

# Decellularized human dermal matrix produced by a skin bank

## A new treatment for abdominal wall defects



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### Decellularized human dermal matrix produced by a skin bank. A new treatment for abdominal wall defects

**BACKGROUND:** Interest is increasing for human decellularized scaffolds for their ability to favor healing and cell infiltration after transplantation, in the treatment of abdominal wall defects. The purpose of the present study is to show the clinical results obtained after the application of human decellularized dermal matrix (HDM) produced by RER Skin Bank, on patients suffering from different abdominal wall defects.

**METHODS:** Between 2012 and 2014, 64 patients, average age 64 years, received HDM, to replace and cover the damage area during abdominal wall surgery. After surgical procedures, all patients were followed weekly for the first month and then monthly up to 6 months postoperative and any major problem or complication were recorded. Six months follow up included abdominal exams, serological tests and MRI analysis in order to evaluate integration of HDM with the patient's surroundings tissues and eventual long-term complications.

**RESULTS:** Incisional hernia was the most frequent clinical condition in which HDM was applied, requiring also the highest amount of human decellularized dermal matrix. One month after the surgical operation, 61 patients revealed a well tolerability of HDM and a normal wound healing was also identified in all the damage areas. Only 3 patients experienced postoperative infections. Moreover the follow up after 6 months reported no signs of dermis rejection and that none of the patients was positive to serological tests.

**CONCLUSIONS:** Human decellularized dermal matrix can be considered a safe and useful bioproduct to treat large abdominal defects, characterized by minor complications and simplicity to be implanted.

**KEY WORDS:** Abdominal wall defects, Human decellularized dermal matrix, Skin Bank, Tissue regeneration

### Introduction

Abdominal wall defects are unusual abdomen openings and can be caused by trauma, burns, treatment of abdominal compartment syndrome and resection of abdominal tumors<sup>1-5</sup>. Although these defects result as

one of the most common surgical procedures performed every year, they still lead to high mortality rate and represent a major challenge for plastic and reconstructive surgeons. Different methods for the repair of abdominal wall defects have been described including the use of autogenous fascial flaps as well as prosthetic implantable materials<sup>6-11</sup>. In particular, the implantation of synthetic biocompatible materials generally allowed a decreased recurrence rate of incisional hernia due to their high tensile strength and reconstructive abilities<sup>8,12-18</sup>. However, several side effects may be related to the implantation of synthetic biomaterials, including immunological reaction, bowel adhesions, fistula formation, surgical site

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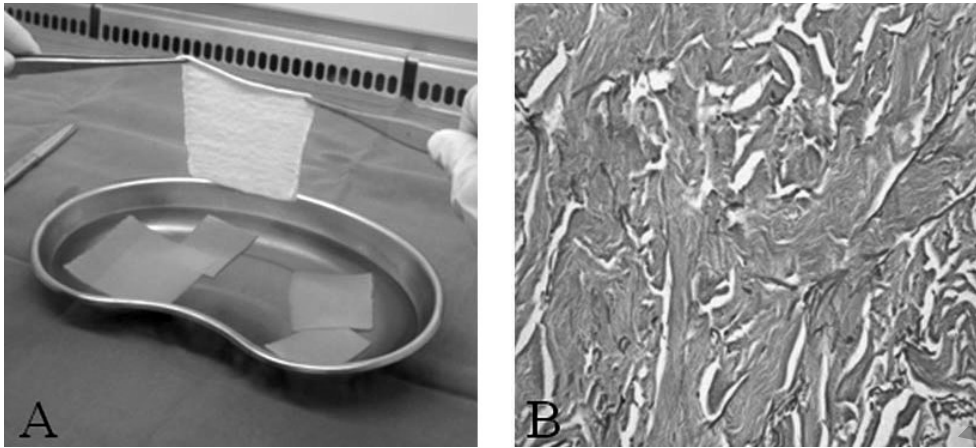


