Acellular Dermal Matrix in Postmastectomy Breast Reconstruction

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Acellulaire dermale matrix bij borstreconstructies na mastectomie

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For my parents, who inspire me to be the best physician that I can be

"Wherever the art of Medicine is loved, there is also a love of Humanity."
– Hippocrates

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Chapter 1

General Introduction and Outline of Thesis

OVERVIEW OF THESIS

Over the last decade the use of acellular dermal matrix (ADM) in reconstructive breast surgery has been transformative. Some authors have gone as far as to suggest that it is the single most important advancement in prosthetic breast reconstruction.[1-6] ADMs are able to provide numerous solutions for the many issues related to inadequate tissue coverage and support such as capsular contracture, implant rippling, and implant malposition.[1,7-10] The notion of a living bra is a fascinating one for both plastic surgeons and patients alike.[1] This advent has mirrored the increased use of nipple and skin sparing mastectomy, BRCA testing, and superior implants where patients are achieving better outcomes than with breast conserving treatments with lumpectomy and radiation.[1] Despite the numerous advantages associated with ADM use, controversies remain. As such this thesis will focus on the current state of the art for ADM use in post-mastectomy breast reconstruction.

BREAST CANCER

The Centers of Disease Control and Prevention (CDC) reports that breast cancer is the most common form of cancer affecting women today.[11] In 2013, the National Cancer Institute estimated 234,580 new breast cancer cases and 40,030 deaths in the United States alone.[12] This has been paralleled by the large number of breast reconstruction procedures performed annually.[13] Twenty percent of breast cancers are linked to a positive family history.[14] The discovery of the BRCA gene in 1994 was a major breakthrough and since then other genes, albeit with less penetrating ability, have recently been discovered (RAD51C and RAD51D).[15-17] In recent years, numerous advances have been made in every aspect of breast cancer care including early detection, diagnosis, and treatment.[18,19] This has resulted in significant improvements in disease-free and breast cancer related survival. Despite these advances, mastectomy remains an important surgical option for the management of this condition. Though mastectomy is not considered a high risk surgical procedure there are obvious aesthetic, functional, and psychological concerns[20-22] as well as potential long-term effects (such as chronic pain) that may affect overall quality of life.[23] Studies have shown however, that patients who undergo mastectomy followed by reconstruction experience improvements in overall well being including improved body image and feelings of sexuality.[24-26]

BREAST RECONSTRUCTION

Breast reconstruction is aimed at restoring a normal appearing breast. The presence of a breast mound alone lacks the characteristics of a native breast.[24] There is now a line of evidence suggesting that reconstruction following mastectomy yields far superior improvements in physical measures and quality of life than mastectomy alone.[27] An overwhelming majority of these reconstructive procedures are tissue expander/implant based because of their relatively straight forward operative technique and reduced operative time.[28,29] Currently, the rate of prophylactic mastectomy of the contralateral side in women diagnosed with early-stage breast cancer is on the rise.[23,30] This is particularly noticeable in younger women.[23,30-34] One study demonstrated a significant increase in the mastectomy rate from 33% to 60% over a 13 year period.[35] Another publication reported that 98% of women would opt to undergo this procedure to decrease their risk of cancer; 95% felt that it gave them peace of mind, and 94% claimed that they believed it would prolong their life.[23] This, despite numerous studies demonstrating similar survival and local control rates with breast conserving therapy and radiation compared to mastectomy.[36,37] These figures suggest a trend toward early implant based breast reconstruction. Furthermore, the increased use of acellular dermal matrix (ADM) to support these procedures is indicative that a paradigm shift in the management of breast cancer is in progress.[24]

The desire to construct better breasts has resulted in considerable innovations in reconstructive breast surgery over the course of the last half century particularly since the introduction of silicone breast implants.[24] In recent years it has become one of the most popular plastic surgery procedures in the United States.[24] Initially, complications were focused primarily on the implants themselves which led to significant improvements in their design including more cohesive gels, barrier layers to reduce gel leakage and a wider range of implant profiles. All of these enhancements have contributed to a more positive attitude about the safety of implants use.[24] Moreover, improved surgical planning has resulted in better outcomes. Such measures consist of tissue analysis and optimization of muscle coverage with the dual plane among numerous modifications.[38-40]

Despite the advancements made, reoperation rates in women undergoing post-mastectomy breast reconstruction are estimated at greater than 1 in 3.[24] This glaring fact emphasizes the inadequacy of traditional approaches when performing implant based breast reconstruction. Following mastectomy, the implant is placed below the pectoralis major muscle which in turn covers the superior and medial poles of the implant. The exposed lateral and inferior poles can then be covered either by elevating the pectoralis minor or serratus anterior, or with subcutaneous tissue.[7,41,42] In the event that coverage

is inadequate, implant malposition, animation deformity, capsular contracture, or visible rippling may result.[6,8,43,44] Alternatively, some patients may already have an inherent deficiency of the soft tissue envelope.[7] Some argue that these potential complications can be alleviated by proper implant selection and technique but a more permanent solution to these issues is needed.[24] The incorporation of ADMs into tissue expander/implant based breast reconstructions serves as a useful option to aid in resolving a lot of these problems.[24]

ACELLULAR DERMAL MATRIX

Basic Scientific Concept

Acellular Dermal Matrix (ADM) is a bioprosthetic material synthesized from animal or human cadaveric sources that have been denuded of the cellular components that cause inflammation and rejection.[45-47] The resulting product is a biologic mesh that enhances angiogenesis, normal tissue in-growth, and intrinsic regeneration by cell repopulation thereby promoting improved integration and post-operative healing with minimal resorption.[47] The professed function of these meshes is to provide a regenerative framework that supports new collagen deposition and matrix remodeling.[48-53] The diverse proprietary processes, decellularization, and sterilization methods employed by the various manufacturers may affect how a given mesh is reacted upon by the recipient tissue. These variations in mesh preparation may affect the biomolecular structure and biochemical properties of the collagen scaffold. This in turn will shape foreign body recognition and antigen presentation.[48] Due to the proprietary nature of mesh production and the heterogeneous nature of mesh/host interactions, it is difficult to determine the effect of biologic manufacture on mesh efficacy and recognition.[48]

Uses of Acellular Dermal Matrix

ADMs were first introduced in the early 90s and since then they have been implemented mainly in breast and abdominal wall reconstruction.[54-59] The list of indications for ADM use has evolved to include other forms of soft tissue coverage; they are now used in dental surgery,[60-62] burn reconstruction,[41,63-65] eyelid reconstruction,[66-68] hand surgery,[69,70] lower extremity coverage,[71] nasal reconstruction[72,73] and less commonly in reconstruction of the hypopharynx,[74] pelvic floor[75] and scalp.[76] In addition, they have been employed in the repair of bronchopleural[77] and oronasal[78] fistulae.

Histology and Proof of Concept

Proof of concept for the use of ADM in the periprosthetic compartment has been made possible by documentation of its histologic behavior.[79] Biopsy specimens obtained at 6

months showed active fibroblasts, organized collagen, unbroken vascular channels and minimal inflammation and scarring.[79]

Collagen Cross-Linking

Collagen cross-linking is done to extend the life-span of the biologic mesh. It enhances the mechanical strength of the matrix and reduces its breakdown by collagenase. Cross-linking is achieved by using hexamethylenediisocyanate, carbodiimide, glutaraldehyde, or photo-oxidizing agents.[80,81] Although cross-linking may be useful in circumstances requiring long-term tissue reinforcement, several studies have shown that it diminishes the immunologic properties of the mesh in both animal models and in the clinical setting.[82-84]

Mesh Integration

Following implantation of the biologic mesh into the host, an acute inflammatory reaction ensues. This will set off a cascade of events that will ultimately affect mesh performance. First, the mesh scaffold is penetrated by mononuclear cells which starts the process of ingrowth, and is frequently accompanied by the proliferation of new vessels. Cytokines and other signaling factors secreted by the mononuclear cells will attract fibroblasts that will in turn promote new collagen synthesis and deposition. These processes occur not only at the mesh/host interface but also within the mesh itself. Good mesh integration is important for improved outcomes.[48]

Foreign body response

An ever-present component of the host response to incorporated biologic mesh is inflammation. This reaction will either help mesh integration or result in mesh degradation.[82,85-88] This fine balance is maintained by cytokines, growth factors, and other chemical signaling molecules released by host macrophages at the site of host/mesh interface. In general, a heightened foreign body response has been linked to the use of cross-linked porcine dermis grafts.[48] This was corroborated in a study where intraperitoneal implantation of Surgisis® (Cook Ireland Ltd., Limerick, Ireland) and CollaMend™ (CollaMend™, CR Bard, Inc–Davol, Inc., Warwick, RI) in rats resulted in the formation of a broad rim of foreign body giant cells and granulomas around the mesh.[89] Having said that, other reports have indicated outcomes to the contrary.[85] To date, the exact clinical significance of the undue activation of macrophages in vitro remains unclear.

Neocellularization and Neovascularization

One of the cornerstones of successful mesh integration is early vascular infiltration. Furthermore, it contributes to a stronger mesh/host interface. If angiogenesis does not occur, remodeling will cease and the mesh will be replaced by a scar.[48] A study in primates demonstrated the presence of functional blood vessels lined with endothelial cells in

human dermis within 1 month of being implanted[83] and was corroborated by a sublay biologic mesh study in rats.[85] In the latter, a normal, non-denatured collagen pattern was observed suggesting remodeling and new collagen deposition. These findings are by and large seen in non-cross linked meshes. Although cross-linking does not exhibit the same degree of cellular infiltration and neovascularization in the early stages, it does not seem to affect final outcomes in the long run (after 1 year).[87] Another interesting finding is the use of porous biologic meshes which have been reported to enhance neovascularization but not in growth and integration.[89] However, this concept is still being investigated.[48]

Matrix Remodeling

Remodeling has been defined as cellular infiltration, neovascularization, extracellular matrix deposition and scaffold degradation.[90] It is perhaps the most important phase following mesh placement during which the mesh is resorbed by the host. Failure of remodeling will result in scar formation. Various factors can influence remodeling, such as rate of scaffold degradation,[90] extracellular matrix deposition, and the use of non-cross linked grafts (which favor remodeling).[88] In a study in which cross-linked grafts were used, remodeling was absent even 6 months following implantation, and the matrix samples were completely degraded by bacteria from associated wounds indicating that these grafts time and again act as permanent foreign body materials.[85] Still, remodeling does not necessarily assure better reinforcement of native tissue repairs in the long run.[48]

Acellular Dermal Matrix in Breast Reconstruction

A majority of patients undergoing reconstructive breast surgery prefer prosthesis-based reconstruction.[91] This can present with various challenges; the skin envelope may be compromised by any tension caused by implant malposition which may lead to wound complications, and visible contour irregularities. Use of ADM offers the ability to offload any mechanical stress caused by the implant on the skin envelope and skin closure thus improving perfusion.[6,92] Furthermore, ADMs have been employed to aid in reconstitution of the inframammary fold, improve definition of the lateral mammary fold, enhance lower pole contour, permit better implant positioning, reduce the chances of capsular contracture, and shorten the filling time required for tissue expansion. Some authors have even suggested that it is protective against the effects of radiation.[7,93-106]

Following mastectomy ADMs can be used in either a single-staged reconstruction to create the implant pocket by expanding the submuscular pocket volume[4,6,42,103] or in a two-stage reconstruction to uphold the inferolateral portion of the tissue expander pocket.[100] In one study were human ADM was used in 13 breast reconstructions because of poor pectoralis muscle coverage, 92% were reported to be stable with added soft tissue padding, decreased rippling and implant visibility.[104] Many different approaches have been

described to attach ADM to local tissue. Perhaps the most prominent of which are the ADM sling[6] and hammock.[2] The use of an ADM sling was reported in a series of 58 breasts (43 patients) for inferolateral support during expansion with a low complication rate and satisfactory aesthetic outcome.[5] These results were corroborated by another study in which use of an ADM sling contributed to better lower-pole projection, good symmetry, and adequate breast volume.[103] The inferolateral ADM hammock is used for creation of an implant pocket that allows for better control of implant position. It is attached to the serratus anterior laterally and rectus abdominis fascia inferiorly. When employed in a study of 67 breast reconstructions no complications were reported and patients were satisfied with the final outcome.[2]

By incorporating ADMs into the reconstructive process, there is a reduction in the time needed for it to ensue.[7] This can be attributed to diminution in the time or need for tissue expansion which in turn will speed up the start of adjuvant chemotherapy and radiation if necessary. Furthermore, by reducing the amount of dissection needed during implant or expander placement when an ADM is used, there has been a reported decrease in postoperative pain.[107] To the contrary, a recent randomized controlled trial by McCarthy et al.[108] demonstrated no statistically significant difference in the rate of postoperative expansion seen between acellular dermal matrix-assisted, tissue expander/implant reconstruction and submuscular tissue expander/implant placement; which they attributed to no differences in immediate postoperative pain or pain during the expansion phase. However, they did suggest that further studies assessing the efficacy of ADM in improving long-term outcomes are still needed.

Acellular Dermal Matrix in Aesthetic Breast Surgery

Data on the use of ADM in aesthetic breast surgery is scarce.[98] Despite this paucity of literature, revision surgery still presents unique challenges.[7,98] First, these patients are for the most part thin and lack an abundance of local breast tissue. Furthermore, the breast envelope is regularly encapsulated or scarred.[7] Addressing this issue may lead to other problems such as surface irregularities and skin dimpling when plicating the thin breast envelope. In addition, these patients tend to have raised expectations and are dissatisfied with the need for revision surgery.[7] Moreover, local tissue rearrangement or capsular excision to conceal surface irregularities may result in a change in implant position.[7] The use of ADM may be helpful in improving the aesthetic appeal in the presence of a complex breast deformity.[7,98,109,110]

Acellular Dermal Matrix to Correct Complex Breast Deformities

The two most prominent breast deformities addressed by acellular dermal matrices (ADMs) are surface irregularities and implant malposition.[7]

Surface Irregularities

Surface irregularity is a broad term that encompasses capsular contracture, rippling or wrinkling and stretch deformity. Capsular contracture is one of the most common and challenging complications following prosthetic based breast reconstruction.[97, 111-113] Traditional options for the treatment of capsular contracture include capsulotomy or capsulectomy with implant removal when indicated.[114, 115] However, results with these techniques have been suboptimal as evidenced by the high rate of reoperation.[113] Several reports have confirmed a low incidence of capsular contracture when ADMs were used.[2,5,6,44,93,116-120] Different approaches have been implemented to correct capsular contracture including a combination of capsulorrhaphy and marionette sutures.[103,121] ADMs can also be laid directly on the capsule if no capsulotomy or capsulectomy is needed. A parachuting technique often aids in placing the graft in the correct location.[5,109] Another approach involves shifting the implant pocket from a subglandular to dual-plane position with incorporation of an ADM graft which is attached to the perichondrium of the rib cage, the pectoralis major muscle, and the serratus anterior muscle flap.[121,122]

Rippling occurs more frequently when saline implants are used and become more noticeable when a thin soft-tissue envelope covers the implant.[79] For these patients a single layer of ADM can be inserted between the overlying soft tissue and the implant for an improvement in contour. The dermal side of the graft is placed in an onlay fashion to reduce the extent of dissection required.[123] In this setting the ADM functions as a "tissue-thickener" to camouflage implant visibility.[7]

Stretch deformity is defined as an increase in the distance between the inframammary fold and the nipple.[98] It is common in patients with breast ptosis, those with larger implants and in weight loss patients. In these cases ADM is used as a sling from the medial to the lateral chest wall to support the implant as an internal hammock and thereby relieving the stress and load on the soft tissues and skin.[98]

Implant Malposition

Implant malposition is the second most common proponent of revision breast surgery following capsular contracture.[98] It may occur due to malposition of the inframammary fold with or without bottoming out of the lower pole, or following capsular contracture.[121] Depending on the type of malposition, it can be classified as superior, inferior (fold malposition), lateral, and medial (symmastia).[98]

Symmastia typically results either when an iatrogenic communication occurs or if the prosthesis is placed too close to the midline. To resolve this issue, medial capsulorrhaphy can be performed followed by suturing the soft tissue to the sternum. If subpectoral im-

plants are used the posterior capsule can be dissected from the rib cage and "rolled up".[7] However, results using this approach have been mixed.[124] ADMs may aid in resolving this issue by being placed over the areas of capsulorrhaphy and secured to the chest wall and capsule.[125] It can also function as a medial, C- shaped sling that is created between the two implants.[124] Outcomes thus far seem positive.[124,125]

Acellular Dermal Matrix in Nipple Reconstruction

There is very little data on the use of ADM in reconstruction of the nipple-areola complex (NAC).[126-128] Despite this, reports thus far have demonstrated promising outcomes.[128] When ADM was used in a modified dermal flap pattern for 30 nipple reconstructions to enhance nipple projection, it was found to be easily reproducible and safe.[126] Another study showed it to be simple and well tolerated.[127] In spite of these successes some have reported loss of projection over time[129] as well as increased incidence of contamination by Staphylococcus in mammary ducts.[109]

Complications with Acellular Dermal Matrix

To date it remains unclear whether acellular dermal matrices (ADM) contribute to elevated postoperative complication rates. Studies have produced conflicting outcomes.[10,42,102,105,116,130-132]

Infection

Theoretically, due to their inherent ability to integrate with host tissues, ADMs should to a large extent be able to resist infection.[105] Though, this process takes time and as such a window period emerges during which infection may come about.[46] In the last few years numerous studies have been published concerning the complication rate in implant based post-mastectomy breast reconstruction using ADM.[10,42,116,117,131] In a study were human ADM placed at the lower pole of the released pectoralis major superiorly, the serratus anterior flap laterally and the chest wall inferomedially in 30 immediate implant-breast reconstructions, the authors reported a 0% complication rate.[6] Similarly, a low complication rate was reported in a study of 41 patients (65 breasts) who underwent staged breast reconstruction with ADMs.[116] Moreover, readmission rates for IV antibiotics in patients undergoing implant based breast reconstruction were found to be similar in both ADM and non-ADM cohorts.[133] A retrospective review showed no increase in the risk of postoperative complications following tissue expansion.[9]

In contrast, others have demonstrated a 5.37 time increase in the rate of infection and a 4.24 time increase in the rate of seroma in a series of 415 implant-based reconstructions where ADMs were used.[131] Analogous to the previous, ADM use was associated with a rise in the rate of infection in breasts larger than 600g.[117] Further, one study reported non-sta-

tistically significant increases in rate of infection with ADM which was linked to individual risk factors such as smoking, higher body mass index, and larger implant size.[42] Another article reported a 3.9% complication rate in 466 breasts (260 patients) of expander-based breast reconstruction with human ADM but no complications after one year follow up.[118]

Tolerance to Radiation

There is controversy regarding the ability of ADM to tolerate exposure to radiation. Most studies seem to point to a higher complication rate in irradiated versus non-irradiated breasts.[5, 105, 118] One study demonstrated a fourfold rise in complications in irradiated versus non-irradiated breasts.[118] Another reported an 11-fold increase in the rate of total complications in irradiated versus non-irradiated breasts (45.5 percent versus 4.3 percent).[5] Other authors have indicated however, that ADM-assisted tissue expander reconstruction seems to resist the effects of radiation better than plain tissue expander reconstructions[5,134,135] with one study demonstrating a risk of infection that did not differ with or without ADM.[105]

AIMS OF THESIS

Several studies were designed to gain a better understanding of the most effective approaches when using acellular dermal matrix (ADM) to yield optimum results, the different types of ADM employed in post-mastectomy breast reconstruction, the impact of ADM use on complication rates, current trends of use among plastic surgeons, and an objective justification as to whether ADM use does indeed improve aesthetic outcome.

Technical Aspects

When incorporating a foreign material into the body, it is vital that one's own experience be compared to those of others in order to supplement our knowledge and skill with theirs. In an effort to gain a better understanding of the role that acellular dermal matrix (ADM) use plays in current practice specifically in post-mastectomy breast reconstruction with regard to complications rates, it was important to evaluate several specific technical aspects:

1. The most reliable techniques when using ADM to reduce the incidence of breast deformities and complications as well as to enhance cosmetic outcome.
2. How the use of a different type of biologic mesh with different properties can affect the success of a procedure in terms of complication rates and aesthetic result.
3. Baseline patient characteristics and co-morbidities to identify high risk patients in relation to complications, and potentially influence the decision as to whether a patient is a suitable candidate for ADM incorporation.

4. The decision to use ADM in the presence of drains, antibiotics, radiated patients, and for nipple reconstruction.

Psychological Aspects

To assess the quality and effectiveness of acellular dermal matrix (ADM) use in breast reconstruction, clinical outcome measures alone are not sufficient. As such, through an online survey, plastic surgeons using ADM for breast reconstruction were asked about what how they perceived patient satisfaction among their individual patient populations. Furthermore, inquires were made into their opinions of the literature concerning the current evidence pertaining to ADM use in plastic surgery and how it has affected their decision to use ADM and type of mesh incorporated. In addition, assessment of aesthetic outcome by a panel of blinded plastic surgeons provided more insight as to the effects of ADM on the final result of breast reconstruction.

Economic Aspects

One of the main deterrents for acellular dermal matrix (ADM) use is it high cost. It is therefore extremely important to take cost and benefit into account. A vital component of ADM use is to demonstrate the economic viability and continued availability of these biologic meshes. A review of the literature looking specifically at the cost of ADM use was performed to gain a better understanding of what others have perceived to be either cost effective or not. This is supplemented by a brief survey in which participating plastic surgeons were specifically asked about whether cost influenced their decision to include or exclude ADM in their breast reconstruction procedures as well as photographic analysis comparing the aesthetic outcome of ADM and non-ADM assisted breast reconstructions to serve as justification for their added expense.

OUTLINE OF THESIS

The studies presented in this thesis were performed in the Division of Plastic and Reconstructive Surgery at the Beth Israel Deaconess Medical Center, Harvard Medical School in Boston, Massachusetts, in collaboration with the Department of Plastic, Reconstructive and Hand Surgery at Erasmus MC in Rotterdam, The Netherlands. These studies were conducted between 2010 and 2013 and incorporated a patient population that underwent post-mastectomy tissue expander/implant based breast reconstruction with acellular dermal matrix.

Chapter 2

Acellular Dermal Matrix (ADM) has been incorporated into primary and secondary breast augmentation, reduction mammaplasty, and post-mastectomy breast reconstruction. In post-mastectomy breast reconstruction they can be used to create an implant pocket for single-stage procedures and the inferolateral portion of the tissue expander pocket when a two-staged approach is preferred. ADM can also be used to address specific deformities such as implant malposition and contour irregularities. The purpose of this study was to highlight the various uses of ADM in breast reconstruction as well as optimal techniques for improved outcomes when addressing various deformities.

Chapter 3

There has been a marked increase in the number of acellular dermal matrix (ADM) products that has paralleled their increased use in various clinical settings and most prominently in breast surgery. In this study, a comprehensive review of the literature was performed to establish a direct comparison of the most commonly used ADMs in breast surgery with regards to physical characteristics, biomechanical properties, level of sterility, and known complications.

Chapter 4

In the current literature, there is controversy as to whether the use of acellular dermal matrix (ADM) in immediate and delayed expander/implant based breast reconstruction is associated with a rise in post-operative complication rates. Thus far, studies have been single institutional and yielded inconclusive results. The American College of Surgeon's National Surgical Quality Improvement Program (ACS-NSQIP) offers the ability to analyze a multi-institutional, national data set. The aim of this study was to compare baseline differences in demographics and co-morbidities as well as post-operative complication rates with and without ADM in post-mastectomy breast reconstruction using the ACS-NSQIP.

Chapter 5

In recent years, the popularity of acellular dermal matrix (ADM) use has been on the rise in plastic surgery especially for breast reconstruction. Despite its many pros, it has a steep learning curve, it is costly which can be concerning in today's economic environment, and questions remain as to its possible contribution to post-operative morbidity. In light of these concerns we sought to describe the collective experience of plastic surgeons with ADM use in post-mastectomy breast reconstruction using an internet based survey.

Chapter 6

Over the years there has been a steady increase in the expectations of women for improved aesthetic outcomes following post-mastectomy breast reconstruction. A majority of these procedures are performed using the tissue expander/implant based approach. This technique does have its drawbacks such as capsular contracture and implant displacement which may necessitate either removal or replacement. Incorporation of acellular dermal matrix (ADM) may help to reduce these occurrences; furthermore, it may result in superior cosmetic outcomes but are expensive. To that end, there has not been any evidence published to justify the use of these costly meshes for improved aesthetic outcomes other than surgeon opinion. The purpose of this study was to provide the first truly objective perspective of the cosmetic outcomes following ADM use in post-mastectomy breast reconstruction using a photographic analysis assessed by a panel of experienced, blinded plastic surgeons.

SUMMARY

In conclusion, this thesis set out to answer the following research questions:

1. What are the best approaches when using ADM in post-mastectomy breast reconstruction to optimize outcomes specifically when addressing various breast deformities? **(Chapter 2)**
2. What are the most commonly used biologic meshes in post-mastectomy breast reconstruction, and how do they compare in terms of physical characteristics, biomechanical properties, level of sterility, and known complications? **(Chapter 3)**
3. Following analysis of the ACS-NSQIP database is there a difference in post-operative complication rates in patients undergoing breast reconstruction with and without the use of ADM? **(Chapter 4)**
4. What are the current trends in terms of plastic surgeon experience when using ADM in reconstructive breast surgery? **(Chapter 5)**
5. Are the high costs of incorporating ADM in breast reconstructions justified by improved aesthetic outcome? **(Chapter 6)**

In the general discussion **(Chapter 7)** the results of these studies are briefly discussed, it will be determined whether the outcomes of each have adequately addressed the aforementioned aims of this thesis, and potential future studies are suggested. The studies described in this thesis are summarized in English **(Chapter 8)** and Dutch **(Chapter 9)**.

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Chapter 2

Acellular Dermal Matrices in Breast Surgery: Tips and Pearls

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KEY POINTS

- Acellular Dermal Matrices (ADMs) are useful in primary prosthetic breast reconstruction as well as in the treatment of secondary deformities.
- A periareolar incision gives excellent access to the breast in secondary revision.
- When implanting ADMs, it is important to use a single, thick layer of the product.
- Patient selection is an important factor; in the postmastectomy setting, ADM-assisted reconstruction is appropriate in patients who have adequate skin envelope.
- ADMs may alleviate the occurrence of complications by reducing the inflammatory changes that cause capsular contracture and capsule formation.
- One drawback to the use of ADMs is their cost.

Acellular dermal matrices (ADMs) have been used for postmastectomy breast reconstruction, primary and secondary breast augmentation, and reduction mammaplasty.[1, 2] In postmastectomy breast reconstruction, ADMs can be used either to create an implant pocket in single-stage reconstruction or to create the inferolateral portion of the tissue expander pocket in 2-stage reconstruction. Specific deformities after cosmetic breast augmentation such as contour irregularities and implant malposition can be addressed with ADMs (Table 1).[1] The benefits of using ADMs include a low complication rate, the ability to provide needed tissue, and the ability to aid in repositioning the implant (Table 2). The disadvantages include the risk of infection and seroma, and high cost. The use of ADMs is a safe alternative for the correction of breast deformities after reconstructive and aesthetic breast surgery.

OVERVIEW OF ADMs IN BREAST SURGERY

ADMs became available in 1994 and the most commonly used ADMs in breast surgery are AlloDerm® (LifeCell, Branchburg, NJ, USA), Strattice™ (LifeCell Corporation, Branchburg, NJ, USA), DermaMatrix® (MTF/Synthes CMF, West Chester, PA, USA) and FlexHD® (Ethicon, New Brunswick, NJ, USA). AlloDerm® regenerative tissue matrix is produced by removing the epidermis and cells from human cadaveric skin.[3] Strattice™ reconstructive tissue matrix (LifeCell Corp., Branchburg, NJ, USA) is derived from porcine dermis denuded of cells and sterilized using electron beam irradiation.[4] DermaMatrix® (MTF/Synthes CMF, West Chester, PA, USA) is human skin in which both the epidermis and dermis are removed from the subcutaneous layer of tissue in a process using sodium

Table 1. Key technical considerations in using ADMs in breast surgery

Reconstructive Breast Surgery	**Aesthetic Breast Surgery**		Reduction Mammaplasty
• ADM used to create implant pocket (single-stage reconstruction) or to cover inferolateral portion of the tissue expander (2-stage reconstruction) • Used as a sling or hammock to anchor lower pole of pectoralis major • Placed with dermal side facing mastectomy skin flaps • Ensure mastectomy flaps are as thick as possible	Surface Irregularities	Implant Malposition	• Used as sling to support the inferior pedicle • Plicate ADM in a horizontal fashion
	• Single layer of ADM placed between implant and overlying soft tissue • Thick or ultrathick sheets most frequently used • ADM placed in an onlay fashion • ADM placed directly on capsule if no capsulotomy or capsulectomy required • Parachuting technique aids in proper graft placement	• ADM placed over areas of capsulorrhaphy and secured to the chest wall and capsule • Dermal side oriented towards the capsule • Avoid tension to prevent dimples and bands	

Table 2. Advantages of using ADMs in breast surgery

Breast Reconstruction	Aesthetic Breast Surgery		Reduction Mammaplasty
	Surface Irregularities	Implant Malposition	
• Provides soft-tissue coverage over prosthesis • Allows control of inframammary fold • Permits creation of a larger implant pocket • Decreases rate of capsular contracture • Reduces time needed for entire reconstructive process • Can expedite postoperative chemotherapy and radiation • Decreases postoperative pain by limiting amount of dissection	• Improved contour • Minimizes the extent of dissection required	• Prevents implant malposition in capsular contracture and symmastia • Requires only a few tacking sutures	• Better cosmetic outcome in terms of nipple-areola position and breast projection • Lower risk of "bottoming out"

chloride solution, rendering it sterile and preserving the original dermal collagen matrix.[5] FlexHD® acellular hydrated dermis is derived from donated human allograft skin.[6]

ADM Biomechanical Differences

A few biomechanical differences that are of clinical relevance exist between the various ADMs. AlloDerm® has been reported to have increased elasticity compared with DermaMatrix®[7] and Strattice™.[8] This quality is relevant in situations in which increased elasticity is preferred, such as in addressing capsular contracture, or when the goal is for the ADM to conform to the inferolateral curvature of the breast.[7] When the ADM is needed to provide support, such as in repositioning a displaced implant, a less elastic ADM like Strattice™ is preferred.[8] Figs. 1–3 provide a comparison of the different biomechanical properties of various types of biologic meshes.

