. We therefore assumed that the increase in vascularization was time-dependent.

Thakker et al. performed a histological examination of fibrovascular ingrowth within hydroxyapatite and porous polyethylene orbital implants wrapped in ADM (25). Similar to the study findings, the authors reported that ADM wrapping supported vascularization without any acute or chronic inflammation manifestations and prevented outer tissue abrasion. Lin et al. similarly reported that implants which were used in cranial defects in a pediatric population undergoing reconstruction surgery with porous polyethylene were not extruded with a preserved tissue layer and good cosmetic results were obtained (26). Wong et al. used alloplastic materials in the prefabricated inferior epigastric-based flaps in rats (27). The composition of the cellular infiltration into the ADM and the time course of the vascularity process were investigated. The authors concluded that the host response to ADM was parallel with normal wound healing and revascularization was satisfactorily achieved, although the flap was covered with silicone. Ribeiro et al. used two alloplastic materials similar to the ones used in the current study (28). Bone defects were filled with bioactive glass and ADM. They observed a large amount of bone formation on days 10 and 30 postoperatively. Similarly, a statistically significant vascularization was reported on day 21 following the implantation of the alloplastic materials. Taufique et al. demonstrated that ADM used in skull base repair surgery was

revascularized rapidly. They observed that ADM was integrated with the dura. The harvested specimen had new blood vessels, as well as spindle cells, indicating the formation of new vessels within the ADM (29). The results of the current study are also consistent with these findings, indicating high revascularization of ADM. We observed the skin sections under a light microscope and found that the number of vessels increased in the ADM group on days 14 and 21 compared to day 7. At the same time, immunohistochemical findings showed that the increase in revascularization over time was significant in the ADM group. In addition, different alloplastic implant materials (silicone, metpor, tricalcium phosphate and titanium) coated with ADM were placed in different subcutaneous pockets in the thoracodorsal region of rats and the revascularization rate was evaluated immunohistochemically after 7, 14, and 21 days. Compared to ADM, the number of vessels was significantly increased in the tricalcium phosphate group on day 7 and in the titanium group on day 14. On day 21, the number of vessels increased significantly in the titanium, tricalcium phosphate, and silicone groups, while no significant change was observed in the Medpor group. Therefore, we concluded that different alloplastic implant materials (silicone, tricalcium phosphate and titanium) coated with ADM affect vascularization in a time-dependent manner.

Overall, these findings suggest that ADM is not rejected, showing a good invasion rate by the host cells, high vascularization, improved tissue quality, and strong integrity with the tissue. Similarly, the study achieved consistent results, although it was utilized only two avascular materials. These findings also suggest that donor site-related morbidity may be reduced in possible tissue, which demonstrated that ADM had a unilateral vascularization pattern, despite the avascular nature of both avascular and inert alloplastic implants used in combination with avascular ADM. No suture material was utilized in the experimental groups to avoid any adverse effect of inflammation secondary to hypersensitivity. The study found no inflammation and foreign body reaction on the vascularization process.

As in previous studies, the number of vessels and the degree of revascularization were investigated in the present study. Based on the histopathological examination of the tissues following the removal of alloplastic implants, increased vascularity was observed on day 21 compared to days 7 and 14. In this study, a statistically significant difference was found in the number of vessels on day 21 compared to the other groups. This can be attributed to the fact that ADM, placed adjacently, has no impact on the revascularization rate despite distinct molecular characteristics of alloplastic materials.

Limitations of the study

The principal limitation of this study is that dermal collagen fibres could not be adequately evaluated because Masson's trichrome staining could not be performed. Another limitation is the use of CD105 as the only marker.

CONCLUSION

The relatively rapid revascularization of ADM in the in vitro setting is the major component of efficacy in the reconstructive surgery. In particular, reconstruction can be performed with alloplastic implants in previously operated complex scars with radiation therapy exposure. In this study, the results suggest that alloplastic implants can be safely used in the repair of clinical defects, since the adjacency of the implants with ADM has no adverse effect on the vascularization rate. Revascularization, as one of the major components of reconstructive surgery in the repair of tissue defects, is the most wanted goal for soft tissue reconstruction. The study may help us develop new surgical and non-surgical suggestions that would improve wound healing.

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Conflict of Interest: The authors declare that they have no conflict of interests regarding content of this article.

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Previously presented: Some part of this study was presented as poster presentation at "15th International Congress of Histochemistry and Cytochemistry" held in Antalya city, entitled as "Effects of revascularization when different alloplastic implant materials are used in adjacently with acellular dermal matrix".

Thesis: This study was prepared by rearrangement of the specialty thesis by Sevin FARİZ, entitled as "Farklı implant materyallerinin asellüler dermal matriks vaskülarizasyonuna etkileri".

Ethical Declaration: Ethical permission was obtained from the Ankara University Animal Experimentations Local Ethics Board for this study with date May 22, 2013 and number 11/78.

Athorship Contributions: Concept: SF, MIK; Design: SF, MIK; Supervision: SF, MIK, SNY; Financing and equipment: SF, MIK, SNY; Materials: SF, MIK, SNY, ZDA, MTS; Data collection and entry: SF, MIK, SNY, ZDA, MTS; Analysis and Interpretation: SF, MIK, SNY, ZDA, MTS; Literature Search: SF, MIK, SNY; Writing: SF, MIK, SNY, ZDA, MTS; Critical Review: SF, MIK, SNY, ZDA, MTS.

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