Fig. 1: Human decellularized dermal matrix (HDM) produced by RER Skin Bank. (A) Gross anatomy of HDM after the patented decellularization procedure. (B) Histological staining of HDM shows intact collagen fibers and bundles with no cellular materials (H&E, original magnification 20x).

infections or mesh extrusion<sup>19</sup>. In order to avoid these complications, in recent decades several biological scaffolds have been designed for abdominal wall defects repair, reducing problems of tolerability and acceptability compared to synthetic materials<sup>20</sup>. Actually different commercial scaffolds deriving from animals and or from human cadaveric donors, obtained through decellularization processes of dermis or fascia lata, are available for surgical repair<sup>21,22</sup>. In particular, interest is increasing for human decellularized scaffolds for their ability to favor the healing process and autologous cell repopulation after transplantation, with no sign of rejection<sup>23</sup>. Human decellularized dermal matrices (HDM) are classified as human tissues for transplantation and each Country has to follow National Regulatory Transplantation Center rules for the control of human-derived tissue transplants<sup>24,25</sup>. In 2008, Emilia-Romagna Regional (RER) Skin Bank of Bufalini Hospital in Cesena in collaboration with Rizzoli Orthopedic Institute in Bologna, produced a cell-free scaffold, totally biocompatible and safe starting from skin of cadaveric donor, patenting a decellularization method able to remove cellular components from dermal tissue (Fig. 1). This scaffold has the potential to interact with the surrounding host tissues, maintaining biomechanical strength and biochemical components<sup>25</sup>, and it is currently applied in different clinical fields such as traumatology for the repair of abdominal wall defects, dermatology, plastic surgery, breast reconstruction and orthopaedics<sup>26</sup>. The purpose of the present study is to show the clinical results obtained after the application of human decellularized dermal matrix (HDM) on patients suffering from different abdominal wall defects.

## Materials and Methods

### TISSUE PROCUREMENT

2-3 mm thick samples of human dermis were first taken from the backs of multi-organ or multi-tissue donors

and then transported to the RER Skin Bank for processing according to national rules on tissues for transplantation (CNT 14/09/2016); here the tissues were aseptically decellularized and stored in nitrogen vapors (-180°C). At 24 hours before surgical implantation, tissue samples of requested sizes were thawed, prepared and then sent in a sterile saline solution from the RER Skin Bank to Emergency Surgery and Trauma, of Bufalini Hospital and here conserved at a temperature of 4°C until its use.

### PATIENT POPULATION AND SURGICAL PROCEDURE

Between June 2012 and December 2014, 64 patients, average age 64 years, received HDM after signing consent forms, to replace and cover the damage area during abdominal wall defects surgery. Abdominal wall reconstruction was performed using the components separation technique by Ramirez *et al.*<sup>27</sup>. Briefly, this surgical technique is based on subcutaneous lateral dissection, fasciotomy lateral to the rectus abdominis muscle and dissection on the plane between external and internal oblique muscles with medial advancement of the block that includes the rectus muscle and its fascia. This release permits medial advancement of the fascia and a closure up to 20 cm wide defects in the midline area. Then HDM was positioned in a bridge onlay technique in aseptic conditions and then it was sutured (Fig. 2a). Finally, the incision was then dressed with a negative pressure wound therapy dressing (Fig. 2b). The number and the size of the drains varied based on the size of the overlying skin flaps. In the case of large abdominal wall defects (Fig. 3a), multiple pieces of decellularized human dermis were sutured together on the operating table and were inset to the fascial edges (Fig. 3b). After surgical procedures, all patients were followed weekly for the first month and then monthly up to 6 months post-operative and any major problem or complication were recorded. Six months follow up included abdominal exams, serological tests for the potential detection of