ADM Size

When deciding on the size of ADM to use, the patient is assessed preoperatively, and any surface irregularities or implant malposition are marked with the patient standing, sitting, lying down, and flexing the pectoralis major muscles. These markings aid in choosing the size of the ADM to be used.[1] Intraoperatively, the sheet of ADM is fashioned to the appropriate size of defect at the time of placement. With respect to the sizes of ADM to use, a 4-cm x 16-cm piece of AlloDerm®[9-11] is typically used; the thickness of ADM varies from 1.3 to 1.8 mm, and the thickness used depends on the indication. Spear and colleagues[12] devised a guideline for selection of AlloDerm® size based on the arc length of the inframammary fold and the lateral mammary fold; for arc lengths of 18 cm or less,

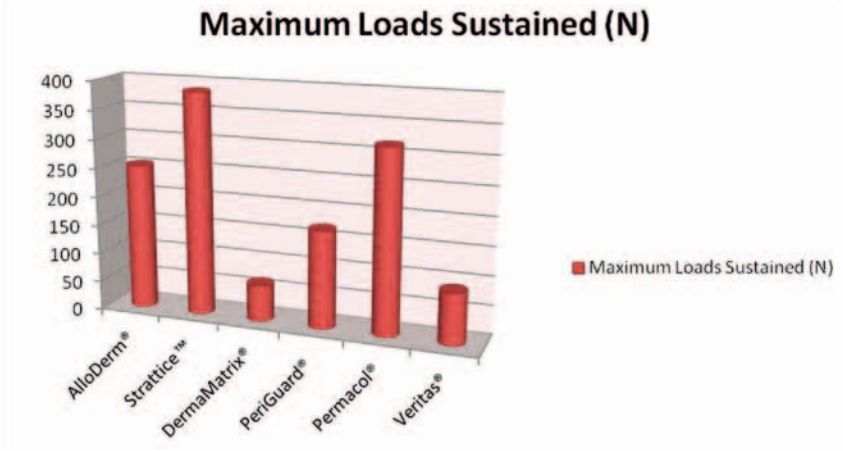

Figure 1. A comparison of maximum loads sustained by different types of biologic mesh

Spear and colleagues advocate a thick piece of 4 x 12 cm. For arc length greater than 18 cm, they advocate a thick piece of 4 x 16 cm.

ADM Preparation

In terms of preparation of the ADM, the matrix is hydrated in saline as instructed by the manufacturer. Different hydration times are required depending on the product; AlloDerm® requires at least 30 minutes of rehydration before its application[3] but DermaMatrix® can be rehydrated in 3 minutes.[5] It is important to examine the ADMs for dermal elements, such as hair, and to remove them if present. Sterile technique must be used when handling ADMs. The dermal matrix is handled by only 1 surgeon, after either changing or cleansing the gloves. The product is taken from the saline bath where it is

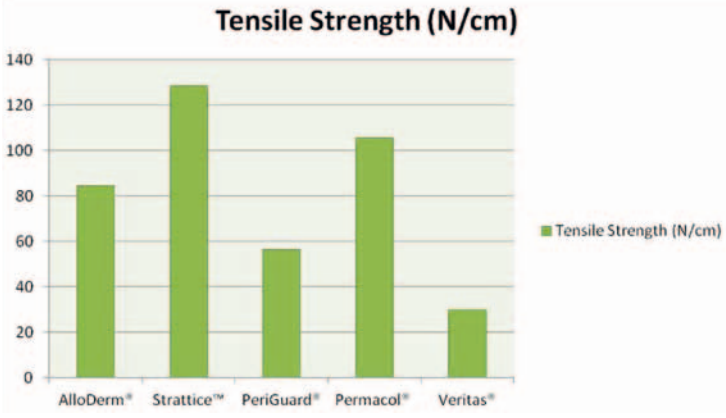

Figure 2. A comparison of the tensile strength of different types of biologic mesh

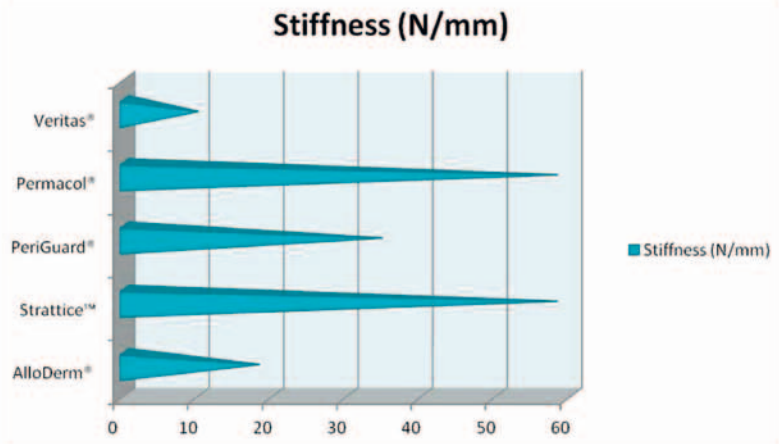

Figure 3. A comparison of the stiffness of different types of biologic mesh

soaking and placed directly in the wound so that it does not contact the operative field or the patient's skin.[13]

ADM Placement

The ADM has a distinct polarity, and this must be identified intraoperatively. The dermal side has a smooth, shiny appearance that seems to absorb blood that it contacts. This side should be placed in contact with the underside of the mastectomy flap because it has been shown to be more likely to revascularize.[14] In addition, the dermal side is potentially more seroma forming, and is thus kept away from the implant. The basement membrane side is dull and rough in appearance, and seems to repel blood that it contacts. This side is placed down so that it contacts the implant.[13] It is important to avoid layering the ADM material because it is an avascular foreign body and this can increase the risk of infection and seroma formation.[1] For postoperative care, soft compression and a surgical bra postoperatively may be helpful in minimizing dead space.[13] Patients should remain on antibiotics to cover gram-positive skin flora for a 7-day period.

USES OF ADMs IN BREAST RECONSTRUCTION

Between one-half and two-thirds of women undergoing postmastectomy breast reconstruction choose alloplastic reconstruction, which makes prosthesis-based reconstruction the most common method of reconstruction in these patients.[15] After mastectomy, an implant[16] or a tissue expander is placed underneath the pectoralis major muscle, and the muscle covers the superior and medial poles of the prosthesis. The exposed inferior and lateral poles can be covered with subcutaneous tissue or by elevating ser-

ratus anterior or pectoralis minor muscles[17]; however, incomplete or inadequate coverage of the prosthesis can result in a higher risk of visible rippling, implant visibility or exposure, and contour irregularities.[7,11,14,18] Some patients have a deficiency of the soft tissue envelope because of either an atrophic pectoralis major, its native insertion site on the chest wall, or because of intraoperative trauma or resection during the course of the mastectomy.[19]

ADMs are a solution to this problem because they can be used either to create the implant pocket in single-stage reconstruction or to maintain the inferolateral portion of the tissue expander pocket in 2-stage reconstruction (Fig. 4).[20] After the mastectomy has been performed, a subpectoral pocket is developed. The boundaries of this pocket are the lateral border of the pectoralis major muscle to the second rib superiorly, the sternum medially, and the level of the contralateral inframammary fold inferiorly.[21] The inferior attachment of the pectoralis major muscle is dissected from the chest wall.[22]

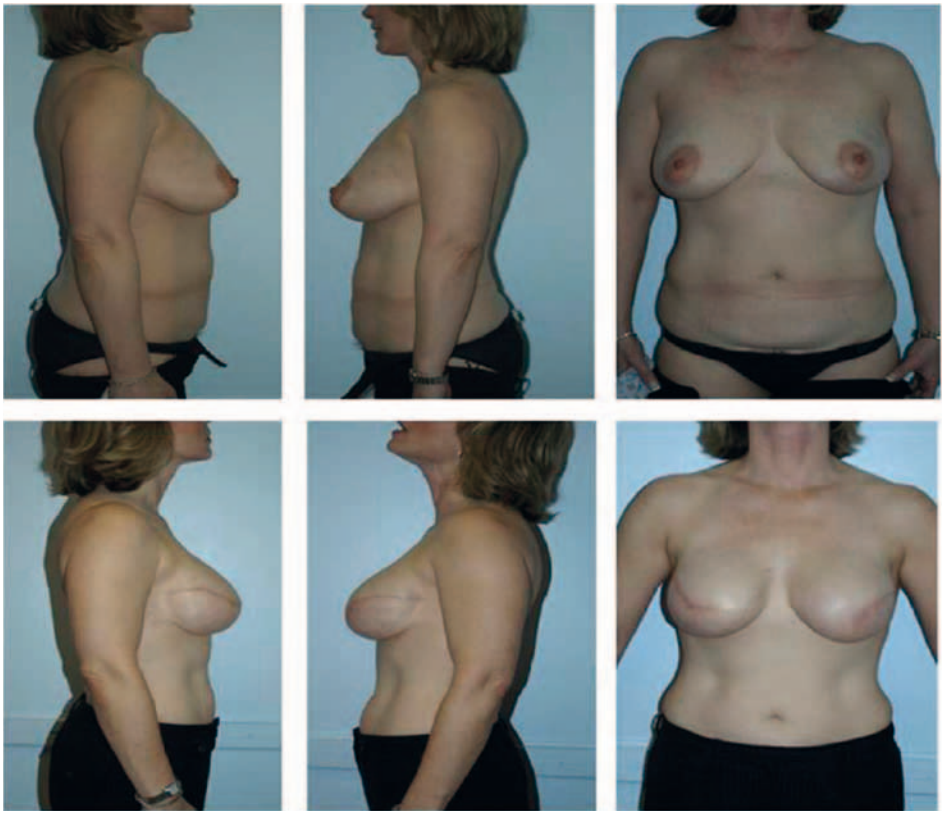

Figure 4. Uses of ADMs for breast reconstruction after mastectomy (preoperative and postoperative)

Box 1. Technique Tips for using ADM in breast reconstruction

- An ADM sling[11] or hammock[23] can be used to anchor the lower pole of the pectoralis major muscle by attaching it to the lower pole of the released pectoralis major superiorly, the serratus anterior flap laterally, and the chest wall inferomedially.
- After irrigating the pocket with bacitracin in sterile saline, the tissue expander or implant is then placed in the subpectoral pocket, covering the superior and medial poles of the prosthesis.
- The ADM is placed with the dermal side facing the mastectomy skin flaps and first secured by suturing it to the chest wall.
- The free edge of the pectoralis is then sutured to the ADM with a running suture.
- Two closed-suction drains are placed below the mastectomy skin flaps; 1 drain is placed in the axilla because this area tends to drain moderate amounts in most cases[13] and the second drain runs along the inframammary fold.
- Mastectomy skin flaps are trimmed to yield bleeding margins for closure in 2 layers and dressed.[22]
- Tension-free closure of the mastectomy flaps is crucial.
- Ensuring that the flaps are as thick as possible is also important.
- It is preferable to orient the incision on top of the muscle as opposed to directly over the ADM.
- Because textured implants can cause noticeable rippling,[24] these implants are to be avoided.

Various techniques have been described to attach the ADM to local tissue. See Box 1 for some technique tips for using ADMs in breast reconstruction. Benefits of using ADMs in postmastectomy reconstruction include:

- Providing soft tissue coverage over the prosthesis, especially when the skin flaps are deficient
- Allowing for control of the inframammary fold, permitting the creation of a larger implant pocket
- Decreasing the rate of capsular contracture.

These factors can potentially improve aesthetic outcomes.[10,20,21,25] ADMs can also augment the perfusion of a vulnerable skin envelope by offloading the mechanical stress caused by the implant weight on the skin envelope and the skin closure.[26] Using ADMs can reduce the time needed for the entire reconstructive process by reducing the time or need for tissue expansion; in turn, this concept can expedite the start of adjuvant chemotherapy and radiation if needed. By limiting the amount of dissection during implant or expander placement, using ADMs may decrease postoperative pain.[25]

USES OF ADMs IN AESTHETIC BREAST SURGERY

Compared with the literature on postmastectomy reconstruction, there are fewer data on the uses of ADMs in cosmetic breast surgery. Despite this paucity of literature, there are unique challenges to be addressed in revision surgery of the augmented breast:

- The patients are frequently thin, have a lack of local breast tissue, and the breast envelope is often scarred or encapsulated.
- Patients tend to have high expectations and are disappointed in the need for revision surgery.
- Addressing 1 problem often leads to another; for example, plicating the capsule in a thin breast envelope can lead to skin dimpling and surface irregularities.
- Capsular excision or rearranging local tissue to cover surface irregularities can lead to an undesired change in the implant location.[1]

Two categories of problems to correct with revision aesthetic breast surgery are surface irregularities and implant malposition.

USE OF ADMs TO CORRECT SURFACE IRREGULARITIES

Postoperative surface irregularities can include rippling or wrinkling, bulging, or capsular contracture. Rippling is often an inherent feature of saline implants and is more obvious when the implant is covered with a thin soft tissue envelope. In addition, tissue expansion often results in some degree of thinning of the overlying tissues, even with submuscular placement.[27]

- In patients who present with a focal area of tissue thinning with rippling or knuckling, a single layer of ADM can be placed between the implant and the overlying soft tissue for an improvement in contour (Fig. 5).
- A periareolar incision provides excellent exposure and limits the amount of additional incisions. Thick or ultrathick sheets are most frequently used.
- The dermal side of the graft is placed in contact with the capsule in an onlay fashion and secured with absorbable sutures at the corners; placement of the grafts in an onlay fashion minimizes the extent of dissection required.[24] In this setting, the ADM is used as a tissue-thickener for camouflaging implant visibility.
- In addition, the ADM can be laid directly on the capsule if no capsulotomy or capsulectomy is needed. A parachuting technique[1,12] often aids in placing the graft in the correct location.

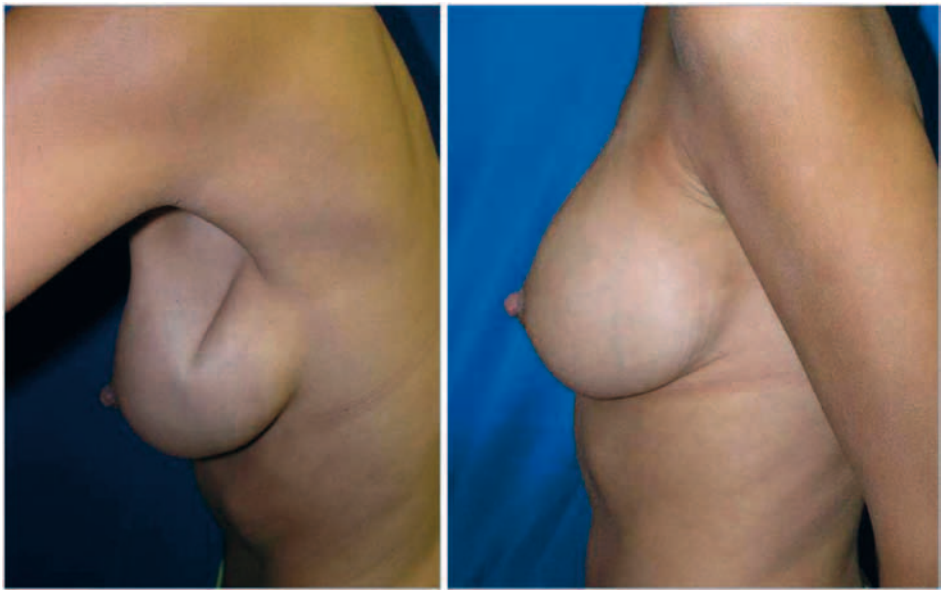

Figure 5. Uses of ADMs for secondary deformities in breast reconstruction (preoperative and post-operative)

ADMs versus Fat Grafting

Although autologous fat injections are gaining popularity as a method of correcting contour deformities, compared with ADMs they have several disadvantages:

- Fat grafting has a high resorption rate
- Fat grafting requires a donor site
- Fat grafting can result in complications such as calcifications, cyst formation, infection, and induration.[28]

In addition, long-term data of fat grafting to the native breast are lacking. There are early reports that are now evaluating the impact of breast cancer surveillance with fat grafting.

USE OF ADMs TO CORRECT IMPLANT MALPOSITION

Implant malposition can occur as a result of capsular contracture or with malposition of the inframammary fold with or without bottoming out of the lower pole.[29] A variety of methods have been used to correct capsular contracture, including using a combination of capsulorrhaphy and marionette sutures.[9,29] Another method involves changing the implant pocket from a subglandular to dual-plane position with the addition of an ADM

graft; the graft is fixed to the pectoralis major muscle, to the perichondrium of the rib cage, and to the serratus anterior muscle flap.[29,30]

Symmastia can result from excessive release of the medial origins of the pectoralis major muscles, resulting in medial displacement of the implants. It occurs when implants are placed too close to the midline or when an iatrogenic communication occurs. One management option involves performing a medial capsulorrhaphy and then suturing the soft tissue to the sternum. The posterior capsule can be dissected from the rib cage and rolled up if subpectoral implants were used. These procedures have been met with variable degrees of success and are prone to failure because of the difficulty of separating the capsular pockets.[31] To correct implant malposition in symmastia, the ADM may be placed over areas of capsulorrhaphy and secured to the chest wall and capsule: the short edge of the AlloDerm® is sutured directly to the displaced fold and then redraped over the capsule of the breast.[32] An ADM can also be used as a medial, C-shaped sling that is created between the 2 implants.[31] A graft of AlloDerm® is sutured to the rib periosteum inferiorly and draped in a C-shaped fashion superiorly to the anterior capsule.[31]

ADMs are secured with 3.0 Vicryl (Ethicon Inc, Somerville, NJ, USA) or Monocryl (Ethicon Inc, Somerville, NJ, USA). Only a few tacking sutures are needed in most cases; however, in the correction of symmastia, more sutures may be required to secure the ADM and avoid permanent suture dimpling of the skin. Tension should be avoided because surface dimples and bands can occur.

USE OF ADMs IN REDUCTION MAMMAPLASTY

A common postoperative finding in inferior pedicle breast reduction is an upward rotation of the nipple-areola complex and descent of the breast parenchyma, otherwise called star-gazing or bottoming out. This finding occurs because of recurrent skin laxity. In attempting to address this issue, Brown and colleagues[2] devised an approach in which AlloDerm® could be used as a sling to support the inferior pedicle and hence prevent this unwanted breast deformity. These investigators describe using an ADM as an "internal brassiere" for support of the pedicle. To help gain a better cosmetic outcome in terms of nipple-areola position and breast projection, the pedicle superior to the ADM was plicated in a horizontal fashion in addition to suturing AlloDerm® to the chest wall as a sling. In the postoperative period, no nipple loss was noted, and 2 patients developed complications; 1 had partial flap necrosis and the other had cellulitis. No bottoming out was seen in any of the patients.

COMPLICATIONS WITH ADMs

The use of ADMs does not seem to significantly increase the risk of postoperative complications[33] but is not without risk.

Microbial Contamination

AlloDerm® is the most widely used ADM product, and when tested to confirm the absence of microbial contamination, it is not terminally sterile.[17] Because AlloDerm® comes from a human donor, there is a risk of transmitting communicable diseases such as viral hepatitis and human immunodeficiency virus (although there have been no such reported cases). The product meets the standards of tissue banking and donor screening established by the American Association of Tissue Banking and the US Food and Drug Administration.

Infection

In the last few years, studies have been published that compare the complication rates of postmastectomy reconstruction using prostheses with or without AlloDerm®. Only 1 of these studies[34] reported a statistically significant increase in infection and 1 study reported an increased seroma rate in the AlloDerm® group.[17] As ADM recellularizes, revascularizes, and becomes incorporated into the host tissue, it has the potential to overcome infection. However, it takes time for the ADM to recellularize and revascularize, providing a window in which infection can occur.[35] In an animal model, Eppley[36] observed that rolled or multilayered ADM revascularized more slowly or, in some areas, not at all when compared with a single flat sheet of ADM. This finding indicates that potential rolling or bunching of ADM can lead to poor vascularization, with an increased risk of infection.[36] When the ADM comes in contact with the nipple-areola complex, it may be exposed to contamination from Staphylococcus species, which can be abundant in the distal mammary ducts. Therefore, it is best to avoid ADM placement in this region.[1]

Radiation Tolerance

There is ongoing debate about the ability of ADMs to tolerate exposure to radiation. Studies that have compared complications in irradiated and nonirradiated breasts have indicated a higher rate of complications in irradiated versus nonirradiated breasts.

- Spear and colleagues[12] observed an 11- fold higher rate of total complications in irradiated versus nonirradiated breasts (45.5% vs 4.3%) after ADM-assisted tissue expander/implant reconstruction.
- Salzberg and colleagues[21] noted a 4-fold higher rate of complications in irradiated versus nonirradiated breasts.
- Nahabedian[8] reported a higher incidence of infection (8.3% vs 3.9%), incisional

dehiscence (13.0% vs 1.3%), and seroma (13.0% vs 2.6%) in ADM-assisted implant-based irradiated versus nonirradiated breasts.

However, overall, the risk of infection did not vary with or without AlloDerm®. Rawlani and colleagues[37] found that the overall complication rate in irradiated breasts was 30.8% (compared with 13.7% in nonirradiated breasts, P=.0749). Despite this higher rate of complications, ADM-assisted tissue expander reconstruction seems to resist radiation effects more than plain tissue expander reconstructions,[12,37,38] or at least have a similar rate of complications.[19]

Diagnostic Dilemmas

There has been a report of a potential diagnostic dilemma, with ADM mimicking a new breast mass in a patient who had had a previous mastectomy.[39] ADMs can undergo reactive inflammatory changes and be confused as masses within the breast, especially with the minimal subcutaneous fat in this area and with thin mastectomy skin flaps. Patients should be informed that ADM use in breast surgery can lead to induration, palpable scarring, and the potential need for further diagnostic studies. With the sophisticated imaging available, it seems that the appearance of ADMs is different from and does not mask recurrences on either a mammogram or a magnetic resonance imaging scan of the breast.[40]

OUTCOMES WITH ADMs

In a retrospective study by Hartzell and colleagues,[1] a single surgeon's experience using ADMs after breast augmentation from 2005 to 2009 was analyzed:

- Twenty-three patients (38 breasts) were included
- Implant malposition was reported in 22 breasts
- Surface irregularities were reported in 28 breasts
- Malposition and surface regularities combined appeared in 12 patients.

After their revision procedures using an ADM

- Twenty patients showed improvement in the aesthetic appearance of their breasts
- Three patients required an additional procedure
- One patient developed an infection and the ADM was removed.

In 78 consecutive patients who underwent revisionary breast augmentation/mastopexies with ADM

- All patients had their implant-related complications successfully corrected by a site change and the use of an ADM.[38]

- No capsular contractures were reported.
- There were 2 complications: implant malposition and hematoma formation.

These data suggest that, with the use of ADMs, the capsular contracture rate after secondary augmentation and augmentation mastopexy procedures may be reduced.[38] Basu and colleagues[41] found that when compared with native breast capsules, ADM had lower levels of inflammatory parameters:

- Capsule fibrosis
- Vessel proliferation
- Granulation tissue formation
- Fibroblast cellularity
- Chronic inflammatory changes
- Foreign body giant cell inflammatory reaction.

AlloDerm® decreases radiation-related inflammation and delays or diminishes pseudoepithelium formation and thus may slow progression of capsular formation, fibrosis, and contraction.[42] These findings suggest that ADM may show certain properties that may reduce formation of a capsule and therefore provide an alternative to total submuscular implant placement in breast reconstruction procedures.[41,43]

Costs of ADMs

One of the drawbacks to the use of ADMs is their cost. A 6-cm x 16-cm thick AlloDerm® sheet cost $3463 (USD) per sheet as of January 2010 (Jansen; economic analysis).[44] However, direct to-implant reconstruction with AlloDerm® was found to be less expensive than 2-stage non-AlloDerm® reconstruction.[44] Strattice™ is less expensive than AlloDerm®. In addition, Strattice™ is available in specific sizes and shapes to reduce cost and minimize waste.[8]

SUMMARY

ADMs have many applications in breast surgery. In addition to postmastectomy breast reconstruction, ADMs may be safe to use with a limited number of complications in the setting of contour deformities after cosmetic breast operations. The 1 drawback is that they are expensive.[44] The use of ADMs is a safe alternative for the correction of breast deformities after reconstructive and aesthetic surgery. Appropriate patient selection, operative technique, and postoperative management are crucial in successful application of ADMs to breast surgery.

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Chapter 3

Acellular Dermal Matrices in Breast Surgery: A Comprehensive Review

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Ann Plast Surg 2013: 70(6):732-8

ABSTRACT

Introduction

Acellular dermal matrices (ADMs) have become increasingly popular for use in plastic surgery. There has been an increase in the number of products that have paralleled their usage in various clinical settings and specifically breast surgery.

Methods

A direct comparison of the most common ADMs used in breast surgery was performed including physical characteristics, level of sterility, maximum load sustained (N), stiffness (N/mm), and tensile strength (N/cm). A comprehensive review of the literature was also performed, detailing known results and complications.

Results

The direct comparison of most common ADMs is detailed along with a review of 26 series of breast reconstruction manuscripts involving the usage of ADMs. Specifically, Strattice and Permacol had the highest values of maximum loads sustained, stiffness, and tensile strength.

Conclusions

ADMs have a role in breast surgery that continues to be defined. Future long-term follow-up remains crucial to the identification of the optimal biologic mesh.

INTRODUCTION

Within plastic and reconstructive surgery, the increasing role of acellular dermal matrices (ADMs) is currently being defined for various settings. ADMs became available in the early to mid 1990's and have frequently been used in breast and abdominal wall reconstruction.[1-6] Since their introduction, the list of indications for ADMs has grown to include burn reconstruction,[7-10] eyelid reconstruction,[11-13] hand surgery,[14,15] lower extremity coverage[16] and nasal reconstruction.[17,18] The various types of ADMs differ in their intraoperative preparation, method of storage and cost.[19]

Increased interest in utilizing ADMs for breast surgery has paralleled the introduction of new products. This review quantitatively compares the physical characteristics of the most commonly used ADMs within breast surgery and a review of the literature.

COMMON TYPES OF ADMs

Table 1 outlines commonly used ADMs within breast surgery and their physical characteristics (e.g. origin, method of proprietary processing, level of sterility). Figure 1 details the maximum loads (N) sustained by each product, with those of Strattice™ and Permacol® being the highest. Figure 2 outlines the stiffness (N/mm) of each product, with Strattice™ and Permacol® having the highest stiffness values. Figure 3 outlines a comparison of tensile strengths (N/cm).

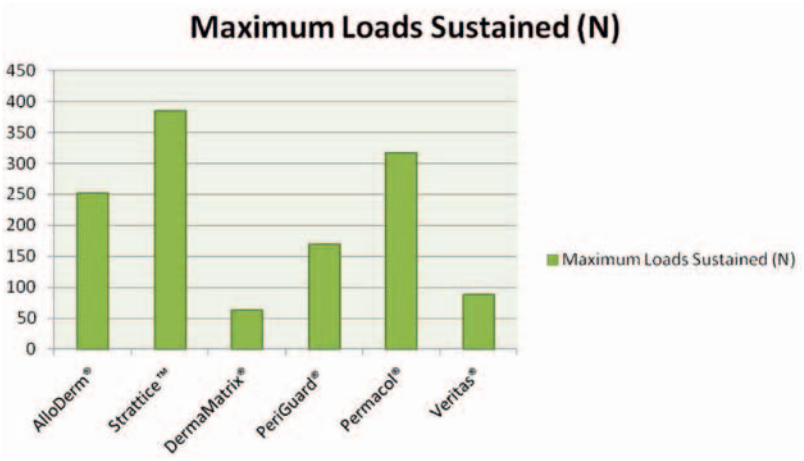

Figure 1: A comparison of the maximum loads sustained by different types of biologic mesh

Table 1: Characteristics of Dermal Matrices

Biologic	Source	Processing	Sterile	Indications	Components	Advantages	Other
AlloDerm®	Cadaveric human skin	Processed to remove cells and antigenic components	No	Breast, pelvic and head and neck reconstruction; abdominal hernia repair	Collagen, hyaluronic acid, elastin, fibronectin, proteoglycans, vascular channels	Tolerates irradiation One of original ADMs; well documented in literature	Non cross-linked; requires rehydration time
Strattice™	Porcine ADM	Proprietary process that removes cells with antigenic response	Yes	Breast reconstruction, abdominal wall repair	Undisclosed	Permits white cell migration, cell repopulation and revascularization Excellent biomechanical strength Can be used in local treatment in the presence of infection Minimizes adhesions to implant	Non cross-linked
DermaMatrix®	Human skin	Sodium chloride used to remove epidermis and dermis	Yes	Nasal, lower eyelid, and breast reconstruction; cleft palate repair, abdominal wall repair	Collagen, elastin	Rapid rehydration Bacterial inactivation Does not need to be refrigerated for storage	Non cross-linked
SurgiMend™	Fetal bovine dermal collagen	Process designed to remove cellular components and potentially infectious agents from raw material,	Yes	Muscle flap reinforcement; hernia repair including abdominal, inguinal, diaphragmatic, femoral, scrotal, umbilical, and incisional hernia repair	Type I and Type III collagen	Easy to handle and suture, rehydrates in minutes Unique shapes & sizes Fenestrated to assist in fluid drainage	Non cross-linked
Veritas®	Bovine pericardium	Proprietary process that caps free amine groups	Yes	Abdominal hernia repair	Collagen	Excellent strength and suture retention Similar to autologous tissue Reduces tissue attachment Remodels for rapid integration into surrounding tissues	Non cross-linked
FlexHD®	Human allograft skin		No	Abdominal hernia repair, breast reconstruction, chest wall reconstruction	Collagen	Prehydrated Low operative costs Minimal elasticity	Non cross-linked

AlloDerm®

AlloDerm® Regenerative Tissue Matrix (LifeCell Corp., Branchburg, NJ) is produced by removing the epidermis and cells from human cadaveric skin; the resultant acellular matrix has reduced in antigenicity.[20,21] As AlloDerm® undergoes cell repopulation and revascularization, it is described to incorporate into the host tissue in 4 stages: 1) damaged tissue is targeted by circulating stem cells, 2) stem cells are deposited, 3) stem cells differentiate, and 4) a new matrix is formed from the differentiated cells allowing for tissue regeneration.[22] AlloDerm® has been described to be partially integrated into the host tissue within 7 days of implantation and increases over a period from 2 weeks to months.[23] AlloDerm® does not have terminal sterility.[24] Within breast surgery, AlloDerm® has been described for post-mastectomy breast reconstruction and aesthetic breast procedures.[25]

Strattice™

Strattice™ Reconstructive Tissue Matrix (LifeCell Corp., Branchburg, NJ) is a sheet of sterile tissue derived from porcine dermis denuded of antigenic cells.[26] This proprietary process causes a marked reduction in 1, 3 alpha galactose epitope, a major component of the xenogenic rejection response. This product behaves as a scaffold repopulated and revascularized by the host. Strattice™ supports tissue regeneration and it is used in implant-based breast reconstruction.[26,27] Strattice™ does not require rehydration and is ready for use as an onlay or underlay following a 2 minute soak.[28] During uniaxial testing of tensile strength in Yucatan minipigs, Strattice™ demonstrated 128.4N/cm compared to an AlloDerm® score of 84.3 N/cm; the maximum loads sustained were 385.1N and 253.0N for Strattice™ and AlloDerm® respectively (Figure 1). The stiffness of Strattice™ was 58.3 N/mm whereas that of AlloDerm® was 18.2 N/mm (Figure 2).[29]

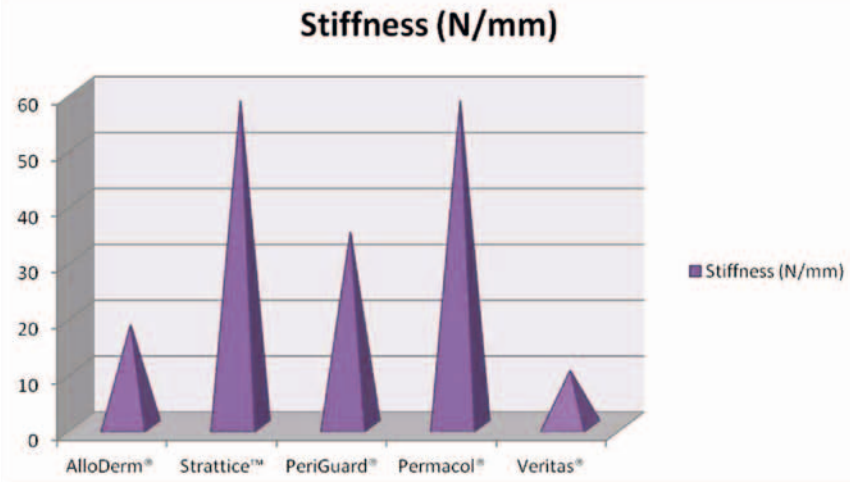

Figure 2: A comparison of the stiffness of different types of biologic mesh

Strattice™ is thicker and stronger than AlloDerm®. Unlike AlloDerm®, Strattice™ is a terminally sterile product that is available in larger pieces (up to 20-25 cm), potentially minimizing wound dehiscence.[30,31]

DermaMatrix®

DermaMatrix® (MTF/Synthes CMF, West Chester, PA) is human skin that undergoes removal of the epidermis and dermis in a process utilizing sodium chloride solution. The product is sterile while preserving the original dermal collagen matrix. Once DermaMatrix® is transferred to the patient, the collagen matrix is infiltrated by host cells promoting neovasularization and fibroblast deposition. DermaMatrix® has advantages of rapid rehydration, bacterial inactivation and it does not need refrigeration for storage.[32-34] Using biomechanical testing, authors found this product to resist an average maximum load of 63.2N before yielding and to exhibit a tensile strength of 14.6N/mm^2 (Figure 3). The ability of DermaMatrix® to oppose deformation was 8.8 MPa compared to other conventional dermal matrices at 5.8 MPa.[32]

Becker et al.[19] compared the use of AlloDerm® and DermaMatrix® in 30 patients (50 breasts) who had immediate expander-based breast reconstruction. The authors found that both dermal matrices were well-incorporated and histological examination showed neovascularization. There was an overall 4% complication rate attributed to wound infection and seroma formation; no significant differences were observed in the complication profiles of either group.

When the biocompatibility profiles of cross-linked versus non cross-linked biologic meshes was compared, strength and integrity did not vary significantly.[29,35] Using his-

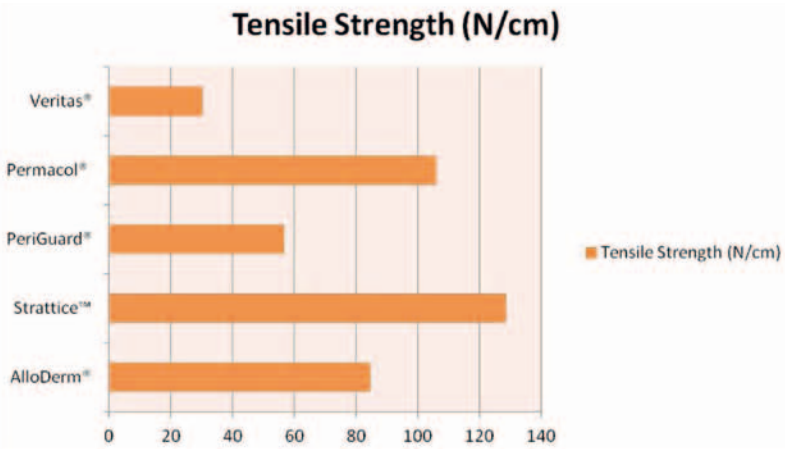

Figure 3: A comparison of the tensile strength of different types of biologic mesh

tologic analysis, Jenkins et al.[36] found there was greater tissue incorporation with fenestrated cross-linked matrices (CollaMend™ FM, CR Bard, Inc–Davol, Inc) than non fenestrated cross-linked matrices (CollaMend™, CR Bard, Inc–Davol, Inc); adhesion scores were similar with both biologic meshes.

SurgiMend™

SurgiMend™ (TEI Biosciences Inc., Boston, MA) is fetal bovine dermal collagen that consists of Type I and Type III collagen.[37] It is non-crosslinked, hydrates in 60 seconds at room temperature, and exhibits a tensile strength of 29MPa.[37] Hwang et al.[38] found on histological examination a decreased inflammatory response using SurgiMend™ compared to lyophilized bovine pericardium, irradiated bovine tendon, and autologous cartilage transplanted subcutaneously into rats. Craft and May[39] found SurgiMend™ to potentially augment the native dermis in staged nipple reconstruction, preserve the integrity of the capsule, and provide adequate vascularization for improved nipple projection and bulk.

Veritas®

Veritas® (Synovis Life Technologies Inc., St. Paul, MN) Collagen Matrix is derived from bovine pericardium. It is manufactured by a proprietary chemical process that caps free amine groups resulting in immunological stability of tissues.[40] Veritas® has the ability to remodel by allowing infiltration of host tissue cells and supporting the rapid formation of new collagen and blood vessels. It is reported to be completely integrated within the host tissue in as little as 1 month.[40] Remodeling does not occur in the presence of synthetic implants because of the formation of a capsule of connective tissue that insulates the host tissue from the implant.[41] It does not require rehydration before use and is thin and strong; reported tensile strength per unit time in Yucatan minipigs during uniaxial testing was 29.9N/cm (time zero), with a maximum load sustained at 89.6N and a stiffness of 10.0 N/mm.[29]

FlexHD®

FlexHD® (MTF/Ethicon, Inc., Somerville, NJ) acellular hydrated dermis is derived from cadaveric human allograft skin. The skin initially undergoes an aseptic process in which both the epidermis and the dermis are removed while maintaining the extracellular matrix.[42] It is delivered prehydrated and does not require refrigeration; furthermore, it exhibits resistance to stretch (tensile strength: 15.7 MPa) and biomechanical strength resulting in a tissue graft that is ready for immediate use, potentially reducing operation room time.[42-45] As a result of its physical properties FlexHD® has been described in breast reconstruction as well as hernia repair and chest wall reconstruction.[46]

Studies by Orenstein et al.[47,48] showed that in vitro, monocyte and macrophage activation was greater in FlexHD® than AlloDerm® and that FlexHD® induced significantly more IL-1 beta. This finding potentially indicates that there is more inflammation associated with the use of FlexHD®. Ngo et al.[45] compared the use of FlexHD® to Strattice™ and found that there were no significant differences in inflammation, neovascularization, adhesion and fibrous tissue formation although tissue ingrowth was significantly faster with FlexHD®. Eberli et al.[49] found FlexHD® maintained biomechanical strength with histological examination revealing good tissue formation and integration similar to AlloDerm®.

The use of FlexHD® in expander-implant breast reconstruction was evaluated by Rawlani et al.[50] who studied 121 breast reconstructions with ADMs; complications occurred in 20 breasts: 2 seromas, 8 partial mastectomy flap necroses, and 9 soft-tissue infections. Explantation was required in 11 of the cases. Patients exposed to radiation prior to having breast reconstruction had a greater rate of complications compared with those not having radiation - 30.8% as opposed to 13.7% respectively.

USES OF ADMs FOR BREAST RECONSTRUCTION AFTER MASTECTOMY

ADMs have gained popularity in implant-based breast reconstruction with reasonable aesthetic results and low complication rates[51,52] (Table 2). ADMs have been used to reconstitute the inframammary fold, to serve as a pectoralis major extension, and to act as a soft tissue "thickener" for contour/surface irregularities. Authors have stated that these characteristics may reduce muscle dysfunction and pain.[19,53] In addition, ADMs may be used for the inferolateral pole to maintain the implant pocket.[19,52-55]

Expander/implant breast reconstruction has specific challenges. Any tension caused by malposition of the implant may result in compromise of the skin envelope; ambiguous perfusion of the skin envelope may cause wound complications, and visible contour irregularities and "windowshading" of the pectoralis major muscle may result when the muscle is released. Thin capsules and periprosthetic atrophy may occur in late cases, and rippling of the medial and superior poles of the muscle may occur as a result of thinning and attenuation of the muscle layer during tissue expansion.

The use of ADMs may be useful in immediate expander breast reconstruction.[56] The use of an acellular dermal sling has been described in a series of 58 breasts (43 patients) in an attempt to provide inferolateral support during expansion. The complication rate was relatively low and the cosmetic outcome was deemed satisfactory.[57] In a study by

Table 2: Published Series of Breast Reconstruction with ADMs

Study	Number of Patients	Number of Reconstructions
Rawlani et al.[50]	–	121
Basu et al.[77]	20	–
Salzberg[58]	49	76
Breuing and Warren[59]	10	20
Gamboa-Bobadilla[60]	11	13
Bindingnavele et al.[51]	41	65
Breuing and Colwell[61]	43	67
Zienowicz and Karacaoglu[52]	24	30
Perminger et al.[62]	90	45
Spear et al.[57]	43	58
Topol et al.[65]	23	35
Losken[56]	22	31
Chun et al.[64]	283	415 (269 with ADMs)
Stevens et al.[78]	25	13
Liu et al.[53]	–	470 (266 with ADMs)
Salzberg et al.[63]	260	466
Hartzell et al.[25]	23	38
Spear et al.[67]	52	77
Duncan[68]	34	–
Baxter[69]	10	–
Brown et al.[70]	27	–
Maxwell and Gabriel[71]	78	78
Nahabedian[72]	361	476 (100 with ADMs)
Nguyen et al.[75]	–	321 (75 with ADMs)
Lanier et al.[76]	–	127 (75 with ADMs)

Losken[56] the morbidity and safety of using NeoForm®, an ADM in tissue expander reconstruction, was evaluated. Thirty-one breasts (22 patients) were included and no cases of seroma, infection, foreign body reaction or rejection were reported.

ADMs permit immediate implant placement after mastectomy by expanding the submuscular pocket volume.[52,53,58,59] Gamboa-Bobadilla[60] used saline implants covered with human ADM in 13 breast reconstructions (11 patients) reported to have poor pectoralis major muscle coverage. Twelve of 13 patients had successful breast reconstructions that were stable with more soft tissue padding, reduced rippling and implant visibility. In an attempt to eliminate the need for tissue expansion, Breuing and Warren[59] created subpectoral-sub-AlloDerm® pockets to completely enclose the breast implant. An AlloDerm® sling was used to anchor the lower pole of the pectoralis major muscle.

Postoperative results demonstrated improved lower-pole projection, good symmetry, and a volume match compared with preoperative size. In a study of 30 immediate implant-breast reconstructions with human ADM over an 8 month mean follow up period, Zienowicz and Karacaoglu[52] placed AlloDerm® at the lower pole of the released pectoralis major superiorly, the serratus anterior flap laterally and the chest wall inferomedially. The authors reported a 0% complication rate (no symmastia, bottoming-out deformity or rippling was reported).

Another breast reconstructive method is the use of an inferolateral AlloDerm® hammock, which attaches to the serratus anterior laterally and rectus abdominis fascia inferiorly to create an implant pocket for control of implant position. This technique was used in 67 breast reconstructions by Breuing and Colwell.[61] No complications were reported over a 6 month to 3 year follow up period, and patients were satisfied with final outcomes.

In a retrospective cohort study, patients who received tissue expander/implant breast reconstruction with AlloDerm® were analyzed for complications and compared to those who underwent conventional tissue expander/implant breast reconstruction without the use of AlloDerm®; the mean rate of postoperative tissue expansion was the same in both groups, and there was no reported increase in the risk of postoperative complications.[62] Salzberg et al.[63] reviewed long-term complications of expander-based breast reconstruction associated with the use of human ADMs in 466 breasts (260 patients) in both prophylactic and oncologic settings. A 3.9% complication rate was reported and did not vary significantly between both groups of patients. In patients who were followed up for more than one year (354 breasts), no complications were reported.

There are recent emerging data that may demonstrate increased complications in certain instances.[53,64] Thus, patient selection and technical factors play roles in the perioperative healing process when using ADMs.[53,64]

Assessing the use of ADMs in reducing the incidence of deformities in immediate 1-stage breast reconstruction procedures following nipple sparing mastectomies, Topol et al.[65] reported findings in 23 patients; the authors observed that the use of a lower chest advancement flap and inframammary fold reconstruction improved outcomes when using ADMs.

One factor that may serve as a deterrent for the use of ADMs in breast reconstruction procedures is their high cost which ranges from $3,536 to $4,856 per breast.[25] In one instance, aesthetic outcomes improved cost as described by Salzberg,[58] where Allo-

Derm® was used in 49 patients (76 breasts) undergoing immediate reconstruction. Using Alloderm®, authors reported outcomes as being favorable by both the physician and patients; they supported this option as a less costly alternative to transverse rectus abdominis myocutaneous flap surgery and expander/implant-based reconstruction following mastectomy. Jansen and Macadam[66] compared baseline and expected costs for direct-to-AlloDerm® and 2-stage non-AlloDerm® reconstruction. They found that using a 6x16-cm AlloDerm® sheet exhibited lower cost than 2-stage non-AlloDerm® reconstruction in both the baseline ($10,240; direct-to-AlloDerm® reconstruction, $10,584; 2-stage non-AlloDerm® reconstruction) and the expected costs ($10,734; direct-to-AlloDerm® reconstruction, $11,251; 2-stage non-AlloDerm® reconstruction). The expected cost decreased to $9673 when using a 6x12-cm AlloDerm® sheet and increased to $11,784 when direct-to-implant operative time went from 2 to 2.5 hours.

ADMs FOR SECONDARY DEFORMITIES IN BREAST RECONSTRUCTION SURGERY

Due to the reported benefits of ADMs in breast reconstruction surgery, ADMs have also been applied to implant-associated breast deformities.[67] Spear et al.[67] reviewed 52 patients who had ADMs with 77 breast prostheses. The authors established indications for use of dermal matrix: deficiency of skin flap, treatment of malposition, rippling, capsular contracture, and implant bottoming-out. Seventy-four of 77 were deemed successful with 3 failures: rippling in the first patient, infection in the second patient, and bottoming out in the third. In a series of 34 patients with breast implant-related problems Duncan[68] found a 2.9% capsular contracture rate with an 85% patient satisfaction rate and an improvement in palpable rippling. To address breast implant rippling, contracture, symmastia and bottoming out, Baxter[69] found stable outcomes using human ADM in 80% of revisions. Over a 52 month follow up period, Salzberg[58] reported a 0% rate of contracture. The same result was observed in studies conducted by Zienowciz and Karacaoglu[52] and Breuing and Colwell.[61]

Brown et al.[70] devised an approach in which AlloDerm® could be used as sling to support the inferior pedicle and prevent bottoming out following inferior pedicle breast reduction in 27 patients. The pedicle was plicated in addition to suturing AlloDerm® to the chest wall as a sling. In the postoperative period, no nipple loss was noted, and 2 patients developed complications; 1 had partial flap necrosis and the other had cellulitis. No bottoming out was seen in the follow up period (5 to 29 months; mean, 19 months) in any of the patients.

ADMs FOR BREAST AUGMENTATION

Patients with deformities following revision breast augmentation and augmentation mastopexy have a significantly higher rate of complications compared to primary procedures due to capsular contracture or stretching of breast tissue.[25,71] Maxwell and Gabriel[71] reviewed 78 patients undergoing breast augmentation and augmentation mastopexies with ADMs for 12 months. No capsular contractures were reported and there were 2 complications: implant malposition and hematoma formation. ADMs may reduce the capsular contracture rate following secondary augmentation and augmentation mastopexy.[71] Hartzell et al.[25] reviewed a single surgeons' experience using ADM following breast augmentation. Of 38 breasts, implant malposition was reported in 22 and surface irregularities in 28, with both appearing in 12 patients. Following their revision procedure with ADM, 20 patients showed improvement in the aesthetic appearance of their breasts, 3 patients required an additional procedure, and 1 patient was found to have incurred an infection for which the human ADM was removed.

COMPLICATIONS ASSOCIATED WITH THE USE OF ADMs IN BREAST SURGERY

Despite the fact that ADMs are treated under aseptic conditions,[53,63] there is a risk of infection. ADMs should be able to resist infection due to their ability to revascularize, recellularize and integrate within the host tissue following implantation.[72] However, time is required for such processes to happen, and a window period emerges where infection can occur.

Another concern with the use of ADMs is their ability to tolerate exposure to irradiation.[57,72,73] Nahabedian[72] found that irradiation had no effect on the rate of infection. Reported complications included seroma (5%), dehiscence (4%) and skin necrosis (3%) which can occur with standard reconstruction when exposed to radiotherapy. Spear et al.[57] found that acellular dermis did not protect the surgical site from radiotherapy effects; they observed a 71.4% rate of all complications in radiated breasts after the first-stage tissue expander placement with ADM.

Komorowska-Timek et al.[74] suggest that the use of AlloDerm® reduces the rate of radiation-related inflammation and pseudoepithelium formation in a study where 2 implants were placed in the backs of 41 rats that were irradiated. The authors observed increased inflammation at 12 weeks in the control group as compared with the AlloDerm® group.

Bindingnavele et al.[51] analyzed the charts of 41 patients (65 breasts) who underwent staged breast reconstruction with ADMs. There was a low complication rate, which con-

Table 3: Reported Complications during the follow-up period

Study	Number of Reconstructions	Complications
Adetayo et al.[1]	–	16% wound infection, 8% seroma formation, 6% breast implant failure
Rawlani et al.[50]	121	2 seromas, 8 partial mastectomy flap necroses, 9 soft-tissue infections.
Salzberg[58]	76	0% rate of contracture
Bindingnavele et al.[51]	65	3 seroma, 2 wound infection, 1 hematoma, 1 expander removal
Breuing and Colwell[61]	54	No complications
Zienowicz and Karacaoglu[52]	30	0% complication rate (no symmastia, bottoming-out deformity or rippling was reported)
Perminger et al.[62]	45	3 cellulitis, 3 seroma, 1 hematoma
Spear et al.[57]	58	12% rate after expander/acellular dermis placement, 2.2% after exchange to implants
Topol et al.[65]	35	2 infection, 1 implant exposure
Losken[56]	31	Skin necrosis in 1 patient
Chun et al.[64]	415 (269 with ADMs)	14.1% seroma, 8.9% infection
Liu et al.[53]	470 (266 with ADMs)	Overall complication rate 19.5%; 6.8% wound infection, 4.9% major infection requiring prosthesis removal
Salzberg et al.[63]	466	3.9% overall complication rate; implant loss 1.3%, skin breakdown/ necrosis 1.1%, hematoma 1.1%, human acellular dermal matrix exposure 0.6%, capsular contracture 0.4%, infection 0.2%. 4 times as high in irradiated breasts
Hartzell et al.[25]	38	22 implant malpositions, 28 surface irregularities, 1 infection
Spear et al.[67]	77	1 rippling, 1 infection, 1 bottoming
Duncan[68]	–	2.9% capsular contracture rate
Baxter[69]	–	Relapse of 1 symmastia repair and 1 case of bottoming out
Brown et al.[70]	–	1 partial flap necrosis, 1 cellulitis
Maxwell and Gabriel[71]	78	1 implant malposition, 1 hematoma formation
Nahabedian[72]	476 (100 with ADMs)	Seroma (5%), dehiscence (4%) and skin necrosis (3%)
Nguyen et al.[75]	321 (75 with ADMs)	8% rate of explantation due to infected fluid collections and extrusion
Lanier et al.[76]	127 (75 with ADMs)	Overall complication rate 46.2%; 28.9% infection, 25.0% reoperation, 19.2% expander explantation

sisted of seroma (3 patients), wound infection (2 patients), hematoma (1 patient), and expander removal (1 patient).

Nguyen et al.[75] found that there were no variations in the readmission rates for IV antibiotics in a series of 321 implant based reconstructions where 75 involved Alloderm® and 246 did not. However, the rate of explantation as a result of infected fluid collections was significantly lower in the control group in comparison to the AlloDerm® group.

In contrast, Chun et al.[64] reported an increase in the rate of infections and seroma in a series of 415 implant-based reconstructions where the use of ADMs contributed to a rise in the incidence of seroma by 4.24 times and of infection by 5.37 times. In another study by Lanier et al.,[76] the increase in rate of infection with use of ADMs was attributed to the weight of the breast being larger than 600g.

Liu et al.[53] used ADM and observed a higher rate of infection, but this was not statistically significant. Other factors that may explain this higher infection rate include individual risk factors such as higher body mass index, smoking and larger implant size.

In a meta-analysis of 53 articles, Adetayo et al.[1] identified the most common complication associated with the use of ADMs in breast and abdominal wall surgery as being wound infection (16%), followed by seroma formation (8%), and breast implant failure (6%). It was also stated that administration of chemotherapy increased the rate of seroma and exposure to radiation raised the incidence of cellulitis (Table 3).

CONCLUSIONS

ADMs are potentially useful not only in primary implant-based breast reconstruction but also in the treatment of secondary reconstruction and augmentation deformities. Despite the fact that there is literature that favors the use of ADMs, long-term follow up is still required to determine the longevity of these results.

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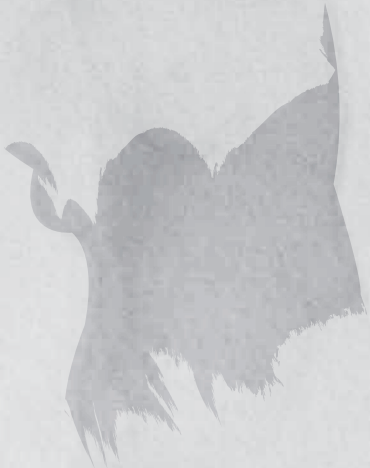
Chapter 4

Analysis of the NSQIP Database in 19,100 Patients Undergoing Implant Based Breast Reconstruction: Complication Rates with Acellular Dermal Matrix



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ABSTRACT

Background

The use of acellular dermal matrices (ADMs) has become increasingly popular in immediate and delayed tissue expander/ implant-based breast reconstruction. However, it is unclear whether their use is associated with increased postoperative complication rates. Using the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database, the authors assessed baseline differences in demographics and comorbidities with and without acellular dermal matrix and determined whether postoperative complication rates varied.

Methods

Using the national surgical database (2005-2011), tissue expander/implant-based breast reconstruction cases were extracted using *Current Procedural Terminology* (CPT) codes. Differences in preoperative demographics and comorbidities were assessed using chi-square and *t*-test analysis using SPSS. The authors analyzed variations in complication rates and determined whether demographics and comorbidities affected outcomes using multivariate logistical analysis. A post hoc power study was calculated.

Results

Of 19,100 cases, 3,301 involved acellular dermal matrix use. Overall complication rates were not statistically significant (acellular dermal matrix, 5.3%; non-acellular dermal matrix, 4.9%; $p = 0.396$). Several risk factors were statistically significant associated factors of complications. Higher body mass index was associated with wound complications in both cohorts. In the non-acellular dermal matrix group, body mass index, smoking, and diabetes were associated with major complications, and radiotherapy and steroid use with minor complications.

Conclusions

Acellular Dermal Matrix use does not appear to increase complication rates in tissue expander/implant-based breast reconstruction in this survey of a national surgical database. There was no significant difference in complication rates between the acellular dermal matrix and non-acellular dermal matrix groups.

INTRODUCTION

Breast cancer is the most common form of cancer in women.[1] In 2011, over 230,000 new cases of breast cancer were diagnosed.[2] The American Society of Plastic Surgeons reported 96,277 breast reconstruction procedures, of which 76,426 (79%) were immediate or delayed tissue expander/ implant-based breast reconstructions in 2011.[3] The use of acellular dermal matrices in tissue expander/ implant-based breast reconstructions has become popular because of its potential for improving aesthetic outcomes and decreasing postoperative pain in breast reconstruction patients.[4,5]

Acellular dermal matrix is bioprosthetic material manufactured from human cadaveric or animal sources.[6] It is reported as having lowered to imperceptible immunogenic levels while maintaining extracellular matrix structure and basement membrane complex.[7,8] Furthermore, they have been described as having circulating stem cells repopulate the area and differentiate into appropriate cell types, maintaining the structural integrity of the autologous tissue.[9] When acellular dermal matrix is not incorporated, complete coverage without resorting to additional muscle or fascial elevation can be an issue. Although complete muscle coverage decreases the risk of infection, this technique may prevent expansion of the inferior pole, thereby resulting in a high riding device placement.[10] Other techniques that solely use the mastectomy skin flap to cover the inferior third of the expander help alleviate such outcomes but may result in increasing rippling and inferior implant migration over time.[11] In addition, if the pectoralis muscle is missing or damaged, the implant comes into direct contact with the skin, potentially causing capsular contracture and subcutaneous scarring.[12] Such reconstructive findings can be improved with the use of acellular dermal matrices; by creating the inferolateral portion of the expander pocket a more natural appearing lower pole can be constructed. Acellular dermal matrices may reduce the mechanical force transferred to the skin flap in order to prevent implant displacement laterally and inferiorly, and their use may spare elevation of the muscle and fascia decreasing postoperative pain and damage to the muscle.[11,12]

It remains unclear whether acellular dermal matrix use increases postoperative complication rates. Previous studies have yielded either inconclusive or conflicting results.[12-16] There is no multi-institutional database literature available that correlates preoperative comorbidities and complications to their use in breast reconstruction. The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database provides a potential opportunity for this analysis. This database quantifies 30-day risk-adjusted surgical outcomes in over 200 sites (community hospitals and large academic centers) across the United States.[17,18] The aim of this study was to determine whether

postoperative complication rates varied between patients who received and those who did not receive acellular dermal matrix in tissue expander/ implant-based breast reconstructions procedures using a multi-institutional national database and to determine associated comorbidities.

PATIENTS AND METHODS

We performed a retrospective analysis using the ACS NSQIP data set collected between 2005 and 2011. Birkmeyer et al.[17] previously detailed the data collection methods. Each participating institution has an ACS trained Surgical Clinical Reviewer (SCR) who collects preoperative through 30-day postoperative data which is detailed in a HIPAA compliant online database. For each case encounter, the dataset contains numerous variables, including patient demographics, baseline comorbidities, preoperative risk factors, intraoperative variables, and 30-day postoperative data. To ensure full 30-day follow-up, patients complete a survey either by telephone or by a letter. For this database, patients are chosen randomly by a systemic sampling method and data collected are input based on standardized data definitions. A Surgeon Champion is also assigned who is responsible for proper program implementation and quality initiatives.[19,20]

To isolate patients pertinent to this study, we used *Current Procedural Terminology* (CPT) codes to search for all cases between 2005 and 2011 that included immediate or delayed tissue expander (CPT: 19357) / implant-based (CPT: 19340 and 19342) breast reconstructions; patients who underwent autologous breast reconstruction with and without the use of acellular dermal matrices were excluded). Patient encounters with a CPT code for reconstruction alone (primary CPT code) or with one for mastectomy and reconstruction (other and/or concurrent CPT code) were included in our study. Cases were subdivided between reconstructions that incorporated acellular dermal matrix (15170, 15171, 15330, 15331, 15350) as the study group and those that did not include it during reconstruction as a control group.