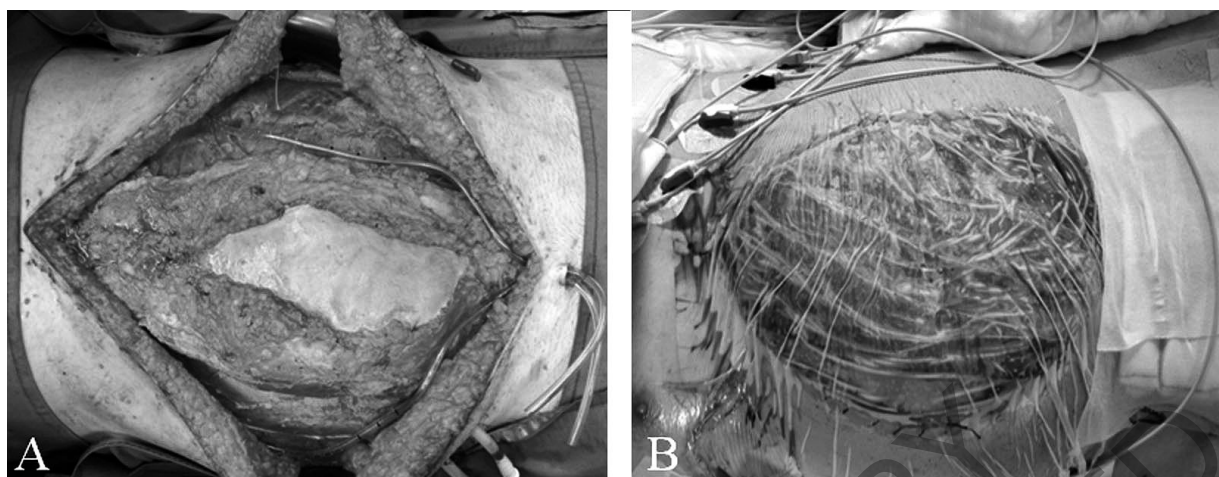


Fig. 2: Digital photographs illustrating surgical technique used by the authors. (A) Bilateral release of the external oblique muscles allowed for a tension-free fascial closure of this large deficit. Then a sheet of HDM was placed as an overlay reinforcement and sutured. (B) The incision was finally dressed with a negative pressure wound therapy dressing.

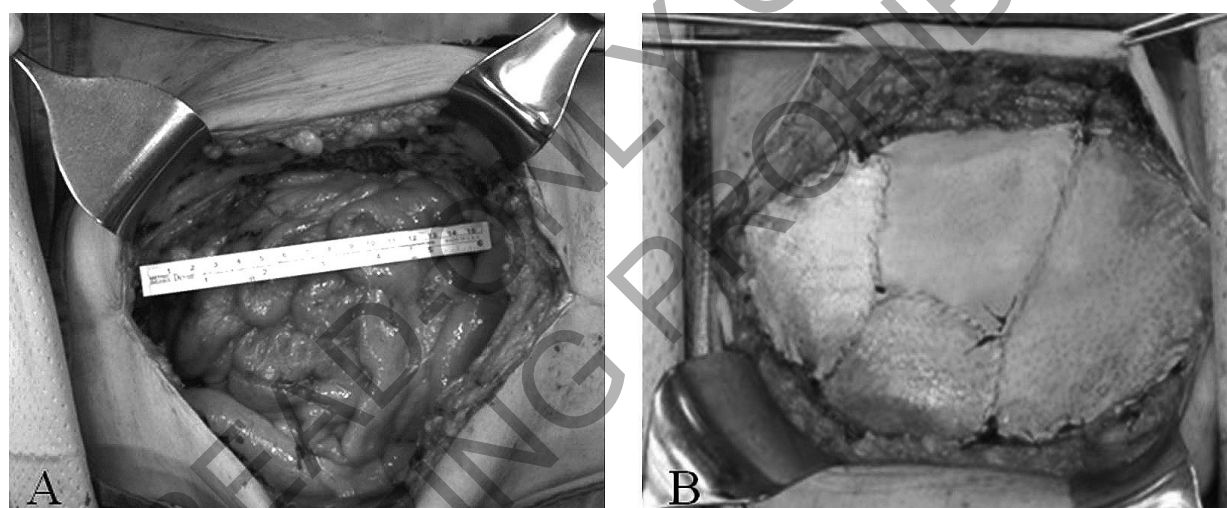


Fig. 3: Digital photographs illustrating one case with large deficit from the series reported by the authors. (A) Large abdominal wall defects. (B) Multiple pieces of decellularized human dermis were sutured together and were inset to the fascial edges.