The primary outcome measurement was the incidence of wound complications within 30 days of surgery. This outcome was characterized as superficial surgical site infection (SSI), deep incisional surgical site infection (ISSI), and wound disruption. Secondary outcomes included major complications (graft/prosthesis/flap failure, sepsis, pneumonia, pulmonary embolism, and deep venous thrombosis (DVT)) and minor complications (urinary tract infections). All individual complication classifications follow standardized NSQIP definitions.[20]

Superficial surgical site infection is defined as an infection that occurs within 30 days following the procedure and involves only the skin or subcutaneous tissue of the incision in addition to at least one of the following:

1. Purulent drainage from the superficial incision with or without laboratory confirmation.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
3. Symptoms or signs of infection that include one of the following: pain or tenderness, redness, heat, localized swelling and deliberate opening of the superficial incision by the surgeon, unless it is culture-negative.
4. A diagnosis of superficial SSI made by the treating physician.

Deep incisional surgical site infection is defined as an infection that occurs within 30 days following the procedure involving deep soft tissues of the incision and appearing to be related to the procedure, in addition to at least one of the following:

1. Purulent drainage from the deep incision and not from the organ/space component of the surgical site.
2. Symptoms or signs of infection that include one of the following: fever (> 38°C), localized pain, or tenderness, and spontaneous dehiscence of the deep incision or deliberate opening by the surgeon unless the site is culture-negative.
3. Direct examination, histopathologic or radiologic examination, or reoperations reveal an abscess or other evidence of infection involving the deep incision.
4. A diagnosis of deep ISSI made by the treating physician.
5. An infection that involves both superficial and deep incision sites.

Wound disruption is defined as separation of the layers of a surgical wound, which may be partial or complete, with disruption of the fascia within 30 days of the operation.

We stratified the data by various preoperative measures to identify confounding factors. Preoperative patient comorbidities included body mass index (BMI), diabetes, hypertension, smoking, and alcohol consumption. Furthermore, we reviewed patients who underwent chemotherapy in the 30 days leading up to surgery, had radiotherapy 90 days before surgery, had a diagnosis of disseminated cancer, took steroids for a chronic condition, had an active wound infection, or had a greater than 10% weight loss 6 months before surgery. Finally, we report cases returning to the operating room.

Statistical analyses was performed using SPSS (IBM Corporation, Armonk, NY) to determine baseline differences in demographics, comorbidities, and postoperative complications between the two study groups. Chi-square analysis was used to analyze categorical

variables, and the *t*-test was used to analyze continuous variables. Statistical significance was defined as $p < 0.05$. A multivariate logistical regression analysis was performed to determine whether various demographics and comorbidities served as predictors for complications in both the acellular dermal matrix and non-acellular dermal matrix groups. Overall complication rates for each group were also determined. Notably, a post hoc power analysis was performed to ascertain the idealized statistical validity of our sample size. The data reported is based on 30-day outcomes from first stage implant breast reconstruction.

RESULTS

Patient Demographics

A total of 19,100 tissue expander/implant-based breast reconstruction patients were extrapolated from the NSQIP database (Table 1). Of these, 3,301 (17.3%) received acellular dermal matrices while 15, 799 (82.7%) did not. In the patient population that did receive acellular dermal matrices, 99.5% (n = 3,283) were reported as female and 0.2% (n = 8) as male. The average age of the patients was 50.7 years ± 10.6 years. In the cohort not receiving matrices, 99.5% (n = 15,714) were female patients and 0.2% (n = 43) were male patients. In this group, the average age was 51.3 ± 10.8 years. Immediate implant-based reconstruction only (CPT: 19340) was performed in 3,429 patients (18%), delayed implant reconstruction only (CPT: 19342) was performed in 1,101 patients (5.8%), a combination of tissue expander and immediate implant reconstruction was performed in 183 patients (1%), and a combination of tissue expander and delayed implant reconstruction was performed in 21 patients in (0.1%).

Patient comorbidities

The baseline difference in comorbidities was not statistically different between the two cohorts, with the exception of chemotherapy in the last 30 days before surgery. In the acellular dermal matrix group the average BMI was 26.6 ± 6.5 kg/m^2. Four hundred fifty-three patients (13.7%) in this group were smokers, 147 (4.5%) had diabetes, 711 (21.5%) had hypertension, and 28 (0.8%) had more than 2 drinks per day. One hundred sixty-three patients (4.9%) underwent chemotherapy, nine (0.3%) underwent radiotherapy, and 28 (0.8%) used steroids. Twenty-seven patients (0.8%) experienced disseminated cancer, 15 (0.5%) had a greater than 10% weight loss 6 months before surgery, 16 (0.5%) had an active wound infection, and 59 patients (1.7%) were operated on 30 days before surgery.

In the non-acellular dermal matrix group, the average BMI was 26.6 ± 6.7 kg/m^2. Two thousand one hundred seventeen patients (13.4%) in this group were smokers, 797

Table 1. Demographics of the Immediate or Delayed Tissue Expander/Implant-Based Breast Reconstruction Cohort*

N = 19,100	Total	ADM group	Non-ADM group	*p*-value
Gender				0.763
Female	18,997 (99.5%)	3,283 (99.5%)	15,714 (99.5%)	
Male	51 (0.3%)	8 (0.2%)	43 (0.3%)	
Unreported	52 (0.3%)	10 (0.3%)	42 (0.2%)	
Race				0.003
White	15,167 (79.4%)	2,740 (83.0%)	12,427 (78.7%)	
African American/Black	1,227 (6.4%)	187 (5.7%)	1,040 (6.6%)	
Asian	538 (2.8%)	96 (2.9%)	442 (2.8%)	
Hispanic	130 (0.1%)	9 (0.3%)	121 (0.8%)	
American Indian/Alaska Native	27 (0.1%)	4 (0.1%)	23 (0.1%)	
Native Hawaiian/Pacific Islander	45 (0.2%)	5 (0.2%)	37 (0.2%)	
Unknown/Unreported	1,966 (10.3%)	260 (7.9%)	1,736 (11.0%)	
Age (in years)	51.2±10.7	50.7±10.6	51.3±10.8	0.004
Year of reconstruction				<0.001
2011	5,323 (27.9%)	1,230 (32.3%)	4,093 (25.9%)	
2010	4,355 (22.8%)	820 (24.8%)	3,535 (22.4%)	
2009	3,713 (19.4%)	548 (16.6%)	3,165 (20.0%)	
2008	2,753 (14.4%)	417 (12.6%)	2,336 (14.8%)	
2007	1,914 (10.0%)	211 (6.4%)	1,703 (10.8%)	
2005-2006	1,042 (5.5%)	75 (2.3%)	967 (6.1%)	
Type of reconstruction				<0.001
Immediate implant (19340)	3,429 (18.0%)	356 (10.8%)	3,073 (19.5%)	
Delayed implant (19342)	1,101 (5.8%)	44 (1.3%)	1,057 (6.7%)	
Tissue expander placement (19357)	14,314 (74.9%)	2,865 (86.8%)	11,449 (72.5%)	
Immediate implant + Tissue expander (19340 + 19357)	183 (1%)	32 (1.0%)	151 (1.0%)	
Delayed implant + Tissue expander (19342 + 19357)	21 (0.1%)	2 (0.1%)	19 (0.1%)	
Immediate implant + Delayed implant (19340 + 19342)	51 (0.3%)	2 (0.1%)	49 (0.3%)	
Immediate implant + Delayed implant + Tissue expander (19340 + 19342 + 19357)	1 (0.005%)	0 (0%)	1 (0.006%)	

ADM = acellular dermal matrix
*n = 19,100. Percentages shown have been calculated as a fraction of respective groups (ADM, n = 3,301; Non-ADM, n = 15,799)

(4.9%) had diabetes, 3,784 (24%) had hypertension, and 183 (1.2%) had more than 2 drinks per day. Six hundred twelve patients (3.9%) had undergone recent chemotherapy, 61 (0.4%) had undergone prior radiotherapy, and 149 (0.9%) used steroids. One hundred two patients (0.6%) experienced disseminated cancer, 55 patients (0.3%) had a greater than 10% weight loss 6 months before surgery, 74 patients (0.5%) had

Table 2. Co-morbidities of the Immediate or Delayed Tissue Expander/Implant-Based Breast Reconstruction Cohort*

N = 19,100		Total	ADM group	Non-ADM group	*p*
Functional status					0.632
	Independent	19,027 (99.6%)	3,284 (99.5%)	15,743 (99.6%)	
	Complete dependence	3 (0.02%)	1 (0.03%)	2 (0.01%)	
	Partial dependence	43 (0.2%)	9 (0.3%)	34 (0.2%)	
	Unreported	27 (0.1%)	7 (0.2%)	20 (0.1%)	
BMI (kg/m^2)		26.6 kg/m^2 ±6.7	26.6 kg/m^2 ±6.5	26.6 kg/m^2 ±6.7	0.973
Smoking		2,570 (13.5%)	453 (13.7%)	2,117 (13.4%)	0.621
Alcohol Consumption		211 (1.1%)	28 (0.8%)	183 (1.2%)	0.203
Diabetes		914 (4.8%)	147 (4.5%)	767 (4.9%)	0.348
Hypertension		4,495 (23.5%)	711 (21.5%)	3,784 (24.0%)	0.003
Dyspnea					0.357
	None	18,440 (96.5%)	3,175 (96.2%)	15,265 (96.6%)	
	Moderate	644 (3.4%)	124 (3.8%)	520 (3.3%)	
	At rest	16 (0.1%)	2 (0.06%)	14 (0.1%)	
History of Chronic Obstructive Pulmonary Disease (COPD)		156 (0.8%)	21 (0.6%)	135 (0.9%)	0.205
Chronic Steroid use		177 (0.9%)	28 (0.8%)	149 (0.9%)	0.605
Radiotherapy in the last 90 days		70 (0.4%)	9 (0.3%)	61 (0.4%)	0.409
Chemotherapy in the last 30 days		775 (4.1%)	163 (4.9%)	612 (3.9%)	0.001
Open wound/active wound infection		90 (0.5%)	16 (0.5%)	74 (0.5%)	0.901
Disseminated cancer		129 (0.7%)	27 (0.8%)	102 (0.6%)	0.272
>10% weight loss 6 months prior to surgery		70 (0.4%)	15 (0.5%)	55 (0.3%)	0.358
Bleeding disorder		125 (0.7%)	23 (0.7%)	102 (0.6%)	0.740
Blood transfusion		7 (0.04%)	0 (0%)	7 (0.04%)	0.226
Previous cardiac surgery		89 (0.5%)	10 (0.3%)	79 (0.5%)	0.170
Operation within 30 days		371 (1.9%)	59 (1.8%)	312 (2.0%)	0.641
Prior transient ischemic attack		93 (0.5%)	15 (0.5%)	78 (0.5%)	0.921
Prior CVA/stroke		111 (0.6%)	17 (0.5%)	94 (0.6%)	0.255

ADM = acellular dermal matrix; DVT = deep venous thrombosis; CVA = cerebrovascular accident
*n = 19,100. Percentages shown have been calculated as a fraction of respective groups (ADM, n = 3,301; Non-ADM, n = 15,799)

an active wound infection, and 312 patients (2.0%) were operated on 30 days before surgery (Table 2).

Patient Complications

Complication rates between acellular dermal matrix and non-acellular dermal matrix groups were not statistically different for primary and secondary outcomes (p = 0.396)

Table 3. Complications of the Immediate or Delayed Tissue Expander/Implant-Based Breast Reconstruction Cohort*

N = 19,100		Total	ADM group	Non-ADM group	*p*
Major Complications (Secondary outcome)	Graft/prosthesis/flap failure	146 (0.8%)	25 (0.8%)	121 (0.8%)	0.900
	Sepsis	78 (0.4%)	17 (0.5%)	61 (0.4%)	0.516
	Pneumonia	17 (0.1%)	3 (0.1%)	14 (0.1%)	0.968
	Pulmonary embolism	31 (0.2%)	2 (0.06%)	29 (0.1%)	0.110
	DVT	44 (0.2%)	9 (0.3%)	35 (0.2%)	0.466
Wound Complications (Primary outcome)	Superficial surgical site infection	316 (1.7%)	70 (2.1%)	246 (1.6%)	0.021
	Deep incisional surgical site infection	198 (1.0)	39 (1.2%)	159 (1.0%)	0.366
	Wound Disruption	113 (0.6%)	15 (0.5%)	98 (0.6%)	0.258
Minor complications (Secondary outcome)	Urinary tract infection	46 (0.2%)	9 (0.3%)	37 (0.2%)	0.682
Return to OR		1,227 (6.4%)	237 (7.2%)	990 (6.3%)	0.136
Operative time (minutes)		193.4±96	188.4±97	217.5±85	0.001
Overall complication rate		5.0%	5.3%	4.9%	0.396

ADM = acellular dermal matrix; DVT = deep venous thrombosis
*n = 19,100. Percentages shown have been calculated as a fraction of respective groups (ADM, n = 3,301; Non-ADM, n = 15,799)

(Table 3). Of the 19,100 patients included in this study, 951 patients (5%) experienced at least one complication. One hundred seventy-five patients (5.3%) and 776 patients (4.9%) experienced at least one complication in the matrix and non-matrix groups, respectively.

Predictors for complications

A multivariate logistic regression analysis was used to assess the impact of various patient demographics and comorbidities (Tables 4-7). Several comorbidities served as statistically significant associated factors of complications primarily in the non-acellular dermal matrix group; BMI served as a predictor for superficial SSI ($p = 0.001$) and graft/prosthesis/flap failure ($p = 0.01$). Both smoking and diabetes were associated with an increased risk of wound disruption ($p < 0.001$ and $p = 0.02$ respectively). Smoking was associated with graft/prosthesis/flap failure ($p < 0.001$). Radiotherapy in the past 90 days was linked to the occurrence of pneumonia ($p = 0.01$) and pulmonary embolism ($p = 0.02$), whereas alcohol consumption correlated with the incidence of DVT ($p = 0.001$). Finally, chronic steroid use was associated with sepsis ($p = 0.04$).

In the acellular dermal matrix group, the likelihood of wound disruption was increased by BMI ($p = 0.01$) and diabetes ($p = 0.02$). Sepsis was associated with BMI ($p = 0.01$) and alcohol consumption ($p = 0.04$), and chronic steroid use was associated with superficial SSI ($p = 0.04$). Moreover, increased BMI was associated with the development of wound complications in both the matrix and non-matrix cohorts ($p = 0.04$ and $p = 0.02$ respec-

Table 4. Statistically Significant Predictors of Individual Complications without Acellular Dermal Matrix

Postoperative Outcome	Co-morbidity	*p* (OR)	HL	C-statistics
Superficial Surgical site infection	History of Chronic Obstructive Pulmonary Disease	0.05	0.667	0.304
	Previous cardiac surgery	0.01		
	BMI	0.001 (1.047)		
Deep incisional surgical site infection	Bleeding disorder	<0.001	0.722	0.304
Wound Disruption	Diabetes	0.009	0.359	0.743
	Smoking	<0.001		
Graft/prosthesis/flap failure	Smoking	<0.001	0.426	0.752
	BMI	0.01 (1.051)		
Peripheral Nerve Injury	Alcohol Consumption	0.001	0.733	0.839
	Operation within 30 days	0.02		
Pneumonia	>10% weight loss 6 months prior to surgery	0.01	0.771	0.831
	Radiotherapy in the last 90 days	0.01		
Pulmonary Embolism	Open wound/active wound infection	0.05	0.518	0.765
	>10% weight loss 6 months prior to surgery	0.01		
	Radiotherapy in the last 90 days	0.02		
	Operation within 30 days	0.01		
DVT	Alcohol Consumption	0.001	0.967	0.844
	Operation within 30 days	0.01		
CVA/Stroke	Prior transient ischemic attack	0.02	0.796	0.916
Unplanned Intubation	Chronic Steroid use	0.01	0.350	0.875
	Blood transfusion	< 0.001		
Bleeding Transfusion	Dyspnea	0.03	0.754	0.792
	Bleeding disorder	0.02		
	Blood transfusion	0.001		
	Chemotherapy in the last 30 days	0.01		
Septic Shock	>10% weight loss 6 months prior to surgery	0.01	0.763	0.849
	Radiotherapy in the last 90 days	0.03		
	BMI	0.05		
Sepsis	Chronic Steroid use	0.04	0.619	0.728
Urinary Tract Infection	Radiotherapy in the last 90 days	0.01	0.645	0.735
	Chronic Steroid use	0.02		
	Prior CVA/stroke	0.05		

Key: OR = Odds Ratio; HL = Hosmer-Lemeshow test; BMI = body mass index; DVT = deep venous thrombosis; CVA = cerebrovascular accident

Table 5. Statistically Significant Predictors of Individual Complications with Acellular Dermal Matrix

Postoperative Outcome	Co-morbidity	*p* (OR)	HL	C-statistics
Superficial Surgical site infection	Chronic Steroid use	0.04	0.240	0.715
Deep incisional surgical site infection	–	–	–	
Wound Disruption	Diabetes	0.02	0.689	0.836
	BMI	0.01 (1.182)		
Graft/prosthesis/flap failure	–	–	–	
Peripheral Nerve Injury	–	–	–	
Pneumonia	Bleeding disorder	0.002	1.000	0.973
Pulmonary Embolism	Dyspnea	0.04	1.000	0.984
DVT	–	–	–	
CVA/Stroke	–	–	–	
Unplanned Intubation	–	–	–	
Bleeding Transfusion	Previous cardiac surgery	0.991	0.850	
Septic Shock	–	–	–	
Sepsis	Alcohol Consumption	0.004	0.945	0.842
	BMI	0.01 (1.125)		
Urinary Tract Infection	Dyspnea	0.04	0.861	0.777

Key: OR = Odds Ratio; HL = Hosmer-Lemeshow test; BMI = body mass index; DVT = deep venous thrombosis; CVA = cerebrovascular accident

tively). Furthermore, along with smoking ($p = 0.02$) and diabetes ($p = 0.03$), BMI ($p = 0.01$) was also associated with major complications in the non-acellular dermal matrix group only. This finding could be attributed to shorter operative times (188.4±97 versus 217.5±85 minutes) in the acellular dermal matrix group; alternatively, surgeons may have elected not to use ADMs in patients with higher risk. Minor complications were associated primarily with radiotherapy in the past 90 days ($p = 0.01$) and chronic steroid use ($p = 0.02$). An a priori power analysis was not possible in this retrospective study, but we nevertheless found that given an alpha of .05 and a power (beta) of 80% our study exhibits sufficient sample size.

DISCUSSION

The popularity of acellular dermal matrix use for breast surgery in conjunction with implant-based reconstruction has increased over the past two decades.[21] A majority of women undergoing post-mastectomy breast reconstruction prefer alloplastic reconstruction, making the use of prostheses the most popular means of reconstruction in these patients.[22] Despite the widespread use of matrices, thus far, studies have yielded

Table 6. Statistically Significant Predictors of Complication Groups without Acellular Dermal Matrix

Complication	Co-morbidity	*p* (OR)	HL	C-statistics
Major Complications	Diabetes	0.03	0.671	0.650
	Smoking	0.02		
	BMI	0.01 (1.037)		
	Prior transient ischemic attack	0.01		
	Operation within 30 days	0.01		
	Blood transfusion	0.003		
Wound Complications	History of Chronic Obstructive Pulmonary Disease	0.03		
	Bleeding disorder	0.004	0.515	0.662
	BMI	0.002 (1.035)		
Minor Complications	Radiotherapy in the last 90 days	0.01		
	Chronic Steroid use	0.02	0.645	0.735
	Prior CVA/stroke	0.05		

Key: OR = Odds Ratio; HL = Hosmer-Lemeshow test; BMI = body mass index

Table 7. Statistically Significant Predictors of Complication Groups with Acellular Dermal Matrix

Complication	Co-morbidity	*p* (OR)	HL	C-statistics
Major	–		0.421	0.726
Wound	BMI	0.04 (1.060)	0.197	0.707
Minor	–		0.861	0.777

Key: OR = Odds Ratio; HL = Hosmer-Lemeshow test; BMI = body mass index

inconclusive results. Some studies have shown that their use contributes to lower complication rates[14,15] whereas others have demonstrated an increase in the rate of infections and overall complication rate associated with individual risk factors; higher body mass index, smoking, and larger implant size.[12,16] For this reason, it has been difficult to identify significant risk factors associated with the development of postoperative complications in single-institution studies.[23]

Defining metrics are established as a means of working toward the development of aiding the reduction in the cost of care related to complications. In the absence of centralized health care in the Unites States, the NSQIP database represents the closest form of a national surgical database that can be used to track these evidence-based changes.[23]

Our data reveals that acellular dermal matrix use was not associated with increased complications in immediate and delayed tissue expander/implant-based breast reconstruction. No significant differences in complication rates were observed between the matrix and non-matrix groups. Based on analysis of the NSQIP data set, the complication rate for

matrix use in prosthesis-based breast reconstruction was significantly lower than previously published single institution reports primarily for wound complications, including seroma formation and infection.[12,16,24,25] Furthermore, the data supports articles favoring the lack of a substantial difference in complications with and without matrix use in breast reconstruction.[13,14,26] It was also found that there were no considerable baseline demographic/comorbidity differences between the two groups. Our analysis also revealed that a higher BMI was associated with increased complication rates in both cohorts regarding wound disruption, graft/prosthesis/flap failure, superficial SSI, major complications, and wound complications. Previous NSQIP studies have reported an association between BMI and higher rates of wound infection following major abdominal surgery.[27,28] In addition, there are several publications supporting the association between higher BMI and wound infections in breast surgery.[29-32] Nonetheless, Al-Rifaie et al.[33] showed that in analysis of an NSQIP data set of patients who underwent major thoracic, abdominal, and pelvic surgery for cancer, no significant association between higher BMI and poor outcomes was found. Nevertheless, higher BMI should be a consideration when attempting to minimize risk.[23]

In the acellular dermal matrix group, chronic steroid use was associated with superficial SSI whereas in the non-matrix group, chronic steroid use served as a predictor for sepsis and minor complications. The analysis by Ismael et al.[34] of the NSQIP database demonstrated that steroid use was associated with not only the incidence of surgical site infection but also a fourfold increase in mortality. This finding was confirmed by Vaid et al.[35] who suggested that steroid use in the preoperative period was an independent predictor of death. Smoking is also an important risk factor for unfavorable postoperative outcomes. This finding has been confirmed by previous NSQIP reports in vascular and gastrointestinal procedures.[36-38] In our non-acellular dermal matrix cohort, smoking was associated with an increased risk for wound disruption, graft/prosthesis/flap failure, and major complications. Not surprisingly, these observations highlight the need for surgeons to advise patients regarding preoperative cessation of steroids and smoking.

Diabetes was associated with wound disruption in both groups. Furthermore, diabetes increased the likelihood of major complications in the non-matrix group. A study by Jordan et al.[39] found that diabetes was a significantly associated with graft/prosthesis or flap failure and 30-day mortality in general reconstructive cases. Bhayani et al.[40] reviewed the NSQIP database and found diabetes to increase the incidence of superficial surgical-site infections. These findings are not unique[41-44] but have not previously been confirmed with the use of acellular dermal matrices in tissue expander/implant-based breast reconstruction.

It is documented that the consumption of alcohol is associated with worse outcomes.[45] Previous analysis of the NSQIP database regarding the effect of alcohol consumption on surgical outcomes of elective surgery revealed that use of alcohol was linked with a longer length of stay following procedures and earlier wound disruption. Furthermore, it was associated with the likelihood of sepsis, pneumonia, and superficial SSI.[45] These findings are similar to our data, which showed that alcohol was associated with sepsis in the acellular dermal matrix group and DVT and peripheral nerve injury in the non-matrix group. However, this finding is contrasted by Khan et al.[46] who found that alcohol abuse had no significant association with mortality in a NSQIP cohort of bariatric patients.

One major concern when using acellular dermal matrices is their ability to tolerate irradiation. Komorowska-Timek et al.[13] suggested that the use of AlloDerm® reduces the rate of radiation-related inflammation and pseudoepithelium formation. The authors observed increased inflammation at 12 weeks in the control group compared with the AlloDerm® group. Nahabedian[26] found that irradiation had no effect on the rate of infection. Thus far, studies have yielded inconclusive results.[13,26] In the current study, we found that irradiation 90 days before surgery was not associated with postoperative morbidity in the matrix group; however prior irradiation was associated with pneumonia and pulmonary embolism in the non-matrix group.

There are several limitations to our study. We found lower complication rates than previously reported, which could be attributed to the large size of our data set. However, we report on the data ascertained from a multi-institutional database making this current study unique. Another limitation is the difference in the definitions of complications. One potential solution is the addition of disease- and operation-specific variables, which would allow for better predictions of undesirable outcomes.[47,48] Birkmeyer et al.[17] suggested that newer versions of the NSQIP take the form of a series of parallel specialty-specific modules. Another factor is that the NSQIP data set reflects outcomes in only academic centers and does not account for many community hospitals and private clinics that perform breast reconstruction. Thirty-day morbidity has become a widely accepted outcome standard in surgery; thus, the database may still be considered a valuable tool for analysis of short-term outcomes.[23] The NSQIP database has previously been utilized for other plastic surgery breast procedure-related outcome studies.[5,48-51]

CONCLUSIONS

In this study of 19,100 patients in a multi-institutional cohort, there was no significant difference in complication rates between the acellular dermal matrix and non-acellular

dermal matrix groups ($p = 0.396$). Based on these data, acellular dermal matrix use was not associated with increased complications in tissue expander/implant-based breast reconstruction. Several comorbidities serve as significant associated factors for negative outcomes in both groups.

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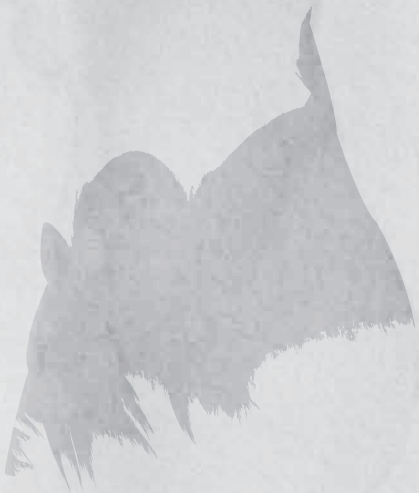
Chapter 5

Use of Acellular Dermal Matrix in Reconstructive Breast Surgery: A Survey of Current Practice among Plastic Surgeons



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ABSTRACT

Background

Acellular dermal matrices (ADMs) in plastic surgery have become increasingly popular particularly for breast reconstruction. Despite its advantages, questions exist regarding its association with a possible increased incidence of complications. We describe a collective experience of plastic surgeons' use of ADMs in reconstructive breast surgery using an internet based survey.

Methods

Members of the American Society of Plastic Surgeons (ASPS) were recruited through voluntary, anonymous participation in an online survey. The web-based survey garnered information about participant demographics and their experience with ADM use in breast reconstruction procedures. After responses were collected, all data were anonymously processed.

Results

Data was ascertained through 365 physician responses of which 99% (n = 361) completed the survey. The majority of participants were males (84.5%) between the ages of 51 and 60 (37.4%). 84.2% used ADM in breast reconstruction including radiated patients (79.7%). ADM use was not favored for nipple reconstruction (81.5%). 94.6% of participants used drains, and 87.8% administered antibiotics postoperatively. The most common complications were seroma (70.9%) and infection (16%), although 57.4% claimed anecdotally that overall complication rate was unchanged after incorporating ADM into their practice. High cost was a deterrent for ADM use (37.5%).

Conclusions

Plastic surgeons currently use ADM in breast reconstruction for both immediate and staged procedures. Of those responding, a majority of plastic surgeons will incorporate drains and use postoperative antibiotics for more than 48 hours.

INTRODUCTION

Acellular dermal matrices (ADMs) in plastic surgery have become increasingly popular.[1] The use of ADMs together with improved techniques have helped to solve surgical problems lacking simple surgical solutions.[2] Not only do these biologic meshes provide increased structural strength, they also promote rapid vascular ingrowth potentially serving as a scaffold for formation of new tissue.[3] Since their availability in the 1990s the list of indications for their use continues to grow.[1] Among other indications, ADMs have been incorporated into abdominal wall reconstruction, extremity surgery, eyelid reconstruction, and nasal reconstruction.[4-7]

Increased interest in ADM use for reconstructive breast surgery has mirrored the introduction of new products.[1] Initially ADM was reported for use in secondary breast deformities such as contracture and rippling but has since evolved to address other shortcomings of implant based reconstruction.[8] ADMs have been described as the most significant innovation impacting prosthetic breast reconstruction in recent years.[9] This statement can be attributed to its numerous potential benefits including improved aesthetic outcome, reduction in postoperative pain, and decreased operative time.[10] Furthermore, it has been reported to provide better control of the mastectomy space, optimize implant positioning, allow for increased intraoperative expansion, and prevent superior migration of the implant.[9] Prior studies have evaluated the outcomes of ADM use in breast reconstruction.[9,11] Despite their advantages, there is literature implicating its association with an increased incidence of postoperative complications particularly infection and seroma formation.[12,13]

While it is not common, ADMs can also be employed in delayed breast reconstruction provided there is an adequate degree of skin laxity. Moreover, ADMs have shown to be successful in patients with different varying breast volumes.[9] ADMs have proven less effective in patients with delayed reconstruction, exposure to radiation, those with a history of smoking, when vascularity to skin flaps has been compromised immediately following mastectomy, and in the morbidly obese.[9,14,15]

Although ADMs provide an added tool for plastic surgeons, their use has a learning curve requiring effort to attain desired outcomes.[9] Another drawback is its high cost.[1,16] In this instance, and in today's economic environment, cost-benefit and cost analysis are essential.[17] In light of the pros and cons of ADM use in breast reconstruction, the aim of this study was to gain a better understanding of the collective experience of plastic surgeons with ADM in post-mastectomy breast reconstruction in terms of the popularity of its use, the most commonly incorporated meshes, patient satisfaction, surgical outcomes, complications, and application in breast revision procedures. In addition, we sought to

investigate the impact of ADM in the setting of drains, antibiotics, nipple reconstruction, and in previously radiated patients.

METHODS

Recruitment

A survey was created using www.surveymonkey.com. An invitation containing a generic link to the survey (that ensured anonymity and prevented tracking) was distributed by email to 365 plastic surgeons who are members of the American Society of Plastic Surgeons (ASPS). Participation was voluntary. After responses were collected, all data were anonymously processed. Only a small cohort of plastic surgeons who are members of the ASPS was included owing to the difficulty in obtaining member emails (lack of an email repository) and based on omission of emails that were either no longer in use by the plastic surgeon (referred to an administrative email) or inactive, in which case the email was not delivered (a delivery status notification failure was received). There were no incentives given for participation in this study and those that did participate were completely random with no pre-selection based on practice patterns or ADM use.

Survey

The web-based survey gathered information about participant demographics including gender, age, practice type, years in practice and geographic setting. Participants were then asked if they utilized ADM in breast reconstruction. Plastic surgeons who did not use ADMs were asked about the use of biologic meshes in other procedures and questioned about their decision not to use ADM in breast procedures. For participants who used ADM in breast reconstruction, inquiries were made about the type of mesh, the reasons for their particular choice, application in either immediate or delayed setting, patient satisfaction with surgical outcomes, and the utilization of ADM in breast revision procedures. Furthermore, to better understand the scope of ADM application, inquiries were made regarding the use of ADM for nipple reconstruction, drain usage, administration of antibiotics postoperatively, and in previously radiated patients. Finally, participants provided insight into their experience with infection rates and complications following ADM use as well as their opinion of the literature concerning the current evidence pertaining to ADM use in plastic surgery.

Statistical Analysis

Statistical analyses were performed using SPSS software version 21.0 (SPSS Inc., Chicago, IL). Associations between the use of ADM (dependent variable) and different independent variables were determined using Chi-square and Fisher's Exact tests. Two sided *p*-values of < 0.05 was deemed statistically significant.

RESULTS

Patient Demographics

The data for this study was ascertained through 365 physician responses of which 99% (n = 361) of the respondents completed the survey. Responses of plastic surgeons that did not complete the survey were excluded (n = 4) (Figure 1). The majority of participants were males (84.5%) who worked as solo practitioners in private practice (51%) in a large urban area (60.1%). Most plastic surgeons were between the ages of 51 and 60 (37.4%) and had been in practice for 11 to 20 years (37.7%). Participant demographics are summarized in Table 1.

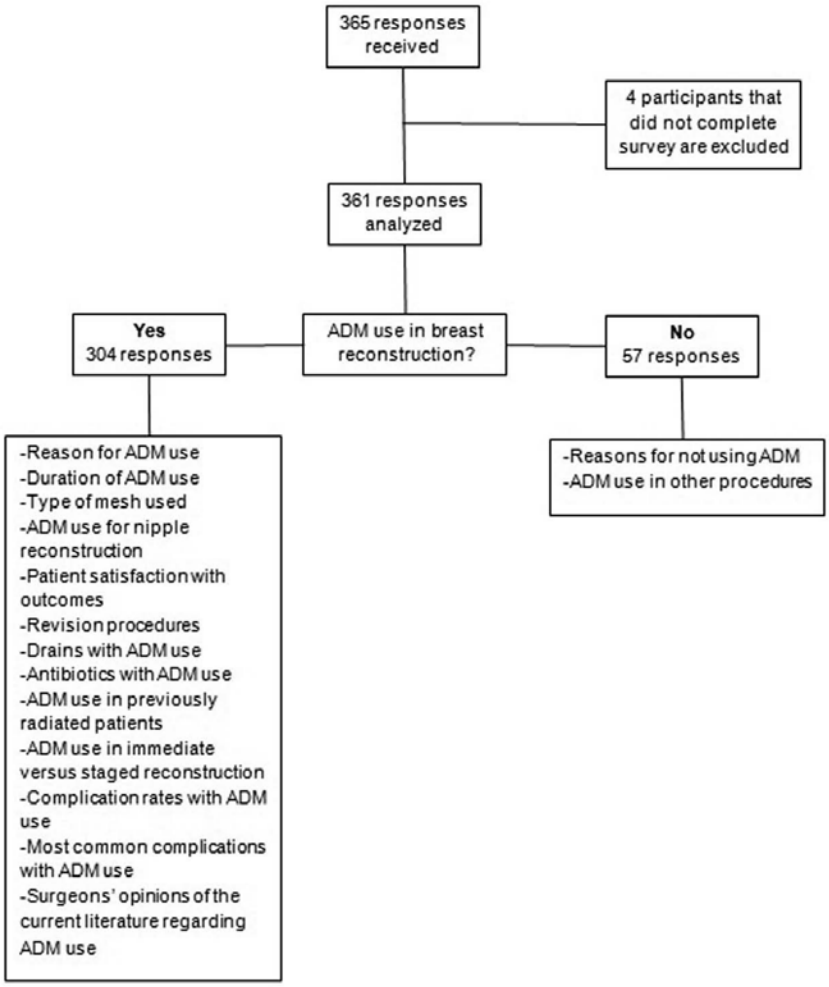

Figure 1. Survey participant selection process

Table 1. Demographic Characteristics of Respondents (N = 361)

	Total (%)	ADM group (%)	Non-ADM group (%)	*p-value*
Gender				
Male	305 (84.5%)	257 (84.5%)	48 (84.2%)	*0.95°*
Female	56 (15.5%)	47 (15.5%)	9 (15.8%)	*0.95°*
Age (yr)				
<30	0 (0%)	0 (0%)	0 (0%)	*n/a*
31-40	20 (5.5%)	20 (6.6%)	0 (0%)	*0.05ˣ*
41-50	118 (32.7%)	104 (34.2%)	14 (24.6%)	*0.15°*
51-60	135 (37.4%)	115 (37.8%)	20 (35.1%)	*0.69°*
>60	88 (24.4%)	65 (21.4%)	23 (24.6%)	*0.01°*
Primary practice type				
Private solo	184 (51.0%)	152 (50%)	32 (56.1%)	*0.39°*
Private group	96 (26.6%)	85 (28.0%)	11 (19.3%)	*0.17°*
Private academic	24 (6.6%)	20 (6.6%)	4 (7.0%)	*1.00ˣ*
Academic community	8 (2.2%)	7 (2.3%)	1 (1.8%)	*1.00ˣ*
Academic university	49 (13.6%)	40 (13.2%)	9 (15.8%)	*0.59°*
Practice setting				
Large urban area	217 (60.1%)	174 (57.2%)	43 (75.4%)	*<0.01°*
Small urban area	126 (34.9%)	114 (37.5%)	12 (21.1%)	*<0.01°*
Rural area	18 (5.0%)	16 (5.3%)	2 (3.5%)	*0.75ˣ*
Years in practice				
<5	5 (1.4%)	5 (1.6%)	0 (0%)	*0.60ˣ*
6-10	57 (15.8%)	53 (17.4%)	4 (7.0%)	*0.05ˣ*
11-20	136 (37.7%)	118 (38.8%)	18 (31.6%)	*0.30°*
21-30	111 (30.7%)	92 (30.3%)	19 (33.3%)	*0.65°*
>30	52 (14.4%)	36 (11.8%)	16 (28.1%)	*<0.01°*

* Percentages shown have been calculated as a fraction of respective groups (N = 304 (ADM); N = 57 (Non-ADM)) ° Chi square test, ˣ Fisher's Exact test

Participants who did not use ADM in Breast Reconstruction

Of the 361 participants that completed the survey, 57 (15.8%) stated that they did not use ADM in breast reconstruction. When these 57 participants were queried as to whether they used ADM for any other procedures (such as abdominal wall reconstruction, head and neck reconstruction, burn surgery, lower limb coverage and hand surgery), 42 (73.7%) claimed that they did not incorporate ADM into any aspect of their practice. The most reported reasons for this were due to cost (n = 15), surgeon preference (n = 10), and increased complications with previous experience (n = 11). Only 15 of the 57 participants (26.3%) stated their use of ADM for other procedures, the most common of which were abdominal wall reconstruction (n = 5) followed by extremity surgery; lower limb cover-

age (n = 4), and hand surgery (n = 3). When asked about the decision not to incorporate ADM in breast procedures, most of the respondents attributed it to the absence of breast reconstruction in practice (n = 7), no clear indication of benefit (n = 3), and cost (n = 2).

Participants who use ADM in Breast Reconstruction

Three hundred and four participants (84.2%) stated they routinely used ADM in breast reconstruction. The majority of respondents in this group had been using ADM in breast procedures for the last 6-10 years (69.5%). The most popular mesh for use in practice was AlloDerm® (71.6%) (Figure 2). The main reason for its popularity was reported to be adequate long-term experience and AlloDerm® being well described in the literature (68.1%). The data suggest that this group of participants chose to incorporate ADM in breast reconstruction to allow for better control of the implant pocket (81.4%), improved aesthetic outcomes (70.1%), a quicker expansion (43.9%), and being able to reduce the incidence of capsular contracture as well as breast deformities (40.2% and 25.6% respectively).

The majority of responding plastic surgeons (81.5%) did not use ADM for nipple reconstruction. When asked about patient satisfaction, 86.4% of the surveyed plastic surgeon population reported that patients were satisfied with aesthetic outcomes; furthermore, 77.9% stated that patients rarely come back for further revisions. In the circumstance when a patient is unsatisfied and ADM has been used for reconstruction, the most commonly performed revision procedures include symmetry procedures (53.9%), fat grafting (19.5%), and capsulotomy/capsulectomy (17.9%).

Drains were used by 95% of respondents in conjunction with ADM in breast reconstruction. 81.5% reported using drains in all breast procedures involving ADM; typically, either one (45%) or two drains (49.6%) were used. 57.5% of respondents stated to

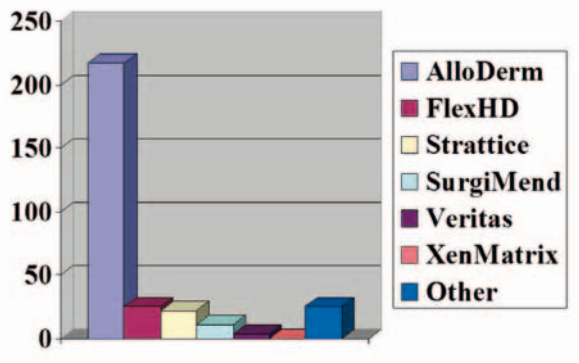

Figure 2. Most commonly meshes used for breast reconstruction

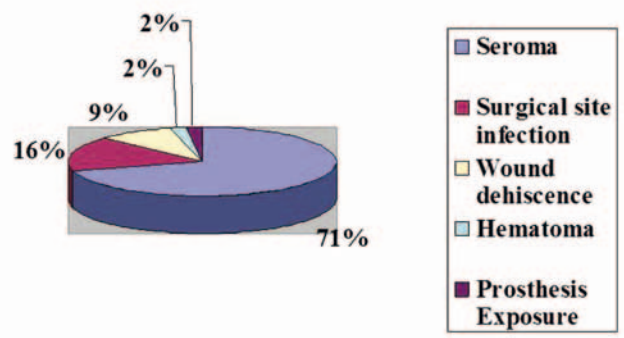

Figure 3. Most common complications with ADM use in breast reconstruction

have left drains in for a longer period of time when they used ADM. Most participants (87.8%) routinely used antibiotics in the postoperative period; however, the number of days of antibiotic use varied from less than 5 days (31.5%), 6-10 days (45%), 11-14 days (15.8%), to more than 14 days (7.7%). We found that 79.7% of respondents had used ADM in previously radiated patients. Of these, 37.4% experienced no change in complication rates, an almost equal number of respondents suspected an increase or decrease in complication rate (24.3% versus 23%), and 15.3% were unsure. Those that reported an increase in complications, implicated seroma (n = 45) and surgical site infection (n = 28), necessitating return to the operating room (OR) 11% to 30% of the time. The majority of participants (72.8%) used ADM in both immediate implant as well as staged reconstruction (tissue expander/implant). Regardless of the type of procedure,

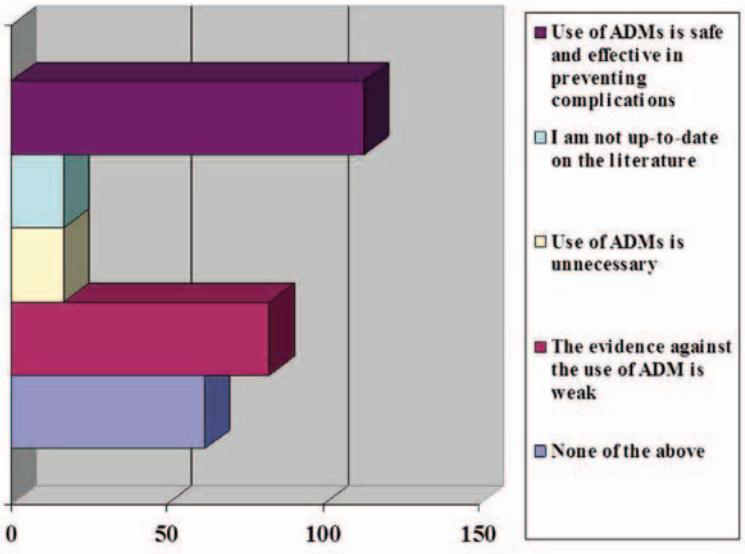

Figure 4. Summary of plastic surgeon opinion of evidence in the current literature for use of ADMs

the most commonly reported complications were seroma (70.9%) followed by surgical site infection (16%), and wound dehiscence (9.4%) (Figure 3). When asked whether ADM use in breast reconstruction contributed to an increased rate of infection, participants responded that it remained unchanged (57.4%). 26.4% of respondents reported an increase and 5.4% a decrease in the rate of infection. Finally when questioned about their opinion of the literature with regard to current evidence for the use of ADM in plastic surgery, 38.7% suggested that the use of ADM is safe and effective in preventing complications while 28.4% reported that the evidence against the use of ADM is weak (Figure 4).

DISCUSSION

The emergence of ADMs has altered the practice patterns of many surgeons in various surgical disciplines.[2] As this technology continues to advance an abundance of new applications will develop. Currently, ADMs are used in a large spectrum of surgical procedures including abdominal wall surgery, chest wall reconstruction, head and neck reconstruction, burns, and in injuries of the extremities.[5,6,18,19] ADMs have gained in popularity for use in breast reconstruction procedures and they are now common practice in implant-based surgery.[20] The rationale behind their application is to improve positioning of the prosthesis, to provide coverage of compromised muscle and fascia (pectoralis or serratus), to reduce the incidence of capsular contracture, to create a more defined inframammary fold and notably to enhance the aesthetic outcome resulting from improved lower pole expansion.[1,21,22] Despite their widespread use there is an ongoing debate about incorporating ADM in breast reconstructive surgery which primarily is attributed to a possible increased risk of postoperative complications. In this study, the practice pattern of plastic surgeons with ADM use in breast reconstruction was investigated.

An amount of literature has been published about the use of ADM in breast reconstruction. However, data about the demographics and its application in breast reconstructive surgery in the general plastic surgery population is less clear. In our study, the majority of responding plastic surgeons performing breast reconstruction have incorporated ADM into their practice (84.2%) regardless of practice type. This support for ADM use was attributed by most surgeons to its published safety and efficacy in the surgical literature. Interestingly, 100% of respondents aged 31-40 years, or less than 5 years in practice, use ADM in breast reconstruction which may suggest a practice pattern that newer graduates are learning and/or choose to use ADM in breast reconstruction at greater rates than surgeons who did not learn to use it during their training This assertion is somewhat confirmed by the finding that 57.4% of respondents suspected that the rate of infection

did not change with ADM. However, a careful review of recent evidence indicates that opinion is divided on whether or not the use of ADM is associated with a higher incidence of postoperative complications.[13,20,23-27] A chart review of 41 patients (65 breasts) by Bindingnavele et al.[26] found extremely low complication rates with biologic mesh use in postmastectomy breast reconstruction: seroma in 3 patients, wound infection in 2 patients, and hematoma and expander removal in 1 patient each. This finding is corroborated in a study by Preminger et al.[28] who reported that AlloDerm® did not increase the risk of postoperative complications. In contrast Chun et al.[12] and Liu et al.[13] observed statistically significant increases in infection rate and seroma rate with Alloderm® use respectively. Only 26.4% of our survey participants reported an increase in postoperative complications the most common of which were seroma (70.9%), surgical site infection (16%) and wound dehiscence (9.4%). A systematic review by Ho et al.[10] showed higher likelihood of seroma and infection in prosthetic-based breast reconstructions using traditional musculofascial flaps while Adetayo et al.[29] identified the most common complications as wound infection (16%), seroma formation (8%), and breast implant failure (6%).

The ability of ADM to tolerate exposure to radiation is still being debated.[21,30] In our study 79.7% of participants claimed to have used ADM in previously radiated patients with most (37.4%) reporting no change in complication rate and equal numbers suspecting an increase (24.3%) or decrease (23%). Nahabedian et al.[24] reported that ADM is able to tolerate radiation exposure, demonstrating that the risk of infection did not vary with or without AlloDerm®. Komorowska-Timek et al.[25] noted that AlloDerm® reduced the rate of radiation-related inflammation. Colwell et al.[31] found that radiation therapy following stage 1 of tissue expander/implant based reconstruction had a significantly lower complication rate than radiation therapy in the setting of breast conserving therapy. On the other hand, Spear et al.[23] and Salzberg et al.[32] observed 11-fold and 4-fold higher complication rates respectively in irradiated versus non irradiated breasts. Despite these high complication rates, Ayeni et al.[21] reported that compared to plain TE reconstructions, ADM-assisted TE reconstruction appeared to have better resistance to radiation or at least have similar complication rates.

No consensus exists on antibiotics use following breast reconstructive surgery. Despite indications that there is no benefit in patients who receive treatment for more than 24 hours[33] a majority of plastic surgeons (87.8%) routinely use antibiotics for 6-10 days (45%) in the postoperative period. Avashia et al.[34] demonstrated a significant decrease in the rate of infection when postoperative antibiotics were taken for at least 48 hours following implant-based breast reconstruction with ADM. In a series of 321 implant based reconstructions of which AlloDerm® was used in 75, Nguyen et al.[35] reported no

variations in the readmission rates for IV antibiotics. However, development of infected fluid collections resulting in explantation was found to be significantly higher in the AlloDerm® group compared to the control group. The use of drains was also prevalent in our surveyed population (94.6%) with just over half (57.5%) leaving drains in for a longer period of time when they used ADM. This finding is consistent with findings by Collis et al.[36] who reported drains to have remained in situ for a significantly longer duration when using ADM.

Few studies have implemented ADM to aid in reconstruction of the nipple-areola complex with the goal of improving nipple projection.[37-39] The survey found that only 18.5% of respondents reported to have used ADM for nipple reconstruction. Although experience with ADM in nipple reconstruction is limited, results thus far may be promising.[39] Garramone and Lam[37] demonstrated that AlloDerm® use in a modified dermal flap pattern for 30 nipple reconstructions was a safe, reproducible and easily performed approach for enhancing nipple projection. In contrast, a review of ADM use in nipple reconstruction by Israeli[20] suggests limited success due to loss of nipple projection over time.

The most frequently used ADM is AlloDerm® (71.6%) which is not surprising given it is the most commonly reported mesh for use in breast reconstruction in the literature.[1] Moreover, 72.8% of surgeons used ADM in both immediate and staged breast reconstruction procedures owing to its many reported benefits.[1, 21, 40] One major deterrent against ADM use in breast procedures is cost which can range from $3,536 to $4,856 per breast;[16] it was implicated as the main reason for not using ADM in practice at all by 37.5% of participants. Regardless, Salzberg[40] found AlloDerm® use in immediate reconstruction to be less costly than TRAM flap surgery and expander/implant reconstruction after mastectomy. Although ADM can be expensive, various reports have demonstrated that in the long-term it is cost effective in breast reconstruction.[1,17,40]

There are limitations to our study. Despite the number of plastic surgeons that completed the survey, only 57 did not use ADM for breast reconstruction. This finding was perhaps due to the voluntary sampling of participants which was utilized and may have resulted in bias toward ADM use. A small sample size may reduce the chances of detecting a true effect by overestimating it. Also, it may decrease the likelihood that a statistically significant result reflects a true effect. Therefore, this may be an incomplete assessment of the actual prevalence of plastic surgeons that do not use ADM in practice. Patient satisfaction with the aesthetic result was based solely based on surgeon opinion which may have also contributed toward bias with ADM use. Another limitation may be interpretation of the term "breast reconstruction" used in our survey which some surgeons may have found to mean reconstruction following mastectomy only rather than also its use in aes-

thetic cases. Furthermore, the term "revision" may be have been interpreted differently by the study participants with some considering it to be further surgical intervention in the operating room and others deeming it a simple outpatient "touch-up". Nevertheless, a majority of our respondents claimed that patients rarely came back for a revision maintaining consistency of our result. Finally, recall bias of the surveyed plastic surgeons may be a factor; however, this issue could potentially be overcome by our sample size and subgroup analysis excluding patients who did not use ADM for breast reconstruction.

CONCLUSIONS

Plastic surgeons use ADM in breast reconstruction for both immediate and staged procedures. Younger generations of plastic surgeons appear more willing to include ADMs in their practice. A majority of responding plastic surgeons incorporate drains and use postoperative antibiotics for more than 48 hours. ADM use for nipple reconstruction is not yet widely accepted. The occurrence of seroma, surgical site infection, and wound dehiscence are the most commonly implicated complications when ADM is incorporated necessitating return to the OR. Despite this, a good number of respondents believe that overall infection rate remains unchanged. In addition, the majority of participants that reported use of ADM in previously radiated patients found that it did not contribute to a difference in complication rate. Most responding plastic surgeons believe that based on existing evidence, ADM use is safe and effective in preventing complications and that the data against its use is weak. The main deterrent against ADM use is its cost. In future studies a larger participant population is needed to eliminate potential bias regarding ADM use.

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Chapter 6

Does Acellular Dermal Matrix Really Improve Aesthetic Outcome in Tissue Expander/ Implant Based Breast Reconstruction?

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Submitted for publication

ABSTRACT

Background

The expectation for improved results by women undergoing postmastectomy reconstruction has steadily risen. A majority of these operations are tissue expander/implant based breast reconstructions. Acellular Dermal Matrix (ADM) offers numerous advantages in these procedures. Thus far, the evidence to justify improved aesthetic outcome has solely been based on surgeon opinion. The purpose of this study was to assess aesthetic outcome following ADM use in tissue expander/implant based breast reconstruction by a panel of experienced, blinded plastic surgeons.

Methods

Mean aesthetic results of patients who underwent immediate implant based breast reconstruction with (n = 18) or without ADM (n = 20) were assessed with objective grading of preoperative and postoperative photographs by five independent blinded plastic surgeons. Absolute observed agreement as well as weighted Fleiss Kappa (κ) test statistics were calculated to assess inter-rater variability.

Results

When ADM was incorporated, overall aesthetic score improved by an average of 12.1%. In addition, subscale analyses revealed improvements in breast contour (35.2%), implant placement (20.7 %), lower pole projection (16.7%), and inframammary fold definition (13.8%). Contour ($p = 0.039$), implant placement ($p = 0.021$), and overall aesthetic score ($p = 0.022$) reached statistical significance. Inter-rater reliability showed mostly moderate agreement.

Conclusions

Mean aesthetic scores were higher in the ADM-assisted breast reconstruction cohort including total aesthetic score which was statistically significant. Aesthetic outcome alone may justify the added expense of incorporating biologic mesh. Moreover, ADM has other benefits which may render them cost-effective. Larger prospective studies are needed to provide plastic surgeons with more definitive guidelines for ADM use.

INTRODUCTION

Over the last decade the expectation for improved results by women undergoing postmastectomy reconstruction has steadily risen.[1] Eighty percent of these procedures are performed using a tissue expander/implant based approach owing to the relatively straightforward operative technique and reduced operative time.[2] Despite this overwhelming majority, implant based breast reconstruction has some drawbacks including capsular contracture and implant displacement which may necessitate implant removal or replacement in up to fifty percent of cases.[3]

Recently, acellular dermal matrix (ADM) has become a sinew of tissue expander/implant based breast reconstruction.[2] Some authors have described it as the most important advancement in prosthetic breast reconstruction over the last several years.[4,5] This is mirrored by the increase in number of products that have paralleled its use.[6] ADM is a biologic mesh consisting of human, porcine or bovine dermis that has been denuded of cellular components that cause inflammation and rejection.[6,7] The resulting product is a tissue matrix that promotes intrinsic regeneration via cell repopulation, angiogenesis, and normal tissue in-growth; allowing better integration with excellent postoperative healing, and minimal resorption.[7]

The unique qualities of ADM have rendered it popular in prosthetic breast reconstruction for coverage of the tissue expander or implant at the inferolateral pole.[8,9] Indeed proponents of ADM use will allude to its numerous advantages in breast reconstruction such as improved lower pole contour, better implant positioning, shortened filling time for tissue expansion, enhanced definition of the lateral mammary and inframammary folds, decreased incidence of capsular contracture, and protection against the effects of radiation.[10-13] Together these advantages can result in superior cosmetic outcomes.[7,10] One factor that may discourage ADM use in breast surgery is its cost which may be as lofty as $4,856 per breast.[14] Some authors have argued that it is more costly not to use the material suggesting that it reduces operative time and the need for additional revisions.[13,15]

Despite the support for ADM use in tissue/expander implant based reconstruction, thus far, the evidence to justify improved aesthetic outcome has solely been based on surgeon opinion.[16,17] To date no study has provided an objective perspective on the aesthetic outcome of implant based breast reconstruction using ADM. As such, the purpose of this study was to assess the aesthetic outcome following ADM use in tissue expander/implant based breast reconstruction by a panel of experienced, blinded plastic surgeons.

PATIENTS AND METHODS

Patient Population

Women who underwent unilateral or bilateral implant based breast reconstruction at the Beth Israel Deaconess Medical Center between 2005 and 2012 were included in this study. All patients were treated in a staged fashion with temporary expander and subsequent final implant exchange. Single-stage reconstructions and patients with follow-up photographs of less than six months were excluded from our analysis. Patients were divided into two groups: those who underwent implant based breast reconstruction with ADM and those without. The patients were operated on by three plastic surgeons (A.M.T., B.T. L., and S.J.L.). To standardize our patient population, only those who underwent implant based breast reconstruction under general anesthesia using the submuscular approach were included. Furthermore, in the ADM group, only patients in which an ADM sling was used were incorporated in our analysis. The ADM sling was used to maintain the inferolateral portion of the tissue expander pocket. This was achieved by anchoring the lower pole of pectoralis major muscle by attaching it to the lower pole of the released pectoralis major superiorly, the serratus anterior laterally, and the chest wall inferomedially. This was done to permit improved control of the inframammary fold allowing the creation of a larger implant pocket as well as to provide additional tissue coverage to improve the final outcome of reconstruction. Those who received an ADM patch were not included in this study. It is important to note that the cases were selected based solely on their inclusion criteria and not the surgeon's best results. Information regarding patient demographics, co-morbidities, breast reconstruction type (with or without ADM), and incidence of complications was recorded. Institutional review board approval was obtained for this study.

Assessment of Aesthetic Outcome

Aesthetic outcome was evaluated by a panel of five board eligible plastic surgeons who were not involved in the direct care of these patients and who were blinded as to which patients received ADM and which did not as well as to the reason for photographic analysis. They were shown a series of standardized preoperative and postoperative photographs for all patients consisting of five images (frontal, oblique and lateral views). Follow-up photographs ranged from 6 months to 7 years postoperative (mean 1.7 years). Representative examples are shown in Figures 1 and 2. These images were presented to each member of the panel in a random fashion. A set of training photographs were presented at the beginning of each session to ensure standardization of scoring between observers. For bilateral cases the raters were asked to provide a score relative to the contralateral side. A single score per category was provided for each patient rather than each breast.