HBV, HCV and HIV virus and magnetic resonance imaging (MRI) analysis in order to evaluate integration of HDM with the patient's surroundings tissues and eventual long-term complications.

## Results

A total of 64 patients, 30 females and 34 males, suffering from abdominal wall defects underwent to surgical procedure with implantation of HDM. Human decellularized dermal matrix was used for patients with different clinical conditions, such as incisional hernia,

TABLE I - Clinical Indications for use of human decellularized dermal matrix (HDM), number of patients treated and average size of the tissue graft.

Clinical indications	Number of patients	Mean size of HDM transplanted (cm <sup>2</sup> )
Incisional hernia	40	186,5
Hartmann recanalization	7	76,8
Post-traumatic wounds	6	120
Abdominal tumors	4	125
Umbilical hernia	4	92,2
Rectovaginal fistula	3	52

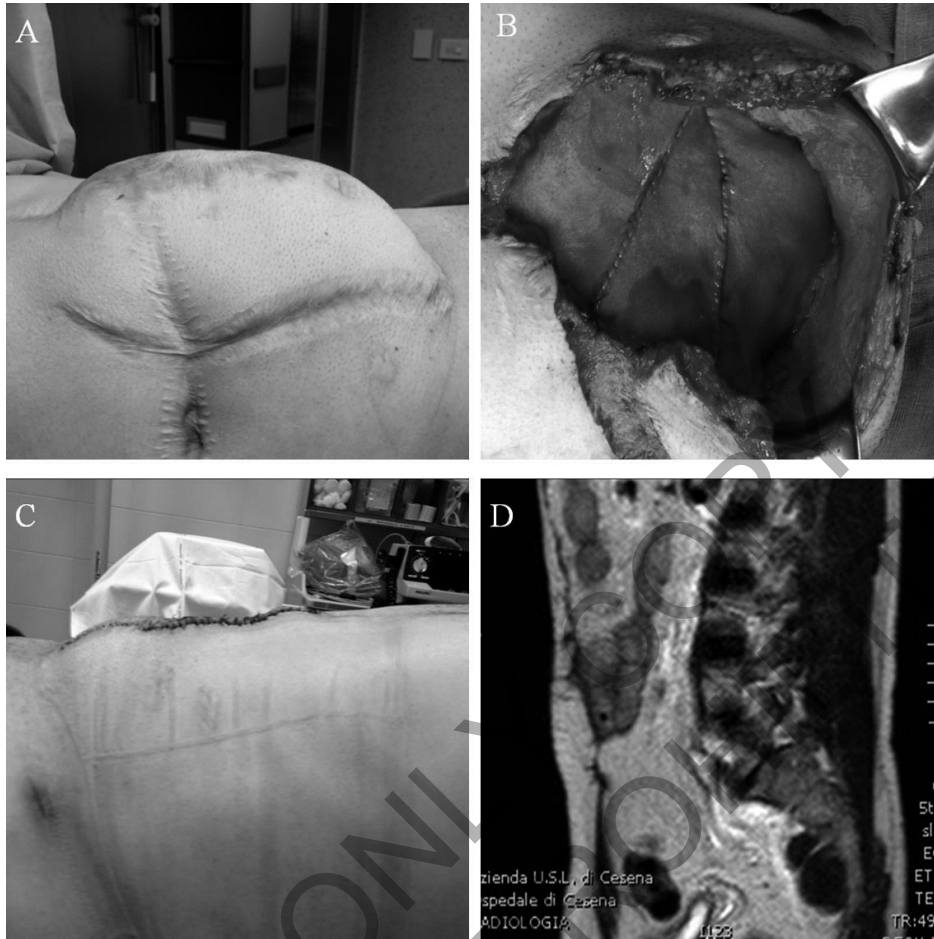


Fig. 4: (A) Male patient with ventral hernia. (B) Intraoperative view of human decellularized dermis. (C) One month postoperative view of patient following abdominal wall reconstruction. (D) Six month follow-up using MRI analysis.

Hartmann recanalization, post-traumatic wounds, abdominal tumor, umbilical hernia and rectovaginal fistula. In particular, incisional hernia was the most frequent clinical condition in which HDM was applied, as shown in Table I, requiring also the highest amount of HDM to repair abdominal wall with an average size of 186,5 cm<sup>2</sup>. One month after the surgical operation, 61 patients revealed a well tolerability of HDM and a normal wound healing was also identified in all the damage areas. Only 3 patients (4,7%) experienced postoperative infections that were treated with appropriate antibiotic therapy without removal of the HDM. Moreover the follow up after 6 months reported no signs of dermis rejection and that none of the patients was positive to serological tests. Fig. 4 depicts the clinical case a 52 years male suffering from incisional hernia (Fig. 4a), that was treated with 3 different sheets of HDM for the reconstruction of abdominal wall, using components separation technique (Fig. 4b). After 1 month the patient demonstrated a total recovery of the damage area (Fig. 4c) and after 6 months follow-up, MRI analysis demonstrated an intact abdominal cavity with no evidence of

hernia and a perfect incorporation of the HDM in the patient surrounding tissues (Fig. 4D). Similar results were also obtained in all patients after MRI analysis, confirming the integration of HDM on the lesion area with the abdominal wall tissues. Further only 4 patients developed long term complications such as seroma, as reported in Table II. Differently from others clinical studies, in which a recurrence hernia frequently occurred, we identified it only in 1 patient.

TABLE II - Long-term complications after MRI analysis.

6 months follow-up: results	Number of patients
Perfect integration of the graft with the host tissue	55
Seroma	4
Laxity	3
Recurrence	1
Incisional hernia in a different area	1

## Discussion

Several studies have demonstrated that human decellularized dermal matrices may achieve excellent results in the treatment of contaminated and complex abdominal wall defects<sup>28-30</sup>. For this reason in recent years different biological materials have been designed with different characteristics for implantation into various surgical defects. Among those, AlloDerm is widely used, as intact human decellularized matrix that promote recellularization and revascularization, as reported by *Buinewicz and Rosen*<sup>16</sup>. In their retrospective review, the application of AlloDerm for incisional hernia provides exceptional safety and tolerability, allowing the tissue replacement over time. Similarly, our human decellularized dermal matrix had comparable biological and clinical features. Moreover, to our knowledge, for the first time a non-commercial decellularized matrix taken from cadaveric donor and produced by a Skin Bank was implanted to close abdominal wall defects. Previous studies on this scaffold confirmed a well maintenance of the biologic characteristics, good mechanical strength and tolerability, reducing high cost of production and distribution, since it derives from a human donation<sup>25,26</sup>. Further our results showed that all the abdominal wall defects were closed successfully with the use of HDM.