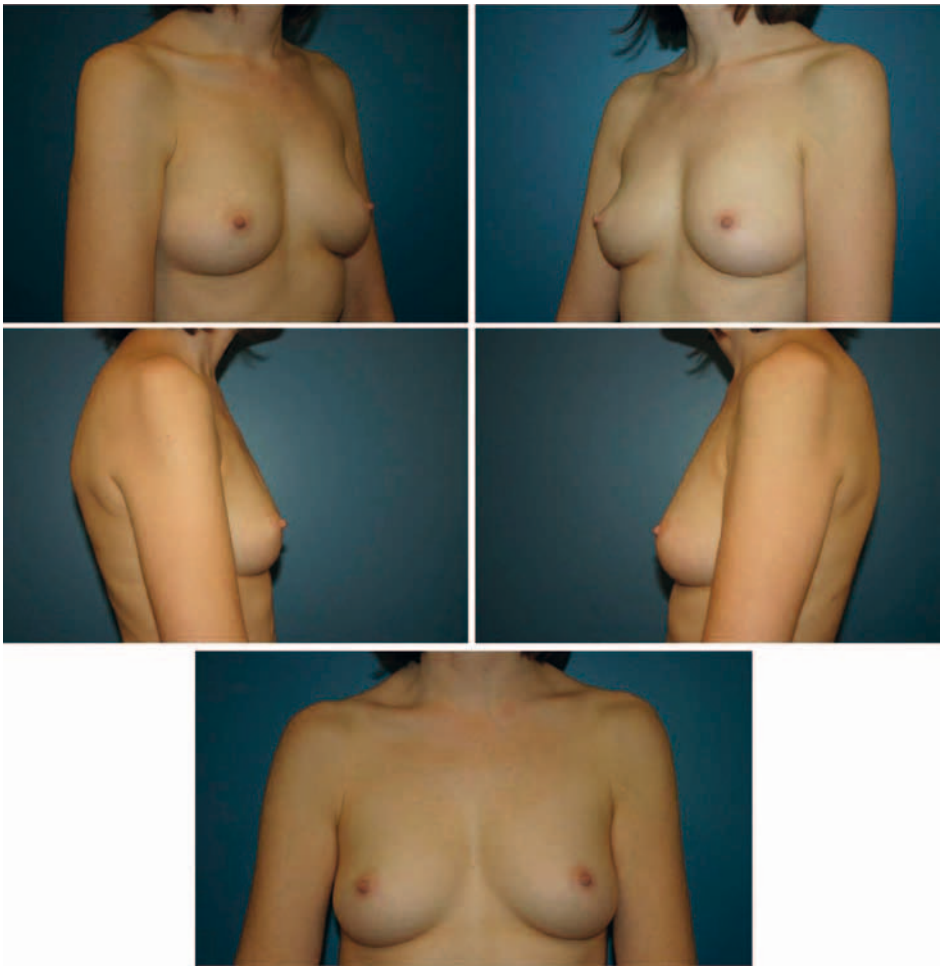

Figure 1. An example of a series of five preoperative standardized photographs presented to the panel of blinded plastic surgeons

A modification of the grading scale used initially by Garbay et al.[18] and later adapted by Carlson et al.[19] and de Blacam et al.[20] was used (Table 1). The validity of this scale was confirmed by Lowery et al.[21] who showed that compared to the four-point scale and visual analogue scale, separating the aesthetic outcomes of breast surgery into subscales renders the rating criteria more explicit and more reliable for ensuring comparability of results. Subscale aesthetic analysis of the individual characteristics of breast appearance was tailored to include volume, contour, placement of implant, scars, lower pole projection, and inframammary fold (IMF) definition. Assessment of breast softness was not included since it was not previously implemented in validated photo-analysis studies. Furthermore, the raters who were blinded did not interact with the patients and thus an accurate assessment of softness could not be ascertained simply by viewing im-

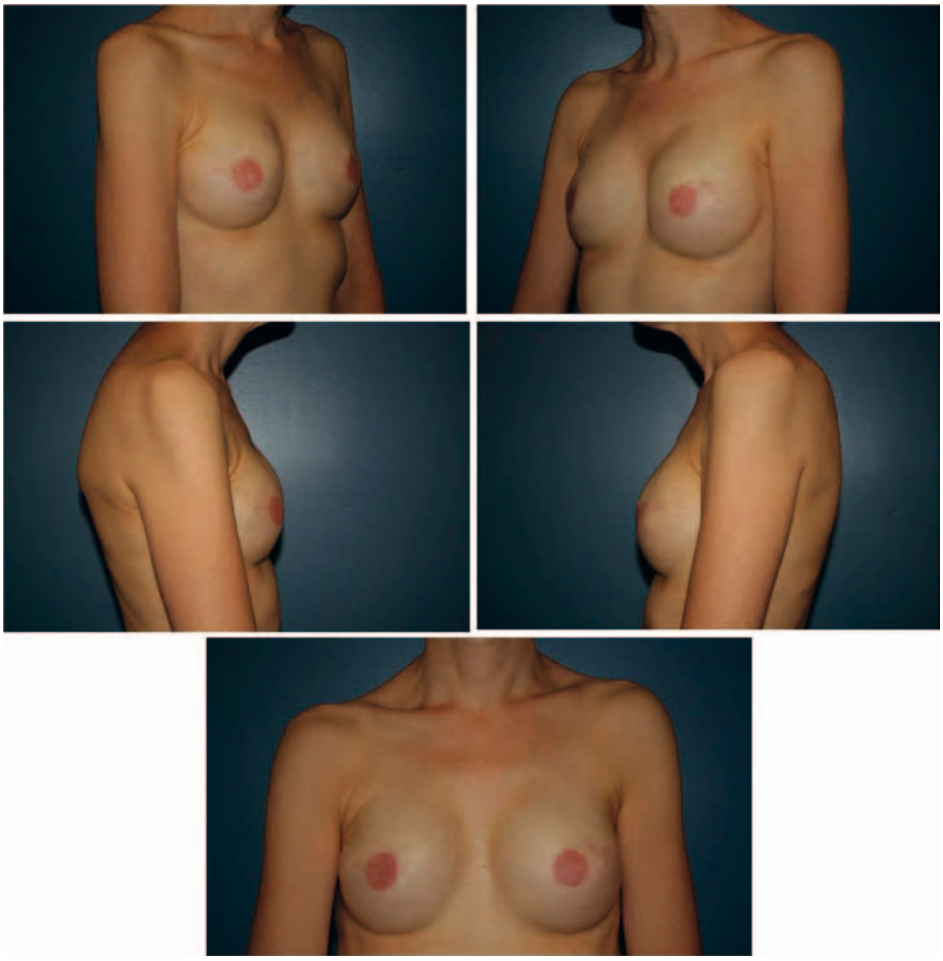

Figure 2. An example of a series of five postoperative standardized photographs (same patient as Figure 1) scored by the panel of blinded plastic surgeons

ages. Grades which ranged from 0 to 2 (0 being the worst outcome and 2 being the best outcome) were obtained from the judges and were averaged for tabulation and analysis. Furthermore, an overall aesthetic score was attained by totaling the subscale averages.

Statistical Analysis

For patient data, Chi-square analysis or Fisher's exact tests were used for categorical variables and Mann-Whitney *U* tests were used for continuous variables. For each of the picture grading subscales and the total sum of those subscales, absolute observed agreement as well as weighted Fleiss Kappa (κ) test statistics were calculated to assess interrator variability.

Table 1. Subscale Analysis of Breast Reconstruction

Subscale	Category 0	Category 1	Category 2
Breast volume	Marked discrepancy relative to perceived aesthetic ideal or contralateral side	Mild discrepancy relative to perceived aesthetic ideal or contralateral side	Symmetric volume
Breast contour	Marked contour deformity	Mild contour deformity or shape asymmetry	Natural or symmetric contour
Placement of implant	Marked displacement	Mild displacement	Symmetric or aesthetic placement
Scars	Marked deformity	Mild deformity	Aesthetically sound appearance
Lower pole projection	Marked discrepancy relative to perceived aesthetic ideal or contralateral side	Mild discrepancy relative to perceived aesthetic ideal or contralateral side	Symmetric or aesthetically sound
IMF definition	Marked discrepancy relative to perceived aesthetic ideal or contralateral side	Mild discrepancy relative to perceived aesthetic ideal or contralateral side	Symmetric or aesthetically sound

Modified from Garbay et al.[18]

Kappa's test statistic is defined as the "chance corrected measure of agreement" between observers. The weighted Kappa test statistic assigns different weights to ordered categories, adjusting for the level of disagreement (e.g. the difference between ratings '1' and '2' is considered smaller than between '0' and '2'). It is first calculated in pairs (5 raters; 10 pairs) and then averaged. The advantage of this technique is that is gives an insight into which raters gave comparable scores and which did not making it a more relevant statistical tool.[22] Based on the weighted κ score, the strength of agreement was defined as follows: almost perfect agreement: 0.81 to 1.00; substantial: 0.61 to 0.80; moderate: 0.41 to 0.60; fair: 0.21 to 0.40; slight 0.00 to 0.20; and poor: less than 0.00.[23] Statistical analyses were performed using SAS statistical software package version 11.2 (SAS Institute Inc., Cary, North Carolina, USA). Statistical significance was defined as two-tailed probabilities < 0.05.

RESULTS

Patient Demographics and Co-morbidities

Thirty-eight female patients aged 27 to 65 years, who underwent implant based breast reconstruction and who met the previously mentioned inclusion criteria were included in this study. Breast reconstruction with ADM was performed in 18 patients (mean age, 47.2±11.8 years) and without ADM in 20 patients (mean age, 43.9±7.7 years; Mann-Whitney *U* test, $p = 0.315$). In the ADM group, 14 patients (77%) underwent bilateral breast reconstruction compared to 12 (60%) in the non-ADM group (Chi-Square test, $p = 0.239$). Average BMI was 25.6±4.4 and 23.0±4.4 in both groups respectively (Mann-Whitney *U*

Table 2. Demographics and Co-morbidities of Patients with Implant-Based Breast Reconstruction

Variable	ADM	Non-ADM	p-value
No. of patients	18	20	
Reconstruction type			*0.239^*
Unilateral Reconstruction	4 (22.2%)	8 (40.0%)	
Bilateral Reconstruction	14 (77.8%)	12 (60%)	
Age (years ± SD)	47.2 ±11.8	43.9 ±7.7	*0.315#*
BMI (kg/m^2 ± SD)	25.6 ±4.4	23.0 ±4.4	*0.074#*
Smoking	2 (11.1%)	1 (5.0%)	*0.595**
Alcohol use	4 (22.2%)	14 (70.0%)	*0.003^*
Drug use	0	2 (10.0%)	*0.168**
Diabetes	0	1 (5.0%)	*1.000**
Hypertension	2 (11.1%)	2 (10.0%)	*1.000**
Peripheral vascular disease	0	0	*N/A*
Radiation	3 (16.7%)	0	*0.097**
Previous abdominal surgery	9 (50.0%)	12 (60.0%)	*0.536^*

ADM: Acellular Dermal Matrix.
Mann-Whitney U test; * Fisher's exact test; ^ Chi-Square test.

test, $p = 0.074$). AlloDerm® (n = 15) was the most commonly used mesh in the ADM group followed by SurgiMend™ (n = 3). Silicone implants were used in all cases except two in the ADM group where saline implants were employed; this was due to patient preference. In terms of co-morbidities, those who underwent radiation therapy prior to their procedure were all in the ADM group (n = 3, 16.7%; Fisher's exact test, $p = 0.097$). The rate of alcohol consumption was significantly higher in the non ADM group (70% versus 22.2%; Chi-Square test, $p = 0.003$). No statistically significant differences were observed for smoking, drug use, diabetes, hypertension, peripheral vascular disease and previous abdominal surgery between the two cohorts. Patient demographics and co-morbidities are summarized in Table 2.

Postoperative Complications

No statistically significant difference was observed in the overall complication rate between the ADM (n = 9 patients) and non-ADM groups (n = 6 patients) (Fisher's exact test, $p = 0.320$). In the ADM group three patients experienced two complications each (seroma and capsular contracture; infection and implant rippling; and implant extrusion and rippling). In the non-ADM group two patients experienced two complications each (both seroma and infection). The rate of seroma ($p = 1.000$), hematoma ($p = 1.000$), infection ($p = 0.595$), capsular contracture ($p = 0.170$), and implant related complications (rupture, N/A; extrusion, $p = 0.474$; rippling, $p = 0.328$; and malposition, $p = 1.000$) were not significantly different between the two cohorts.

Interobserver Agreement for Aesthetic Analysis

Absolute observed levels of agreement between the raters ranged from 77.9% to 87.1%. Chance-corrected, weighted Kappa's showed a moderate level of agreement in breast volume ($\kappa = 0.598$), breast contour ($\kappa = 0.532$), IMF definition ($\kappa = 0.505$), implant placement ($\kappa = 0.447$), and lower pole projection ($\kappa = 0.412$). Only evaluation of scar formation accounted for fair agreement ($\kappa = 0.387$) (Table 3).

Table 3. Interobserver Variability in Breast Reconstruction Ratings by a Panel of Five Independent Plastic Surgeons

	Observed Agreement	Weighted Kappa
Breast Volume	87.1%	0.598
Breast Contour	82.4%	0.532
Placement of implant	79.0%	0.447
Scars	77.9%	0.387
Lower Pole Projection	80.0%	0.412
Inframammary fold Definition	80.1%	0.505

Aesthetic Outcome

Mean aesthetic outcome was evaluated per patient for each of the variables (breast volume, breast contour, placement of implant, scars, lower pole projection, and IMF definition) by the independent reviewers using the subscale analysis shown in Table 1. The overall aesthetic score improved by an average of 12.1% when ADM was incorporated into the breast reconstruction procedure. The greatest degrees of improvement were observed in the scores for breast contour (35.2%), implant placement (20.7%), and lower pole projection (16.7%). These were followed closely by IMF definition (13.8%). There was no improvement in aesthetic scores for breast volume ($p = 0.991$) and scar formation ($p = 0.875$) between the two cohorts. Although the mean aesthetic scores all favor ADM use, only contour and implant placement were shown to have a statistically significant improvement ($p = 0.003$ and $p = 0.021$ respectively). None of the other subscales (lower pole projection, $p = 0.060$; IMF definition, $p = 0.130$) were shown to be statistically significant between the two groups. Despite this, overall aesthetic score did show a statistically significant improvement ($p = 0.022$) when ADM was used (Table 4). Of note, within the ADM group, the aesthetic outcome did not vary between patients who suffered complications and those who did not.

Table 4. Mean Panel Aesthetic Scores for Implant-Based Breast Reconstruction with and without ADM

	Volume (0-2)	Contour (0-2)	Implant placement (0-2)	Scars (0-2)	Lower pole projection (0-2)	IMF definition (0-2)	Subscale Total (0-12)
Without ADM (n = 20)	1.49	0.88	1.16	1.36	1.08	1.16	7.13
With ADM (n = 18)	1.49	1.19	1.40	1.34	1.26	1.32	7.99
Change in score	0	+35.2%	+20.7%	−1.5%	+16.7%	+13.8%	+12.1%
p-value[#]	*0.991*	*0.003*	*0.021*	*0.875*	*0.060*	*0.130*	*0.022*

ADM: Acellular Dermal Matrix. IMF: Inframammary Fold.

[#]Student's *t*- test.

DISCUSSION

Acellular Dermal Matrix (ADM) has now become common practice for use in tissue expander/implant based breast reconstruction.[24] It can expand the submuscular pocket volume allowing for immediate implant placement.[5] Breuing and Warren[25] demonstrated improved volume, symmetry and lower pole projection when ADM was used to create a subpectoral pocket to enclose the implant, and as a sling to anchor the lower pole of the pectoralis major muscle. Zienowicz and Karacaoglu[5] experienced similar success reporting no rippling, symmastia or bottoming-out deformity in their case series. ADM has also been used as an inferolateral hammock to create an implant pocket and permit better control of the implant with good outcomes and few complications.[9] In patients with poor pectoralis major muscle coverage ADM can be used in an onlay fashion to cover the implant which has shown to improve breast shape, soft tissue padding and stability while reducing the implant visibility and rippling.[26]

Although ADM use is associated with high patient satisfaction, surgical success, and low revision rates, it is an expensive material (with costs fluctuating depending on size and thickness).[13,14,27] As such, superior aesthetic outcome should be justified. Salzberg[28] reported that using Alloderm® in expander/implant based reconstruction proved to be less costly than a TRAM flap. A cost analysis by Jansen and Macadam[15] found that both baseline and expected costs where lower when direct-to-AlloDerm® reconstruction was used compared to two-stage non-AlloDerm® reconstruction (baseline: $10,240 versus $10,584; expected: $10,734 versus $11,251). In contrast Hartzell et al.[14] questioned the widespread use of ADM in self-pay patients despite promising cosmetic outcomes. In this study, the aesthetic outcome of tissue expander/implant based breast reconstruction with ADM was investigated for justification of its use despite the high costs. To our knowledge this is the *first* study to provide an objective assessment of the cosmetic result evaluated by a panel of blinded plastic surgeons when using ADM in breast reconstruction.

Aesthetic improvements were observed in all subscales as well as for the total aesthetic score in the ADM cohort. The greatest cosmetic improvements were demonstrated for breast contour, implant placement and lower pole projection. There was no advancement in cosmetic result for breast volume and scars. Similar findings were reported by Nguyen et al.[29] in their retrospective comparative analysis of aesthetic outcome with ADM use. Despite this, none of these improvements were statistically significant except for breast contour and implant placement. Regardless, there was significant enhancement in overall aesthetic score when ADM was incorporated in breast reconstruction. These results suggest that ADM use in implant based breast reconstruction does indeed contribute to a major difference in the overall aesthetic outcome, justifying its added expense. A view that is echoed by another study that found ADM to improve cosmetic results.[29] Furthermore, based on our findings, the added cost for ADM use is warranted in patients with medium or small sized breasts who may lack a sufficient soft tissue envelope or have an atrophic pectoralis major muscle. Moreover, it can prove useful in women with grade 1 to 2 ptosis.[1,10] In addition, it has added benefits in revision surgery when addressing various breast deformities and so should be considered.[12,13] Finally, our analysis suggests that ADM use is safe and does not contribute to an increased incidence of postoperative complications; similar to a previously reported study including 19,100 cases.[30] It may be cost-effective in the long-run by reducing the number of revision procedures as well as operative time.

In general, the process of evaluating breast reconstruction from the aesthetic perspective can be highly subjective.[20] Bias may exist when recorded by the operating surgeon together with the patient.[31] However, the value of photographs for evaluation of breast aesthetics is validated by results comparable to physical examination.[32] This is all the more true when photographs are presented in digital form and displayed on a computer monitor.[33] Encouraging results have been ascertained using this approach, but there are limitations. Some anatomical landmarks may not be clearly visible; moreover, many of them rely a great deal on the anatomy of the nipple-areola complex which may not be reflective of the various independent features of the breast mound.[31] In our study, to compare the aesthetic outcome in breast reconstruction with and without the use of ADM, a subscale analysis using pre and postoperative digital images was used. This approach to picture grading offers a more objective assessment which is optimized further using a panel of blinded plastic surgeons.[20]

Visual assessment of the aesthetic appearance of the breast is typically reported using a gradation scale that is qualitative and subjective.[31] The use of common scales consisting of four grades of cosmetic change ($\kappa = 0.21$ to 0.31) have demonstrated substantial variability.[21] As such, it has been recommended that subscales with more specific criteria

for each of the aesthetic variables be used.[21] The subscale analysis implemented in our study was adapted from those used by Garbay et al.,[18] Carlson et al.,[19] and de Blacam et al.[20] and advocated by Lowery et al.[21]

A lack of agreement between different raters can contribute to certain disadvantages when subjective scales are used.[34] This can lead to variable internal consistency and reproducibility calling for a standardized means of evaluating cosmetic outcome.[31] This need is demonstrated in one study where using four-point subscales resulted in significantly greater variations in aesthetic scoring.[35] In another study, a global five-point scale contributed to better internal consistency but poor interobserver agreement among surgeons.[36] This is in contrast to findings by Visser et al.[37] who showed good inter-rater agreement among five observers as evidenced by high intraclass correlation coefficient values. In the current study, inter-rater reliability scores using five observers showed a moderate level of agreement which is superior to identical plastic surgery articles using two observers and the same scoring system.[21,38-40] This was perhaps due to an increase in the number of data points improving their distribution and allowing for more valid analyses. A notion reinforced by the fact that even though the raters were trained at different institutions they had similar outcome preferences. Furthermore, although all experienced, variation in the level of experience did not affect the final outcome.

This study is not without its limitations. Although data obtained from a panel of blinded surgeons can decrease variability, it does not improve accuracy.[31] Moreover, the female breast is a three-dimensional gland, which may limit rating aesthetic appearance using two-dimensional photographs. This could perhaps be overcome by the evaluation of aesthetic outcome in future studies using three-dimensional imaging. This would permit accurate assessment of breast volume, contour, symmetry, size, and surface area.[31] Three-dimensional images can be easily created using laser scanning and digital photography.[20] This could potentially aid objective outcomes analysis in addition to proving useful in preoperative surgical planning. In addition, inclusion of patient perspectives and satisfaction scores should be considered for future studies. Furthermore, our small sample size may have affected the statistical power of our analyses. The use of representative cases with appropriate matching, and inclusion and exclusion criteria only may have limited the number of patients included in this study but served to provide more accurate analysis. Other limiting factors may include the use of both unilateral and bilateral cases, the fact that all cases that had undergone radiation in our patient cohort were in the ADM group only, and that type of mastectomy did not serve as a means to exclude patients from our analyses. These may serve as possible sources of confounding that could have affected cosmetic outcome. However, these cases were included to increase the sample size of our study population. Therefore, a larger prospective study is needed to give more

conclusive assistance to plastic surgeons contemplating the use of ADM in implant based breast reconstruction.

CONCLUSIONS

The best breast reconstruction technique is one that is able to produce high patient satisfaction and aesthetic outcomes while minimizing postoperative complications and proving to be cost effective. In our study, we have demonstrated increased mean aesthetic scores in ADM-assisted breast reconstruction across most graded subscales as well as for total aesthetic outcome; indeed, a statistically significant improvement was demonstrated in the overall aesthetic score between the ADM and non-ADM cohorts. This suggests that aesthetic outcome alone may justify the added cost of ADM use. Moreover, ADMs are supposed to have numerous pros which can render them cost-effective in the long-term. Larger prospective studies are needed to provide plastic surgeons with more definitive guidelines for ADM use.

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Chapter 7

General Discussion

This thesis addresses the technical, psychological, and economic aspects associated with acellular dermal matrix (ADM) use in post-mastectomy breast reconstruction. In this chapter, the findings of each individual study will be correlated to the aims of this thesis as outlined in the general introduction. Furthermore, the strengths and weakness of our methodological approaches will be presented, and the results and conclusions will be outlined in the context of the current literature. Finally, an overall conclusion and recommendations for future research and clinical practice will be made.

MAIN FINDINGS

Research Question 1: What are the best approaches when using ADM in post-mastectomy breast reconstruction to optimize outcomes and when addressing various breast deformities?

Our experiences using ADM in breast reconstruction in terms of the best approaches for optimizing aesthetic outcome and when addressing the various complications necessitating revision surgery are presented in **chapter 2**. ADMs can be used to either create the implant pocket in single-stage reconstruction or to create the inferolateral portion of the tissue expander pocket in two-stage reconstruction. The implant or a tissue expander is placed in between the pectoralis major muscle which covers the superior and medial poles of the prosthesis. The exposed inferior and lateral poles can be covered with subcutaneous tissue or by elevating the serratus anterior or pectoralis minor muscles.

When incorporating ADM, the best outcomes are attained when a single, thick layer of the product is used. In addition, better results are seen in patients who have an adequate skin envelope. An ADM sling or hammock can be used to secure the lower pole of the pectoralis major muscle by attaching it to the released pectoralis major superiorly, the chest wall inferomedially, and the serratus anterior flap laterally. The tissue expander or implant is then placed in the subpectoral pocket, covering the superior and medial poles of the prosthesis following irrigation of the pocket with sterile saline and an antibiotic (either bacitracin or a combination of cefazolin and gentamicin depending on regional protocols). The ADM is then secured by suturing it with a running suture to the chest wall and to the free edge of the pectoralis with the dermal side facing the mastectomy skin flaps, because it has a smooth surface with a tendency to absorb blood and therefore is likely to revascularize.[1] It is also potentially more seroma forming and therefore should be kept away from the implant.[2] The mastectomy skin flaps should be as thick as possible; they are trimmed and then closed in 2 layers. Textured implants should be avoided as they can cause rippling.[3,4] Al-Sabounchi et al. reported that using textured implants led

to a very high incidence of skin rippling and wrinkling (37.5%) in a series of 49 women undergoing aesthetic breast augmentation.[5]

Breast deformities including contour irregularities and implant malposition can be addressed by ADM. The use of a periareolar incision provides precise access to the breast in revision surgery. When addressing contour irregularities, it is important that a single layer of ADM be placed in an onlay fashion between the prosthesis and the soft tissue. The parachuting technique assists in proper placement of the graft. For implant malposition, the ADM is secured to the chest wall and capsule, and placed over the areas of capsulorrhaphy. Tension-free closure will reduce the incidence of dimples and bands. By decreasing the inflammatory changes leading to capsular contracture and capsule formation, ADMs may alleviate the development of complications. ADM use is a safe alternative for the correction of breast deformities following reconstructive and aesthetic surgery.

Research Question 2: What are the most commonly used biologic meshes in post-mastectomy breast reconstruction, and how do they compare in terms of physical characteristics, biomechanical properties, level of sterility, and known complications?
A direct comparison of the most commonly used ADMs in reconstructive breast surgery was performed in **chapter 3** including physical characteristics, level of sterility, maximum load sustained (N), stiffness (N/mm), and tensile strength (N/cm). Furthermore, a comprehensive review of the literature was done detailing known complications. In **chapter 5** plastic surgeons reported that AlloDerm® (LifeCell Corp., Branchburg, NJ) was by far the most commonly used biologic mesh in breast reconstruction followed closely by Strattice™ (LifeCell Corp., Branchburg, NJ). This was attributed to adequate long-term experience and has been well described in the literature. In terms of biomechanical properties, Strattice™ and Permacol® (Covidien, Dublin, Ireland) are able to sustain the greatest maximum loads (N), and have the highest stiffness (N/mm) values and tensile strength (N/cm). AlloDerm®, DermaMatrix® (MTF/Synthes CMF, West Chester, PA) and FlexHD® (MTF/Ethicon, Inc., Somerville, NJ) are derived from human tissue while Strattice™ (porcine), SurgiMend™ (TEI Biosciences Inc., Boston, MA) (fetal bovine dermal collagen) and Veritas® (Synovis Life Technologies Inc., St. Paul, MN) (bovine pericardium) come from animal sources. All the meshes evaluated in **chapter 3** are sterile when opened except for AlloDerm® and FlexHD®. Analysis of physical characteristics showed that they are non-cross linked and composed primarily of collagen except for Strattice™ whose components are undisclosed.

A review of complications revealed inconclusive data concerning complications. The most commonly reported complications included seroma, infection and implant failure but these were associated with pre-existing co-morbidities such as high body mass

index, smoking and larger breasts or implant size. Moreover, there is a general consensus that AlloDerm® has no added benefit in irradiated patients. However, some authors are adamant that it is radiation resistant. Despite the abundance of literature describing the different properties and characteristics of ADM, long-term follow up is still required to determine the longevity of the data.

Research Question 3: Following analysis of the ACS-NSQIP database is there a difference in post-operative complication rates in patients undergoing breast reconstruction with and without the use of ADM?

In **chapter 4** we analyzed complication rates following implant based breast reconstruction in two cohorts; with and without ADM, and determined whether demographics and co-morbidities affected outcomes. Thus far, studies investigating complication rates with ADM have been single institution, non-randomized and consist of a small patient population. In our study, we utilized the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database which quantifies 30-day risk-adjusted surgical outcomes in over 200 sites. This database offers a potential opportunity for analysis of nationally validated, multicenter data in a large patient cohort.

Nineteen thousand, one hundred patients were included in our study. There was no statistically significant difference in overall complication rate between the ADM and non-ADM groups ($p = 0.396$). A total of 5.3% (n = 175) and 4.9% (n = 776) experienced at least one complication in the ADM and non-ADM groups, respectively. Several co-morbidities were associated with an increased risk of complications primarily in the non-ADM group; BMI served as a predictor for superficial surgical site infection (SSI; $p = 0.001$) and graft/prosthesis/flap failure ($p = 0.01$). Both smoking and diabetes were associated with an increased risk of wound disruption ($p < 0.001$ and $p = 0.02$, respectively). Smoking alone was associated with graft/prosthesis/flap failure ($p < 0.001$) and chronic steroid use was linked with sepsis ($p = 0.04$). In the ADM group, BMI ($p = 0.01$) and diabetes ($p = 0.02$) contributed to the likelihood of wound disruption, BMI ($p = 0.01$) and alcohol consumption ($p = 0.04$) were associated with sepsis, and chronic steroid use lead to increased incidence of superficial SSI ($p = 0.04$). In both the ADM and non-ADM cohorts, a higher BMI raised the likelihood of wound complications ($p = 0.04$ and $p = 0.02$ respectively). Based on the data from this study, incorporating ADM into tissue expander/implant based breast procedures is not associated with increased complications compared to performing these procedures without ADM. Furthermore, several co-morbidities serve as significant predictors for negative outcomes in both groups. This emphasizes the importance of the patient selection process prior to performing breast surgery.

Research Question 4: What are the current trends in terms of plastic surgeon experience when using ADM in reconstructive breast surgery?

In **chapter 5** we looked at the collective experience of plastic surgeons' use of ADMs in reconstructive breast surgery using an internet based survey. Three hundred-and-sixty-one (99%) physician responses (members of the American Society of Plastic Surgeons) were analyzed. Three hundred and four of these plastic surgeons (84.2%) stated that they routinely using used ADM in breast reconstruction. A total of 69.5% of participants claimed to have been using ADM in breast procedures for the last 6-10 years. As previously reported, the most commonly used ADM in practice was AlloDerm® (71.6%) which was ascribed to its extensive presence in the literature as well as long-term surgical experience. The surveyed plastic surgeons chose to use ADMs in their reconstructions for better control of the implant pocket (81.4%), improved aesthetic outcomes (70.1%), a quicker expansion (43.9%), as well as for reduced incidence of capsular contracture and breast deformities (40.2% and 25.6% respectively). Most of the respondents (81.5%) did not use ADM for nipple reconstruction. Ninety-five percent of participants used drains together with ADM in breast reconstruction with 57.5% of the respondents claiming to have left drains in for a longer period of time when ADM was used. A majority (87.8%) routinely used antibiotics in the post-operative period most frequently for 6-10 days (45%). When asked about whether ADM contributed to an increased rate of infection, most participants (57.4%) said that it remained unchanged. In the event that complications did occur, the most common were seroma (70.9%) followed by surgical site infection (16%), and wound dehiscence (9.4%). At total of 79.7% of respondents stated to have used ADM in previously radiated patients, of these, 37.4% experienced no change in complication rates and only 24.3% reported an increase in complications. Those that reported an increased rate of complications implicated seroma (n = 45) and surgical site infection (n = 28).

When asked about patient satisfaction, 86.4% reported that patients were satisfied with the aesthetic outcome, and 77.9% claimed that patients rarely come back for further revisions. Finally when questioned about current evidence for the use of ADM in plastic surgery 38.7% said using ADMs is safe and effective in preventing complications and 28.4% reported that the evidence against the use of ADM is weak. Statistical analysis revealed a positive correlation between ADM use, age ($p = 0.01$), practice setting ($p = 0.036$) and the number of years in practice ($p = 0.008$).

Of the 57 respondents that did not use ADMs in breast reconstruction, the most popular reasons for this were high cost (n = 15), surgeon preference (n = 10), and increased complications with previous experience (n = 11). The results of this study indicate that most responding plastic surgeons use ADM in breast reconstruction for both imme-

diate and staged procedures. They believe it to be safe and effective in preventing complications.

Research Question 5: Are the high costs of incorporating ADM in breast reconstructions justified by improved aesthetic outcome?

Justification for the use of ADM in breast reconstruction, despite its high cost, is examined in **chapter 6**. To date, enhanced aesthetic outcome with ADM use has been based solely on surgeon perspective. In our study we provide the first objective assessment of aesthetic outcome by a panel of experienced, blinded plastic surgeons. Thirty-eight patients were included, of these, 20 underwent breast reconstruction without ADM and 18 with ADM. Mean age (43.9±7.7 years and 47.2±11.8 years respectively, $p = 0.315$) and BMI (23.0±4.4 and 25.6±4.4 respectively, $p = 0.074$) were identical between the two cohorts. The most commonly used mesh was AlloDerm® (similar to **chapter 5**). Comparison of overall complication rate showed no statistically significant difference between the non-ADM and the ADM groups ($p = 0.320$) reaffirming our findings in **chapter 4**.

Aesthetic scores were higher in the ADM group across most subscales of analysis with the greatest improvements observed in breast contour (35.2%, $p = 0.003$), implant placement (20.7%, $p = 0.021$), lower pole projection (16.7%, $p = 0.060$), and IMF definition (13.8%, $p = 0.130$). Furthermore the overall aesthetic score improved by 12.1% ($p = 0.022$). Despite these improvements, except for breast contour and implant placement, the findings were not statistically significant. No improvements in the aesthetic outcome were noted for breast volume ($p = 0.991$) and scar formation ($p = 0.875$). Within the ADM group, there was no variation in cosmetic result between patients who suffered at least on complication and those that did not.

Interobserver scoring ranged from 77.9% to 87.1% based on absolute observed levels of agreement. Weighted Kappa's showed a moderate level of agreement in breast volume ($\kappa = 0.598$), breast contour ($\kappa = 0.532$), IMF definition ($\kappa = 0.505$), implant placement ($\kappa = 0.447$), and lower pole projection ($\kappa = 0.412$). These outcomes are superior to those in previously published plastic surgery photographic analysis studies.[6-9] Data from this study suggest that ADM use is associated with improvement of aesthetic scores, a notion that is reinforced by the statistically significant improvement in overall aesthetic score ($p = 0.022$). As such, aesthetic outcome alone may justify the added expense. Furthermore, ADMs have many advantages aside from their cosmetic effects. They can be helpful in women who do not have large breasts that may lack the necessary tissue coverage. In addition, it has proven benefit in addressing complex breast deformities. Despite the outcome of this study, the lack of statistical power necessitates the need for further long-term studies.

TECHNICAL ASPECTS

Methodological Considerations

Data for the technical aspects of acellular dermal matrix (ADM) use in post-mastectomy breast reconstruction were ascertained from surgeon experience at the Beth Israel Deaconess Medical Center, a comprehensive review of the literature, analysis of a national database, a survey of plastic surgeons performing these procedures, and photographic analysis by a panel of experienced blinded plastic surgeons. Statistical analyses were performed using SPSS (IBM Corporation, Armonk, NY). These methods are not without their limitations. In **chapters 2 and 3**, extensive literature reviews were performed. The benefits of this method include versatility in terms of type and depth of information included, collection of a large amount of data, and provision of a conceptual framework for further planning. However, it is restricted because the information obtained is about what happened in the past, is not from our own experience and therefore it limits the provision of data about current actual "behavior". Ultimately the pros outweigh the cons.

In our analysis of the ACS-NSQIP data set, we observed lower complication rates than previously reported. This could be attributed to the large size of our sample population and also because not all complications traditionally reported in the plastic surgery literature such as seroma formation were included in the database. The fact that the information ascertained is from a multi-intuitional database is unique and could perhaps overcome this issue. Furthermore, differences in the interpretation of the definition of various complications may also serve as a source of confusion. For example, seroma formation is absent from the data set which may affect the overall complication rate. A potential resolution to this issue may be the inclusion of disease- and operation-specific variables. This would permit better predictions of undesirable outcomes.[10,11] It was suggested by Birkmeyer et al.[12] that updated versions of NSQIP take the form of a series of parallel specialty-specific modules.

With only a 30 day postoperative window available to determine postoperative complications, it is impossible to assess long term outcomes related to aesthetic results or quality of life. Moreover, it is only representative of outcomes from academic medical centers and does not take into account the private clinics and community hospitals that also perform breast reconstruction. Despite these limitations, data collection and input for NSQIP is standardized, reducing the extent of observer bias in reporting and recall bias that may be associated with retrospective single institution studies. In addition, it provides sufficient statistical power for logistic regression analyses that is not always feasible in smaller series. Furthermore, the NSQIP database has been used previously for other plastic surgery breast procedure related outcome studies.[11,13-16] In **chapter 4**, categorical variables were analyzed using chi-square and continuous variables using

a t-test. Statistical significance was defined as $p < 0.05$. To determine whether various demographics and co-morbidities contributed to complications in both the ADM and non-ADM groups, a multivariate logistical regression analysis was performed.

With regard to data collection in **chapter 5**, there may also exist some discrepancies. Although a large number of plastic surgeons completed the survey, 57 did not incorporate ADMs in their breast procedures. This could be the result of voluntary sampling of participants which in turn may have resulted in bias toward ADM use. As such, this might lead to an inaccurate representation of the plastic surgeons that do not use ADM in their practice. Furthermore, use of the term "breast reconstruction" is very general and may have been interpreted as reconstruction after mastectomy only and not aesthetic breast surgery. Also, with survey studies recall bias may be a factor. This could potentially be overcome by our large sample size and exclusion of those who did not use ADM.

Interpretation of Results

Technique

In **chapter 2**, we discussed the most reliable approaches for ADM use in reconstructive breast surgery as well as for the correction of various breast deformities. ADMs can be used to create an implant pocket (single stage) or to cover the inferolateral portion of a tissue expander (two stages).[17] ADM use has the advantages of adequate tissue coverage, creation of a larger implant pocket, control of the inframammary fold, reduction in the incidence of capsular contracture and of postoperative pain by limiting dissection, and shortening the reconstructive process. ADM also improves breast contour. It reduces the extent of dissection required and aids in correction of implant malposition.[18]

Complications and Baseline Patient Co-morbidities

As shown in **chapter 3**, mesh type used can also potentially affect the final outcome of breast reconstruction. Different manufacturers produce various mesh types with distinct properties. AlloDerm® and DermaMatrix® have both been described being well-incorporated with neovascularization and comparable complication rates.[19] Strattice™ (which is stronger and thicker than AlloDerm®) contributes to a potentially lower incidence of complications.[20,21] FlexHD® on the other hand demonstrated greater monocyte and macrophage activation but similar integration to AlloDerm® in vitro.[22-24] Jenkins et al.[25] reported less tissue incorporation with non-fenestrated cross-linked matrices (CollaMend™, CR Bard, Inc–Davol, Inc) than fenestrated cross-linked matrices (CollaMend™ FM, CR Bard, Inc–Davol, Inc) but maintained that adhesion scores were similar. Alike, other studies showed that cross-linked and non cross-linked biologic meshes had comparable strength and integrity.[26,27]

In general, the overall complication rate reported in **chapter 4** was less than in previously published single institution reports. As noted, perhaps this is because seroma formation was not included for analysis as a limitation of the data set.[28-31] Nevertheless, we showed that there was no significant difference in complication rates between the ADM and non-ADM cohorts which is supported by other studies that revealed similar outcomes.[32-34] Analogous findings were reported in **chapter 5** where only 26.4% of our survey participants reported an increase in postoperative complications.

Our study in **chapter 4** is unique in that it is the first multi-institutional data set analyzed for this purpose. Different patient co-morbidities contributed to increased complication rates in our ADM cohort including higher BMI, diabetes, alcohol consumption, and chronic steroid use. This is corroborated by data from previous studies.[35-44] Although these findings are not exclusive[45-48] this is the first time that it has been reported in a patient population undergoing tissue expander/implant based reconstruction with ADM. Interestingly, smoking and exposure to radiation did not affect outcomes in our ADM cohort. Thus far, the effect of ADM on radiation has yielded inconclusive results.[34,49] Akin to smoking, radiation 90 days before surgery was not connected with increased post-operative morbidity in our ADM cohort which is supported by Nahabedian[49] who showed that irradiation had no significant effect on infection rate when ADM was used. This is confirmed by the opinions of our surveyed plastic surgeon population in **chapter 5**, 37.4% of which reported no change in complication rate and equal numbers suspecting either an increase (24.3%) or decrease (23%). In **chapter 2** we observed that ADM-assisted reconstruction seemed to have improved resistance to radiation or at least have comparable complication rates.[18]

There is limited data on the relationship of ADM with drains and antibiotic use following reconstructive breast surgery. In our surveyed population **(chapter 5)**, 94.6% of responding plastic surgeons incorporated drains into their breast procedures in the presence of ADM, conversely, drains were kept in for a longer duration than normal. This was akin to a study by Collis et al.[50] who reported significantly longer duration of drains in situ when using ADM. With regard to antibiotic use, 87.8% of our participants routinely employed antibiotics in the post-operative period. The number of days of antibiotic use varied from less than 5 days (31.5%), 6-10 days (45%), 11-14 days (15.8%), to more than 14 days (7.7%). Avashia et al.[51] demonstrated a significant reduction in infection rate following implant-based breast reconstruction with ADM when antibiotics were administered for at least 48 hours.

The use of ADM in reconstruction of the nipple-areola complex (NAC) has not been widely documented. Our survey demonstrated that only 18.5% of respondents used

ADM for NAC reconstruction. SurgiMend™ was found to enhance nipple projection and bulk in staged nipple reconstruction while preserving the integrity of the capsule and providing adequate vascularization.[52] Similarly, studies by Garramone and Lam[53] and Nahabedian[54] demonstrated favorable outcomes. To the contrary, Israeli[55] and Hartzell et al.[56] suggested limited long-term success and possible contamination of the graft by organisms in the mammary ducts.

PSYCHOLOGICAL ASPECTS

Methodological Considerations

An internet-based survey was used to obtain data on how plastic surgeons using ADMs perceived their patient satisfaction. General bias and recall bias were taken into consideration for the survey results. From a psychological perspective, cognitive dissonance may have played a role in plastic surgeons' attitude toward use of ADM in breast reconstruction and the type of mesh used. To clarify, cognitive dissonance is the discomfort experienced while having two or more conflicting opinions at the same time. This may be due to inconsistencies in an individual's own attitudes, beliefs, and actions resulting in a need to avoid this dissonance by altering one's own behavior.[57] Plastic surgeons that have used ADMs for a longer period of time were more likely to respond to the survey and justify their choice of treatment, consequently, affecting their response to our questionnaire.

Traditional methods for the assessment of patients' satisfaction and quality of life include the Breast Q patient questionnaire Health-Related quality of life (HR-QOL) and the European-Quality of Life (EuroQol) questionnaires.[58,59] However, **chapter 5**, focused specifically on the application of ADM for breast reconstruction application in the general practice population; and thus, these tools were not used. However, our results are similar to those of previously used by Breast Q patient satisfaction questionnaires for ADM use in breast reconstruction.[58] Patients undergoing primary reconstruction will undoubtedly compare their reconstructed breast(s) to their natural breast(s) and might be more critical which can ultimately affect the outcome of a satisfaction study. It is widely reported however, that reconstruction following mastectomy results in more acceptable improvements in overall satisfaction.[60-62]

Health-related quality of life (HR-QOL) refers to physical condition and well being that affects the daily lives of individual patients. It specifically relates to the health domain of the patients' existence by evaluating measures of patient preferences and values, health perceptions, symptoms, and function.[63] These factors are converted to numeric values typically ranging from 0 (mortality) to 1 (perfect health/patient satisfaction). The European-

Quality of Life (EuroQol) assessment tool was the result of the joint development of the European Quality of life group.[64] It was developed as a standardized non-disease-specific instrument for describing and giving value to health-related quality of life.[64] This tool was intended to complement other forms of quality of life measures. It was designed as a self-completion survey with four instrument components: 1. Description of the respondent's own health; 2. Rating of own health by means of visual analogue scale; 3. Valuation of standard set of health states; and 4. background information about respondents.[65-70]

Regardless of the methods used to evaluate patient satisfaction, one study determined that even the best patient-reported outcome measures fail to take into account all key elements of surgery-specific and psychometric issues of oncologic breast surgery patients.[71] Another study demonstrated that existing approaches for judging aesthetic outcomes following breast reconstruction differ significantly and suggested that outcome reporting is inconsistent. To more thoroughly assess outcomes after breast reconstruction and informed decision-making, a valid patient centered approach is needed.[72-74]

To assess the aesthetic outcome using ADM on the final result of breast reconstruction, a photographic analysis was undertaken in **chapter 6**. The premise of judging the cosmetic result following reconstructive breast surgery can be somewhat subjective; in addition it fails to eliminate potential bias.[6,75] It will always be an indefinable outcome due to the differences that exist in terms of ethnicity and culture which may ultimately influence personal preference. The physical components that define breast appearance can serve as tools to better evaluate the aesthetic outcome and permit objective analysis. This is typically done using a gradation scale that is both qualitative and subjective.[75] Studies have demonstrated substantial variability when a scales consisting of four grades of cosmetic change were used.[76,77] As such, it is important that an evaluation method be developed that is practical and exhibits high reliability and reproducibility.[75] A detailed, qualitative scale with standardized terminology on which quantitative calculations based on digital two-dimensional images are ascertained is ideal and would be both reliable and reproducible.[75] Our subscale analysis was performed using pre and postoperative digital images adapted from those implemented by Garbay et al.,[78] Carlson et al.,[79] and de Blacam et al.[6] This approach offers a more objective assessment that is enhanced using a panel of five blinded plastic surgeons. For patient data, Chi-square analysis or Fisher's exact was used for categorical variables and Mann-Whitney *U* tests were used for continuous variables. Statistical significance was defined as $p < 0.05$.

Interrater variability can also be an issue when evaluating images. Marked disparity between observers' opinions can result in variable internal consistency and reproducibility once again emphasizing the need for a standardized rating system.[75,80-82] To this

point, one study reported significant differences in aesthetic scoring when four-point subscales were used.[83] This is emphasized in another study, where a global five-point scale demonstrated better internal consistency but poor interobserver agreement among surgeons.[84] In our study interrater reliability scores were superior to similar studies in the plastic surgery literature.[7-9,76]

Although a panel of blinded plastic surgeons can help to alleviate variability it does not necessarily improve accuracy.[75] Three-dimensional imaging can provide a solution to this limitation by allowing more accurate assessments of the various anatomical features of the breast; however, considerable development using this technology is still needed.[75,85,86] Without the availability of an absolute standard for evaluation of aesthetic outcomes, quantitative comparative assessment by patients and their treating physician in conjunction with patients' satisfaction is useful in the identification of factors that may affect a woman's quality of life following breast reconstruction. The presence of a highly reliable outcomes scale would provide better comparisons not only of cosmetic results but also of cost-effectiveness among surgical techniques. Such an outcome scale would be pertinent in breast reconstruction as well as other plastic surgery procedures.[75]

Interpretation of Results

Patient Satisfaction

Patient satisfaction varies from one individual to another; some patients may be pleased with what a plastic surgeon would consider a suboptimal result while others may criticize what is deemed a technically outstanding outcome. Timing and laterality of a patient's breast reconstruction may largely serve as their points of reference. Their personal expectations will most likely determine whether they will opt for a revision procedure or not. In **chapter 5** a majority of the responding plastic surgeons (86.4%) claimed that their patients were satisfied with the final outcome of their reconstructed breast when ADMs were used. Moreover, most participants (77.9%) reported that their patients rarely ever came back for a revision procedure. In the event that a patient was unsatisfied with the result of their breast surgery, the most frequently performed secondary procedures were reportedly symmetry procedures (53.9%), fat grafting (19.5%), and capsulotomy/capsulectomy (17.9%). The findings of our study are corroborated by Rinker et al.[87] who reported that a cohort of 16 patients that underwent tissue expander based breast reconstruction with dermal autografts, 88% (n = 14) were "very satisfied" with their outcome. However, in a prospective case series by Wu et al.[58] satisfaction in patients undergoing breast reconstruction with ADM using a modified version of the Breast Q patient questionnaire was similar to that of non-ADM patients.

Characteristics of Mesh Use

The most popular mesh reportedly being used in practice is AlloDerm®. This support for AlloDerm® use was attributed by most surgeons to its published long-term outcomes, safety, and efficacy in the literature. Statistical analysis revealed that experienced plastic surgeons were more likely to incorporate ADM into their breast reconstructions to obtain the desired outcome. Interestingly, in the 31-40 age group and those less than 5 years in practice, 100% of participants used ADM. This may be indicative of a trend toward changes in practice patterns where recent graduates are more familiar with these biologic meshes during their training and thus feel more confortable incoprorating them into their practice than surgeons surgeons who did not use ADMs in their training.

Aesthetic Justification

The final appearance of a reconstructed breast can have implications on a patient's psychological, social, emotional, and functional status.[88] Its positive effects on sexuality, self esteem, and body image are well documented.[88-91] There is strong support in the literature that reconstruction following mastectomy is a vital determinant of a patient's long-term health and well being.[88] It is therefore important that the aesthetic outcome of breast reconstruction be pleasing to the patient. It has been widely suggested that ADMs help to improve aesthetic outcome but are expensive. In **chapter 6** mean aesthetic scores of breast reconstruction with ADM were determined. Cosmetic enhancements were seen in most of the analyzed subscales specifically breast contour, implant placement, lower pole projection, and IMF definition as well as in the total aesthetic outcome with statistical significance in breast contour, implant placement, and overall aesthetic outcome. This data suggests that the aesthetic improvements produced by incorporating these meshes may be sufficient to justify their high costs.

This, of course, does not take into account the other advantages ADMs provides in terms of tissue coverage in patients with small or medium sized breasts or poor pectoralis major muscle coverage;[18,92] They have also achieved well documented benefits in the management of complex breast deformities.[93,94] Gamboa-Bobadilla[4] reported that the incorporation of ADM enhanced breast shape, soft tissue padding and stability while also reducing the implant visibility and rippling. Baxter[95] employed it for the management of symmastia and implant malposition with no graft-related complications. Such enhanced outcomes will likely result in high patient satisfaction and surgical success ultimately leading to improvements in the patient's psychological well being.[56,93,96] More definitive guidelines for ADM use, however, need to be established to provide plastic surgeons with clearer indications for its use.

ECONOMIC ASPECTS

Methodological Considerations

It is important when performing economic health evaluation to take into account cost and benefit. From a community perspective, the association between cost and benefit should be reasonable to warrant the expense. It is no secret that ADMs are costly and can increase economic burden to the health care system. It is therefore important to measure their cost-effectiveness and to evaluate whether their costs are worth the benefit. This can be looked at from different viewpoints: society, the primary payer, or the hospital.[97] When conducting cost analyses, a societal perspective is recommended by the Panel on Cost-Effectiveness in Health and Medicine which takes into account those affected by a particular intervention and whether they are indeed the ones who received the intervention.[98] Pooling results from multiple randomized controlled trials is the gold standard when evaluating the clinical effectiveness of a new intervention prior to an economic analysis. Due to the scarcity of such trials that compare the cost benefits of surgical interventions, data is obtained from lower levels of evidence such as observational studies. With regard to breast surgery in particular, several factors should be considered including quality of life, patient satisfaction, aesthetic outcomes, and complication rates. The appropriate measurements must be made for accurate estimation of cost. Furthermore, the cost of one intervention may diverge between locations and thus result in conflicting conclusions on cost-effectiveness. One example is the comparison of cost in the United States (multiple third party payers) to Canada (1 part payer) with the latter most likely being a fraction of the fee. In addition, resource costs such as nursing time and the cost to others affected by the intervention must also be considered.[97]

As mentioned, patient satisfaction and quality of life in addition to clinical outcome measures such as complication rate are required to determine the cost effectiveness of an intervention.[99-102] Quality of life measures that integrate both time and health outcomes allowing for the development of a numeric value using quality and quantity of life include Quality adjusted Life Years (QALY) and disability-adjusted life years (DALY), health-adjusted life expectance, potential years of life lost, and years of healthy life.[103] QALY in particular has been implemented as an outcome measure for cost-utility analysis for various breast reconstruction techniques.[104-106] This tool primarily functions to assess health outcome benefit with complete benefit requiring the inclusion of other factors such as aesthetic result and number of operations, among many others.[107-109] Data from all of the aforementioned tools can be extrapolated to educate decision-makers and as a result influence the allocation of health care resources to improve population health. With these tools, it is assumed that community preferences can be representative of individual preferences.

There are a multitude of costs that require consideration prior to a formal evaluation of the use of AM in reconstructive breast surgery. Such knowledge should include cost of patient time expanded for the intervention, cost of potential outcomes, economic costs of the employer, friction costs (absenteeism), and costs associated with care giving.[97,110] Furthermore, it is vital that all relevant outcomes be determined and whether they differ with ADM use or not. As of April 2012, Macadam and Lennox[97] reported only 9 published series on ADM use in aesthetic breast surgery and 27 on reconstructive breast surgery. Although the number has increased since then, it is still difficult to know with great certainty whether ADM use contributes to improved, inferior, or equivalent outcomes due to the differences in reported outcomes. As such, a randomized controlled study with and without ADM is required which we have presented in **chapter 4**.

Our survey study in **chapter 5** provides some insight into whether cost was a prominent deterrent for ADM use in breast reconstruction procedures. This, however, is limited because only 15.8% of responding plastic surgeons did not incorporate ADMs into their breast procedures. This may be due to the voluntary sampling of participants leading to bias for ADM use and thereby may not be entirely representative of the responding population at large. In addition, as with any survey study, recall bias may be a problem. These issues could ultimately be overcome by increasing our surveyed sample size.

Finally using photographic analysis in **chapter 6** we were able to provide objective justification for the incorporation of ADM despite its high cost. Aesthetic evaluation of breast reconstruction can be a highly subjective process and can be biased.[6] We felt that the picture grading offered an objective assessment which was further enhanced by the fact that five blinded plastic surgeons served as reviewers. The subscale analysis used in this study was a modification of that supported by Lowery et al.[76] Our study demonstrated individual subscales with mostly moderate agreement between the observers which is better than other articles using this same scoring system.[7-9,76,79] Perhaps the quality of our study could have been improved using three-dimensional imaging to permit a more accurate evaluation of breast volume, symmetry, contour, size, and surface area.[75,85,86]

Interpretation of Results

Review of the Literature

Perhaps the most important deterrent for ADM use is their high cost. At the Beth Israel Deaconess Medical Center the cost of this material equates to $3,536 to $4,856 per breast depending on the thickness and size of the sheet.[56] Contrary to popular belief, further review of ADM cost effectiveness in **chapters 2 and 3** is favorable.[111,112]

Jansen and Macadam[113] formed a comparison between baseline and expected costs for direct-to-AlloDerm® and two-stage non-AlloDerm® reconstruction. They reported a lower baseline cost ($10,240 versus $10,584) as well as a lower expected cost ($10,734 versus $11,251) when using a 6x16-cm AlloDerm® sheet. Expected cost was further reduced (to $9,673) when a 6x12-cm AlloDerm® sheet was incorporated. Strattice™ is cheaper than AlloDerm® and is available in specific shapes and sizes to lower cost and diminish waste.[49] Butterfield[114] found that when using equally sized units of each, AlloDerm® costs $1,024 more per breast than Surgimend™. Chepla et al.[115] suggested that using a partial AlloDerm® sling can reduce the cost associated with ADM use in breast reconstruction. In contrast Bank et al.'s[116] analysis mesh use actually reduced the number of visits required for reconstructions of 350 ml or more. However, the direct cost of ADM use ($2,727.75 for large reconstructions and $3,290.25 for small reconstructions using AlloDerm®, $2,167.75-$2,739.25 with Strattice™) did not make up for cost expenditure despite less visits. Regardless, despite the high cost of ADM use, it is indeed cost-effective in the long-run by reducing the number of revision procedures as well as operative time. Furthermore, the wide variety of biologic meshes available on the market provides both the patient and the plastic surgeon with options regarding expenditure and cost savings.

Survey Outcome

In **chapter 5**, the minority of responding plastic surgeons who chose not to incorporate ADM into their breast reconstructions largely attributed their decision to high cost. This fact was reinforced by participants who chose not to use biologic meshes in any aspect of their practice. This is not at all surprising considering the current economic setting and the increased financial pressures on individual physicians, hospital boards, and insurance companies. As such there may be a shift toward cheaper and more profitable operations.

Aesthetic Justification

From the perspective of aesthetic outcome, **chapter 6** demonstrated that this alone may be enough to justify the added expense of incorporating ADM into breast reconstruction procedures. However, it is important to note that due to our small patient population, further studies are needed to establish adequate statistical power. It is important to consider the other benefits of ADM in secondary aesthetic breast surgery and the support that ADM can provide in women with smaller breasts who lack much needed tissue coverage. In addition, as previously reported it is indeed cost-effective in the long-run by decreasing operative time as well as the number of revision procedures. Furthermore, with advancements in technology, instrumentation, and surgical technique the added advantages of ADM use will continue to develop.

OVERALL CONCLUSIONS

Numerous approaches for breast reconstruction exist. They vary in technique, duration, materials used, recovery period, complication rates, cosmetic outcome and overall cost. Several factors must be considered when determining which procedures best suit the patient. Meticulous patient selection is necessary and may impact outcomes. Moreover, involving patients in the decision making process is important for raising patient satisfaction. The incorporation of acellular dermal matrices (ADMs) into post-mastectomy breast reconstruction represents one aspect of the emerging field of regenerative medicine in which scaffolds promoting tissue growth are being used to replace like with like tissue.[60] Recent histologic analysis has revealed that ADM can even serve as a template for seeding with adipose derived adult stem cells demonstrating the ability of penetration, proliferation, and differentiation. This concept has the potential to extend beyond skin replacement and implant support to serve as models for wound healing.[117] All the same, the breast implant periprosthetic space has its own challenges; a strong and yet limber layer of tissue is required for proper implant coverage and support.

We performed a series of studies examining different facets of breast reconstruction when using ADM in the hopes of improving our knowledge of the optimal approaches, best materials, and cost effectiveness of these meshes. ADMs have a multitude of applications in breast surgery. They are safe to use in the setting of post-mastectomy breast reconstruction as well as for correction of deformities following aesthetic breast surgery. Based on our data, ADM use was not linked to an increased incidence of complications, rather there was no significant difference in overall complication rates between the ADM and non-ADM groups in tissue expander/implant based breast reconstruction. Several co-morbidities exist that may contribute to negative effects necessitating the need for proper patients selection, operative approach and post-operative management to optimize outcomes. Plastic surgeons are incorporating ADMs into both immediate and staged procedures with younger generations appearing more willing to include them in their clinical practice.

Drain and antibiotic use are still favored in the postoperative setting; however nipple reconstruction using ADM is still limited. Finally, photographic analysis revealed improvements in aesthetic outcome across most subscales when ADMs are used and a statistically significant improvement in overall aesthetic outcome which may justify the high cost of incorporating these meshes into breast reconstruction procedures, and warrant consideration of their use in smaller breasted women as well as in the correction of complex breast deformities. Furthermore, they reduce operative time and the number of revision procedures, therefore may be cost-effective in the long-term.

The use of ADM offers the ability of regenerative medicine to possibly lower complication rates and meet the requisite clinical needs.[60] Although ADMs are expensive, as advancement in approaches, instrumentation and new products emerge, and operative time is reduced, their use will most likely increase with more plastic surgeons willing to incorporate them into their procedures.[93] Lessons learned from proof-of concept studies and the experience of surgeons with ADM use will undoubtedly serve as guide for future studies.[60]

RECOMMENDATIONS

For Future Research

Overall, the outcomes of our individual studies have met the aims of this thesis as put forward in **chapter 1**. The various strengths and weaknesses of these studies have been addressed in the discussion. As with any relatively new material there are still many unknowns.[118] Although an abundance of data has been collected and evaluated for the purposes of this thesis, in order for more definitive answers for the aforementioned questions to be ascertained, prospective randomized trials that are sufficiently unbiased to sustain rigorous peer review are needed. In **chapter 4** we performed the *first* retrospective review of prospectively collected information from a national multi-institutional data set. Perhaps the inclusion of data beyond the first 30 days as well as plastic surgery disease- and operation-specific variables would have allowed for better and more accurate predictions of undesirable outcomes.