The most common complication in the peri-operative period was infection and the most common complications in the long-term period were seroma. Another encouraging result is that we had only one patient with a recurrence of hernia, compared to higher reported rates of recurrence of other studies<sup>31</sup>. This can be due to the thickness of our scaffold, which can increase the strength of the tissue graft reducing the recurrence rate. In fact it was suggested that the use of thicker products can prevent stretching of the material over time<sup>32</sup>. In addition, all patients are negative for serological tests at 6 months from surgery to rule out diseases such as hepatitis B or C or HIV disease, even if the risk of transmitting infectious diseases is extremely low, because of strict human donor control as well as physical and chemical treatments when processing and storing the tissue. As demonstrated, our decellularized scaffold is easy to suture into several parts, so we can combine different patches and treat very large abdominal wall defects. On this basis, this human decellularized dermal matrix can be considered a safe and useful product to treat large abdominal defects, characterized by minor complications and simplicity to be implanted.

## Riassunto

I difetti di parete addominale possono essere causati da traumi, ustioni, trattamento di sindromi addominali e resezioni di tumori addominali. Differenti metodi per la riparazione di questi difetti sono stati descritti, tra cui

l'utilizzo di lembi autologhi e di biomateriali sintetici impiantabili. Tuttavia diverse reazioni avverse sono state evidenziate dopo l'impianto di biomateriali sintetici, quali reazione immunologiche, formazioni di fistole, aderenze ed infezioni. Al fine di evitare questi effetti indesiderati, negli ultimi anni il mercato ha commercializzato numerosi scaffolds biologici, ottenuti attraverso vari metodi di decellularizzazione e utilizzati sempre più frequentemente per il trattamento di difetti addominali. Queste membrane decellularizzate sono classificate come tessuti ad uso trapiantologico e ogni Paese deve seguire le proprie regole riguardo la donazione di Organi e Tessuti. Nel 2008 è stato avviato presso la Banca Regionale della Cute dell'Emilia-Romagna (Azienda USL della Romagna, Cesena) uno studio mirato alla progettazione e produzione di un sostituto cutaneo decellularizzato unicamente biologico a partire dalla lavorazione di derma omologo di donatore multiorgano e/o multitessuto. Questo bioprodotto, ad oggi autorizzato dal Centro Nazionale Trapianti (CNT), viene distribuito a livello nazionale in svariati ambiti di applicazione clinica, in particolare per la riparazione di difetti di parete, in dermatologia e in ortopedia. Lo scopo del seguente studio è la valutazione clinica ottenuta dopo trapianto di derma omologo decellularizzato utilizzato in pazienti affetti da difetti di parete addominale. Nel biennio 2012-2014 sono stati trattati 64 pazienti, con un'età media di 64 anni. Il derma decellularizzato, di 2-3 mm di spessore, è stato posizionato con tecnica chirurgica onlay, suturato e trattato con terapia topica a pressione negativa (vac therapy). In seguito, tutti i pazienti sono stati seguiti ogni settimana per il primo mese e poi ogni 6 mesi per monitorare la guarigione tissutale e possibili complicazioni. Il follow-up a 6 mesi comprende esami sierologici, per valutare possibili infezioni da HBV, HCV and HIV virus trasmesse dal tessuto trapiantato e la risonanza magnetica, per verificare l'integrazione del derma decellularizzato con i tessuti circostanti del paziente stesso. Nello specifico, sono stati trattati diversi tipi di difetti di parete addominale: in particolare, l'ernia addominale ha mostrato la maggiore incidenza. Inoltre, ad un mese dall'operazione chirurgica, sono stati rilevati 61 casi di normale guarigione della ferita, mentre solo 3 pazienti hanno sviluppato infezioni post-impianto. Questi ultimi sono stati trattati con esito positivo con terapia antibiotica. Infine il follow-up a lungo termine ha evidenziato 4 casi di sieroma e che, diversamente da altri studi in cui vengono utilizzate matrici commerciali, solo 1 paziente ha sviluppato un'ernia secondaria, mentre nessun paziente era positivo ai test sierologici. Da questa valutazione clinica possiamo concludere che il derma omologo decellularizzato prodotto dalla Banca Cute di Cesena è un ottimo bioprodotto in grado di riparare questo tipo di patologie, integrandosi con i tessuti circostanti del paziente senza creare reazioni avverse.

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