Breast reconstruction has evolved greatly over the last several decades and will continue to change with the development of new technology. This shift will affect the overall cost and outcome of procedures. The high cost of acellular dermal matrix (ADM) continues to be an issue. To our knowledge, this thesis presents the *first* objective assessment of the aesthetic outcome following ADM use for justification of its high cost in **chapter 6**. Perhaps the inclusion of extramural medical and non-medical costs may have also affected our analyses of cost-effectiveness. Furthermore, it is warranted that the same patient population be assessed in 5 to 10 years for evaluation of the long-term results and verification of cost-benefit. Subjective patient satisfaction is also needed which can then be compared to the opinions of our panel of experts. Although patient satisfaction is briefly included in **chapter 5**, this is solely from the perspective of the treating plastic surgeon. Several of the technical changes suggested in **chapter 2** are currently being implemented at our medical center in an effort to boost outcomes.

For Clinical Practice

Breast reconstruction following mastectomy has proven to have a positive effect on the physical and psychological well being of breast cancer patients. It is therefore vital that we reinforce the need to educate treating physicians as well as patients on the reconstructive indications and options available to them. The attitudes of women toward breast reconstruction have changed as reflected by the rise in the rate of preventative bilateral mastectomy and reconstruction in women diagnosed with early-stage breast cancer.[119,120] ADM use in breast reconstruction is slowly gaining momentum given the fact that numerous surgeons have pointed to its enhanced aesthetic outcome and lower complication rates. Furthermore, it can be used to address breast deformities alleviating the need for further operations. When deciding on a single stage reconstruction with ADM versus a two stage approach, it is important that patient characteristic such as low body mass index and smaller breasts be taken into account as this may contribute to a lower risk of complications. Not all plastic surgeons however are able to offer this option because of the added expense. Regardless, surgeons should be able to objectively inform patients of all their options and if need be refer them to a colleague who is able to perform the type for reconstruction they want. With changing attitudes toward breast construction and enhanced means of screening for women who may be more likely to develop breast cancer, the rate of breast surgeries will continue to rise. For patient management to be successful it is vital that there be proper coordination between the various medical disciplines involved in patient care with much needed improvements in reimbursement for the choice to use ADM in breast reconstruction. Furthermore, definitive guidelines need to be established to clarify to plastic surgeons the proper indications for ADM use which inadvertently save on cost.

For Cost-Analysis

The current literature has provided little guidance with regard to ADM use in breast reconstruction. As such the plastic surgeon is left alone to decide on whether to include these meshes into practice. There are currently two randomized controlled studies under way which can provide outcomes data that can be used for formal cost analysis. The first of these is being undertaken at the University of Toronto by Zhong et al.[59] whose focus is a comparison of 1-stage breast reconstruction with ADM to 2-stage breast reconstruction without ADM. The second is being performed at Memorial Sloan Kettering Cancer Center who are comparing 2-stage breast reconstruction with and without ADM.[97] Furthermore, in the future, cost-utility analysis can be made easier by patient-reported data. In this way decision makers will have access to more definitive data enabling them to reliably consider the benefits versus the risks of ADM use in breast reconstruction. Similarly, this could be applied in aesthetic breast surgery but would require the inclusion of private-pay patients which could prove difficult. In this way the impact of ADMs on the cost of

cosmetic breast surgery can be assessed by the long-term clinical outcomes of large prospective observational studies with standardized techniques.[97]

For Health Care Policy

Currently there are a little over 7000 plastic surgeons in the United States serving a population of over 300 million people (with unequal geographic distribution and not taking into account those that perform aesthetic surgery only as well as physicians trained in other disciplines who receive subspecialty training in plastic surgery-related procedures). Clearly there is a need to increase the number of reconstructive surgeons in order to offer the large patient population the option of breast reconstruction as routinely as mastectomy procedures. As such there should be financial restructuring with regard to performing breast reconstruction and a willingness to incorporate ADM to enhance the final outcome. Issues related to variations in pricing from state to state and from surgeon to surgeon need to be resolved at both the clinical level as well as in health care policy. With health care becoming more patient centered, and with patients demanding higher quality outcomes, health care policy reform is needed to aid surgeons in providing the utmost standard of care to reflect advances in technology and the emergence of new materials which may ultimately include the incorporation of ADMs in breast reconstruction procedures.

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Chapter 8

English Summary

Breast reconstruction is aimed at restoring the normal contour and appearance of an amputated breast mound. This in turn will contribute to improvements in patients' well being, feelings of sexuality, and body image. Prosthetic based breast reconstruction is the most popular approach owing to it straight forward operative technique and shortened operative time. Despite the progression made in reconstructive breast surgery, reoperation rates remain high. This is primarily a result of inadequate coverage that may lead to capsular contracture, visible rippling, implant malposition, and animation deformities. Acellular Dermal Matrix (ADM) can help to reduce the occurrence of these issues by aiding in the creation of an implant pocket in single-stage reconstruction or maintaining the inferolateral portion of the tissue expander pocket in two-stage reconstructions. Thus far reports in the literature have failed to provide concrete evidence as to the ability of ADMs to resist infection and tolerate radiation. Furthermore, there has not been any objective evidence to support the enhanced aesthetic outcome correlated to ADM use in order to justify its high cost which has been a deterrent for many plastic surgeons.

The studies included in this thesis were performed to provide a global view of the most effective approaches when using ADM in breast reconstruction to maximize the aesthetic outcome, the various types of meshes used, the impact of ADM use on complication rates using a multi-institutional data set, current trends of ADM use among plastic surgeons, and cost justification based on aesthetic outcome. These are correlated to the technical, psychological and economic aspects of ADM use in post-mastectomy breast reconstruction.

TECHNICAL ASPECTS

In **chapter 2** we discuss how to optimize the surgical outcomes and address the breast deformities associated with implant based breast reconstruction using acellular dermal matrix (ADM) from our own experience and a brief review of the literature. We reported that the most commonly used techniques for creations of an implant pocket are the ADM sling or hammock that is anchored to the lower pole of the pectoralis major. In revision procedures the periareolar incision is preferred. Contour irregularities can be addressed by ADM placement directly over the implant or the capsule if further procedures are not required. Proper placement of ADM can be facilitated using the parachuting technique. Implant malposition is reduced by placing ADM over the capsulorrhaphy.

In **chapter 3** we reviewed the most frequently used meshes in breast reconstruction and focused specifically on the physical characteristics, level of sterility and biomechanical properties of these grafts. Furthermore, review of the literature was performed to ascertain data on published experiences with regard to complication rates. AlloDerm®

was the most cited mesh in the literature by far. AlloDerm®, DermaMatrix® and FlexHD® are derived from human tissue while Strattice™, SurgiMend™ and Veritas® come from animal sources. With the exception of AlloDerm® and FlexHD® all meshes in this study were terminally sterile. In terms of physical properties all the mentioned meshes are non-cross linked with the exception of Strattice™ whose components are undisclosed.

Our literature review showed inconclusive data with regard to complication rates. It was apparent that some studies were greatly in favor of ADM use reporting incidences as low as 0% while others staunchly confirmed elevated rates of infection. Seroma, infection and implant failure were the most widely reported complications and were likely associated with the presence of pre-existing co-morbidities such as smoking and high BMI. Similarly, there remains conflict as to the role of ADM in tolerance to radiation with some authors alluding to no added benefit and others suggesting that it is radio-resistant. A multi-institional, prospective study with long-term follow-up was recommended by most authors to validate the reliability and longevity of this data.

The *first* multi-institutional evaluation of complication rates with and without ADM in tissue expander/implant based reconstruction using the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) was performed in **chapter 4**. There were a total of 19,100 patients included in this study. No statistically significant difference in overall complication rate was observed between the ADM and non-ADM groups ($p = 0.396$). However, several co-morbidities were linked to a greater incidence of complications mainly in the non-ADM group. In the ADM group BMI ($p = 0.01$) and diabetes ($p = 0.02$) contributed to wound disruption, BMI ($p = 0.01$) and alcohol consumption ($p = 0.04$) were associated with an increased likelihood of sepsis, and chronic steroid use raised the incidence of superficial surgical site infection ($p = 0.04$). Furthermore, BMI also increased the rate of wound complications in both cohorts. From the data collected in this study it can be said that ADM use in breast reconstruction procedures does not lead to higher complication rates when compared to a non-ADM cohort. Moreover, it emphasizes the importance of meticulous patient selection before performing a breast procedure owing to the numerous co-morbidities that may contribute to worse outcomes.

In **chapter 5** data on ADM use in the presence of drains, antibiotics and for nipple reconstruction were obtained. This study showed that 94.6% of our surveyed plastic surgeon population incorporated drains into their reconstructive breast surgeries. When ADM was used, drains were kept in for longer than they normally would have been. Alike, 87.8% of our respondents used antibiotics in the post-operative period without hesitation. Finally our survey demonstrated that only 18.5% of participants incorporated ADMs into their nipple reconstructions reaffirming the rarity of its use in such procedures.

PSYCHOLOGICAL ASPECTS

The effectiveness and quality of acellular dermal matrix (ADM) use in breast reconstruction cannot be determined by clinical outcomes measure alone. Plastic surgeons' perception of a successful outcome with regard to patient satisfaction as well as aesthetic appearance and the reasons behind their decision to incorporate ADM (including the type of ADM) into their procedures is investigated in **chapters 5 and 6**.

In **chapter 5**, our internet based survey revealed that over 86% of responding plastic surgeons believed that their patients were satisfied with outcome of their breast reconstruction when ADM was used. This was supported by the fact that 77.9% reported that patients almost never returned for secondary procedure to correct any deformities. In the rare occasion that a patient was dissatisfied with the final result, the most frequently requested revision surgeries were symmetry procedures (53.9%), fat grafting (19.5%), and capsulotomy/capsulectomy (17.9%). AlloDerm® was found to be the most popular mesh used in reconstructive breast surgery. This was attributed to the extensive availability of published safety, efficacy and long-term outcomes studies using AlloDerm® in the literature.

Our data also showed that younger generations of plastic surgeons appear more willing to use ADMs with 100% of those in the 31-40 age group, or less than five years in practice choosing to include these meshes in their practice. Furthermore, statistical analysis revealed that plastic surgeons with experience using ADMs were more willing to incorporate them into their breast procedures than those without.

An objective assessment of aesthetic outcome to justify the high cost of ADM was performed in **chapter 6**. The results of this paper demonstrated that the use of ADM did indeed enhance the final aesthetic outcome, perhaps supporting the additional expense of incorporating these meshes. Furthermore, it is important to take into account its many benefits in revision surgery and in patients with poor tissue coverage. If using ADMs to address these issues will improve patient satisfaction and thus psychological well being perhaps guidelines should be established to provide clear indications for its use.

ECONOMIC ASPECTS

One of the major concerns regarding the use of ADM in breast reconstruction is its high cost. In **chapter 5** it was revealed that only a small number of plastic surgeons do not use ADM in their breast produces which they claimed was mainly due to the additional

expense of the mesh. Of these respondents only 26.3% incorporated ADM in other procedures, primarily in abdominal wound reconstruction. This does not come as a surprise however in the current setting of budget cuts and economic constraints where surgeons may consider cheaper and more profitable options. The fact that a majority of plastic surgeons continue to use ADM despite its expense is reinforced by our comprehensive reviews of the literature in **chapters 2 and 3** which examined cost-effectiveness of ADM use based on the experience of others. Depending on the thickness and size of the mesh used, the cost can vary. At our institution it ranges from $3,536 to $4,856 per breast. Only one study suggested that the direct cost of ADM use did not result in cost savings in the setting of second-stage exchange for a permanent implant. Others revealed no significant difference in terms of total overall cost with and without ADM in immediate single-stage implant reconstructions (taking into account the need for a revision procedure), and even suggested it as a less pricier option than TRAM flap reconstruction. In a comparison between baseline and expected costs for direct-to-AlloDerm® and two-stage non-AlloDerm® reconstruction both baseline and expected costs were lower when using a 6x16-cm AlloDerm® sheet and further reduced when a 6x12-cm AlloDerm® sheet was used.

One of the advantages of biologic meshes is the different types of mesh available on the market which provides options in terms of material properties and cost expenditure. Strattice™ for example is cheaper than AlloDerm® and is present in difference sizes and shapes. Another more affordable alternative is SurgiMend™ which was found to cost $1,024 less per breast than AlloDerm®. The technique employed can also aid in cost savings with one author suggesting the use of a partial AlloDerm® sling to decrease overall expenditure. It is clear from the current literature that there is overwhelming data to support the cost-effectiveness of ADM in the long-run owing to its ability to reduce operative time and minimize the need for revision procedures despite the initial additional expense incurred.

Photographic analysis in **chapter 6** revealed that the extent of cosmetic improvement when ADM was incorporated into breast reconstruction was statistically significant. In addition, these meshes exhibit many advantages in secondary aesthetic breast surgery and for reconstruction in women who do not possess large breasts. This finding suggests that aesthetic outcome alone may provide justification for the added cost, and with advances in surgical approach, technology and instrumentation, ADM use will continue to evolve.

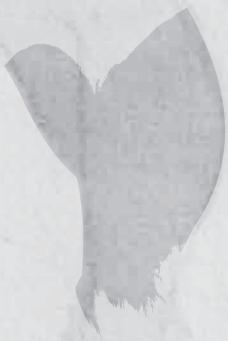
CONCLUSION

The studies presented in this thesis cover the various aspects of acellular dermal matrix (ADM) use in breast reconstruction. We demonstrated that ADMs are safe and reliable not only in primary prosthesis-based breast reconstructions but also in the management of secondary breast deformities yielding high patient satisfaction. Younger generations of plastic surgeons appear more inclined to incorporate ADMs into their clinical practice suggesting a paradigm shift in the approach to patient management following mastectomy; though it is still not widely used for reconstruction of the nipple areola complex. Significantly, based on data from the NSQIP, the use of ADM does not contribute to increased complication rates although several co-morbidities may affect outcomes and as such, careful attention should be paid to the patient selection process. ADM use has not changed the way plastic surgeons use drains or antibiotics to try and minimize complications.

Most plastic surgeons believe that based on existing evidence, ADM use is secure and effective in preventing complications and that the data against its use is weak. The main deterrent against ADM use is its price. Aesthetic outcome alone may justify its high cost. Also, the other benefits of its use should be considered; a multitude of cost-analysis studies have revealed cost-benefit in the long-term. Over the last decade the expectation for improved outcomes by patients undergoing breast reconstruction has steadily risen. Our data suggests that patients are at least entitled to explore all options and possibilities when considering implant based breast reconstruction specifically regarding operative technique as well as the incorporation of a biologic mesh even if that may result in greater expense to reach the desired outcome.

Chapter 9

Nederlandse Samenvatting



Borstreconstructies na amputatie proberen de normale contour en uiterlijk van een borst te herstellen. Dit kan een belangrijke bijdrage leveren aan verbeteringen in het welzijn, zelfbeeld en eigenwaarde van patiënten. Borstreconstructies door middel van prothesen worden het meest uitgevoerd vanwege de relatief ongecompliceerde procedure met een relatief korte operatieduur. Ondanks de verbeteringen in prothese borstreconstructies die gedurende de afgelopen decennia hebben plaatsgevonden, blijft het aantal re-operaties hoog. Dit is voornamelijk het gevolg van de ontoereikende bedekking door de m. pectoralis major over de prothese, hetgeen kan leiden tot kapselcontractuur, plooivorming, malpositie van het implantaat en vormveranderingen. Acellulaire dermale matrix (ADM) producten kunnen helpen om het ontstaan van deze problemen te verminderen door het creëren van een beter bedekte ruimte voor de prothese in een één-etappe reconstructie of het handhaven van het inferolaterale gedeelte van de weefselexpander ruimte in een twee-etappe reconstructie. Tot op heden bestaat er in de literatuur geen concreet bewijs voor het vermogen van ADM producten om infecties te weerstaan of bestraling te tolereren. Bovendien is er geen bewijs dat verbetering van het esthetisch resultaat correleert met het gebruik van ADM producten. Door de relatief hoge kosten van ADM producten wordt het gebruik hiervan door veel plastisch chirurgen niet gerechtvaardigd.

De studies in dit proefschrift werden uitgevoerd om een overzicht te verschaffen van de meest effectieve aanpak bij het gebruik van ADM producten bij borstreconstructies met als doel het esthetisch resultaat te optimaliseren. Er werd een overzicht gemaakt van de verschillende soorten ADM die worden gebruikt, de invloed van ADM op complicaties met behulp van een nationale database, de huidige trends van ADM gebruik onder plastisch chirurgen, en de rechtvaardiging van de kosten op basis van esthetische resultaat. De resultaten werden gecorreleerd met de technische, psychologische en economische aspecten van ADM gebruik bij borstreconstructies na mastectomie.

TECHNISCHE ASPECTEN

In **hoofdstuk 2** wordt besproken hoe de chirurgische resultaten geoptimaliseerd kunnen worden en wordt een uiteenzetting gegeven van vormveranderingen die geassocieerd kunnen zijn met het gebruik van ADM bij implantaat borstreconstructies, zowel vanuit onze eigen ervaring als door een kort overzicht van de literatuur. De ADM "sling" die is verankerd aan de onderrand van de musculus pectoralis major wordt besproken als meest gebruikte techniek voor het creëren van een ruimte voor het implantaat. In revisieprocedures wordt de voorkeur gegeven aan een periareolaire incisie. Contour onregelmatigheden kunnen worden behandeld door plaatsing van ADM direct over het implantaat danwel over het kapsel als verdere procedures onnodig zijn. De juiste

plaatsing van ADM kan worden vergemakkelijkt door middel van een parachute techniek. Malpositie van het implantaat kan worden verminderd door de plaatsing van ADM over het gereefde kapsel.

In **hoofdstuk 3** wordt een overzicht gegeven van de meest gebruikte ADM producten bij borstreconstructies, specifiek gericht op de fysieke kenmerken, mate van steriliteit en de biomechanische eigenschappen van deze producten. Daarnaast werd een review van de literatuur uitgevoerd om gegevens over de gepubliceerde ervaring met betrekking tot complicaties te beschrijven. AlloDerm® was veruit het meest geciteerde ADM product in de literatuur. AlloDerm®, DermaMatrix® en FlexHD® zijn afgeleid van humaan weefsel, terwijl Strattice™, SurgiMend™ en Veritas® afgeleid zijn van dierlijk materiaal. Met uitzondering van AlloDerm® en FlexHD® waren alle ADM producten in deze studie steriel. Met betrekking tot de fysieke eigenschappen waren alle genoemde ADM producten niet gecrosslinked (behalve Strattice™, waarvan de exacte bestanddelen onbekend zijn).

Onze literatuurstudie bleek geen afdoende gegevens met betrekking tot complicaties op te leveren. Het werd duidelijk dat sommige studies die sterk vóór het gebruik van ADM waren, infectiepercentages van 0% rapporteerden, terwijl andere studies verhoogde infectiepercentages lieten zien. Seroomvorming, infectie en het falen van implantaatintegratie waren de meest gerapporteerde complicaties en waren waarschijnlijk geassocieerd met de aanwezigheid van reeds bestaande risicofactoren, zoals roken en een hoge BMI. Ook blijft er onduidelijkheid bestaan over de rol van ADM in de tolerantie van ioniserende straling, waarbij sommige auteurs geen bijkomende voordelen omschreven, terwijl anderen een beschermend effect suggereerden. Om de betrouwbaarheid te valideren, adviseerden de meeste auteurs om een multi-institutionele, prospectieve studie met een lange-termijn follow-up uit te voeren.

De *eerste* multi-institutionele analyse van complicaties mét en zonder ADM bij reconstructies met weefselexpanders en implantaten werd beschreven in **hoofdstuk 4**, aan de hand van analyse van de American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database. In totaal waren er 19.100 patiënten opgenomen in deze studie. Er kon geen statistisch significant verschil in algemene complicaties worden waargenomen tussen de ADM en non-ADM groepen ($p = 0.396$). Echter, verscheidene risicofactoren vertoonden een relatie met een hogere incidentie van complicaties, voornamelijk in de non-ADM groep. In de ADM groep waren BMI ($p = 0.01$) en diabetes ($p = 0.02$) geassocieerd met een verstoorde wondgenezing, BMI ($p = 0.01$) en alcohol ($p = 0.04$) met een verhoogde kans op sepsis en chronisch steroïdengebruik met oppervlakkige postoperatieve wondinfecties ($p = 0.04$). Een hoog BMI vergrootte ook de mate van wondcomplicaties in beide cohorten. Uit de gegevens in dit onderzoek kan

worden afgeleid dat het gebruik van ADM bij borstreconstructies niet leidt tot hogere complicatiecijfers in vergelijking met het non-ADM cohort. Het belang wordt benadrukt van een zorgvuldige selectie van patienten bij het uitvoeren van reconstructtieve mammaprocedures, dit vanwege de vele co-morbiditeiten die kunnen bijdragen aan verminderde resultaten.

In **hoofdstuk 5** werden gegevens verkregen over ADM gebruik in relatie tot drains, antibiotica en tepelreconstructie. Deze studie toonde aan dat 94,6% van onze ondervraagde populatie van plastisch chirurgen drains gebruikt bij mammareonstructies. Indien ADM werd gebruikt, bleek dat drains langer in situ werden gelaten dan normaliter. Van de respondenten gebruikte 87,8% zonder enige aarzeling antibiotica in de postoperatieve fase. Tot slot bleek uit onze studie dat slechts 18,5% van de plastisch chirurgen het gebruik van ADMs heeft opgenomen tijdens tepelreconstructies; dit bevestigt de zeldzaamheid van ADM gebruik in dergelijke procedures.

PSYCHOLOGISCHE ASPECTEN

De effectiviteit en kwaliteit van Acellulaire Dermale Matrix (ADM) in borstreconstructies kan niet enkel worden bepaald door klinische uitkomstmaten. De perceptie van een succesvol resultaat met betrekking tot de tevredenheid van de patiënt, het esthetisch resultaat en de redenen achter hun beslissing om ADM (waaronder het type ADM) op te nemen in hun procedures werd onderzocht in **hoofdstuk 5 en 6**.

In **hoofdstuk 5** worden de resultaten van onze enquête beschreven, waaruit blijkt dat meer dan 86% van de reagerende plastisch chirurgen geloofden dat hun patiënten tevreden waren met het resultaat van hun borstreconstructie indien ADM werd gebruikt. Dit werd ondersteund door het feit dat 77,9% rapporteerde dat patiënten vrijwel nooit terug kwamen voor secundaire procedures om eventuele vormveranderingen te corrigeren. In het zeldzame geval dat een patiënt ontevreden was met het uiteindelijke resultaat, betroffen de meest verzochte revisies procedures ter verbetering van de symmetrie (53,9%), transplantatie van vetweefsel (19,5%) en capsulotomie/capsulectomie (17,9%). AlloDerm® bleek het meest populaire ADM product te zijn bij reconstructieve borstoperaties. Dit werd toegeschreven aan de grote beschikbaarheid van gepubliceerde literatuur over AlloDerm® met betrekking tot veiligheid, werkzaamheid en resultaten op lange termijn.

Uit onze gegevens bleek ook dat jongere generaties van plastisch chirurgen meer bereid lijken om ADMs te gebruiken. In totaal koos 100% van de plastisch chirurgen tussen de

31-40 jaar of minder dan vijf jaar in de praktijk voor het implementatie van ADM in hun dagelijkse praktijk. Bovendien liet statistische analyse zien dat plastisch chirurgen met ervaring in het gebruik van ADMs voor andere doeleinden meer bereid waren om deze te integreren in hun mammaprocedures.

Een objectieve beoordeling van het esthetisch resultaat die de hoge kosten van ADM zouden kunnen rechtvaardigen werd beschreven in **hoofdstuk 6**. De resultaten van deze studie laten zien dat het gebruik van ADM inderdaad leidt tot verbetering van het uiteindelijke esthetisch resultaat, wat wellicht de extra kosten van het ADM product verantwoordt. Verder is het belangrijk om rekening te houden met de vele voordelen van ADM tijdens revisiechirurgie en bij patiënten met een onvolledige weefseldekking. Indien de incorporatie van een ADM product patiënttevredenheid en dus mogelijk ook het psychologisch welzijn verbetert, zouden richtlijnen moeten worden opgesteld welke duidelijke indicaties stellen voor het gebruik hiervan.

ECONOMISCHE ASPECTEN

Een van de grootste zorgen betreffende de toevoeging van ADM in borstreconstructies is de hoge kostprijs. In **hoofdstuk 5** werd beschreven dat slechts een klein aantal plastisch chirurgen geen gebruikt maakt van ADMs, wat vooral te wijten was aan de extra kosten van het product. Van deze respondenten verklaarde slechts 26,3% ADM wel te gebruiken tijdens andere procedures, met name bij buikwandreconstructies. Echter, in de huidige context van bezuinigingen en andere economische beperkingen waar chirurgen vaak goedkopere en winstgevendere opties overwegen, komt dit niet als een verrassing. Het feit dat een meerderheid van de plastisch chirurgen ADMs blijft gebruiken ondanks de additionele kosten, wordt versterkt door ons uitgebreide review van de literatuur in de **hoofdstukken 2 en 3**, die de kosteneffectiviteit van ADM gebruik onderzocht op basis van de ervaring van anderen. Afhankelijk van de dikte en grootte van het ADM product kunnen de kosten variëren. In onze instelling varieert dit van $3.536 tot $4.856 per borst. Slechts één studie suggereert dat de directe kosten van ADM niet resulteerden in kostenbesparingen in de context van secundaire wissel met definitieve prothesen. Anderen hebben geen significante verschillen beschreven in de totale kosten met en zonder ADM bij één-etappe prothesereconstructies (rekening houdend met de noodzaak tot een revisie), en hebben het gebruik van ADM zelfs voorgesteld als een minder dure optie dan een TRAM lap reconstructie. In een vergelijking tussen de basiskosten en verwachte kosten van de één-etappe AlloDerm® en twee-etappe non-AlloDerm® reconstructies waren zowel de basis- als de verwachte kosten lager indien een 6x16cm AlloDerm® werd gebruikt, met zelfs verdere verlaging bij 6x12cmAlloDerm®.

Een van de voordelen van biologische ADM producten is de variatie aan verschillende typen die op de markt zijn. Dit biedt opties indien het gaat om de materiaaleigenschappen en kostenverbruik. Strattice™ is bijvoorbeeld goedkoper dan AlloDerm® en is verkrijgbaar in verschillende maten en vormen. Een ander, meer betaalbaar alternatief is SurgiMend™, waarvan de kosten per borst $ 1.024 minder bleken dan AlloDerm®. Ook kan de gebruikte techniek helpen bij kostenbesparingen. Eén auteur suggereert een afname van de totale kosten bij het gebruik van een partiële AlloDerm® sling. Analyse van de huidige literatuur laat zien dat er een overweldigende hoeveelheid aan data bestaat die de kosteneffectiviteit van ADM producten op de lange termijn ondersteunen. Dit als gevolg van vermindering van operatietijd en de noodzaak van revisieprocedures, ondanks de initiële extra uitgaven.

Fotografische analyse in **hoofdstuk 6** toonde een statistisch significante verbetering van het esthetisch resultaat bij gebruik van ADM producten bij borstreconstructies. Bovendien vertonen ADMs veel voordelen bij secundaire esthetische procedures en in geval van borstreconstructies bij vrouwen die geen grote borsten bezitten. Deze bevinding suggereert dat het esthetische resultaat afzonderlijk kan dienen als rechtvaardiging van de extra kosten. Met de continue vooruitgang in chirurgische benadering, technologie en instrumentatie, zal het ADM gebruik zich verder blijven ontwikkelen.

CONCLUSIE

De studies in dit proefschrift beschrijven de verschillende aspecten van Acellulaire Dermale Matrix (ADM) gebruik bij borstreconstructies. Er werd aangetoond dat ADMs veilig en betrouwbaar zijn, niet alleen in geval van primaire prothese borstreconstructies, maar ook in het beleid rondom herstel van secundaire vormveranderingen van de borst. Dit alles met een hoge patiënttevredenheid. Jongere generaties plastisch chirurgen zijn meer geneigd om ADMs te gebruiken in de dagelijkse praktijk, wat een verschuiving in de aanpak van borstreconstructies na mastectomie suggereert. Echter, ADMs worden nog steeds niet op grote schaal gebruikt bij de reconstructie van de tepelhof en tepelhofcomplex. Op basis van data uit de NSQIP blijkt dat het gebruik van ADM niet leidt tot een verhoogde kans complicaties, hoewel verscheidene risicofactoren de uitkomsten wel kunnen beïnvloeden. Zorgvuldige aandacht moet worden besteed aan het selectieproces van patiënten. De toepassing van ADM heeft geen invloed op het beleid rondom postoperative drains en antibiotica met betrekking tot de beperking van complicaties.
De meeste plastisch chirurgen zijn van mening dat op basis van bestaande gegevens ADM gebruik veilig en effectief is in het voorkómen van complicaties en dat de gegevens tegen het gebruik ervan zwak zijn. De belangrijkste drempel tegen het gebruik van ADM

producten is de prijs. Alleen het esthetisch resultaat kan de hoge kosten rechtvaardigen. Daarnaast moeten tevens de andere voordelen van het gebruik in acht worden genomen. Een groot aantal kosten-baten analyses hebben voordelen op de lange termijn getoond. In de afgelopen tien jaar zijn de verwachtingen van patienten naar betere resultaten gestaag toegenomen. Onze gegevens suggereren dat patiënten ten minste recht hebben om alle opties en mogelijkheden te onderzoeken bij het overwegen van implantaat borstreconstructies om het gewenste resultaat te bereiken. Dit geldt met name ten aanzien van de operatietechniek en de eventuele implementatie van een biologische mesh, zelfs als deze kunnen leiden tot hogere initiële kosten.

Appendices

Acknowledgements

This thesis was put together thanks to the support and effort of many. I would like to take this opportunity to show my gratitude to everyone involved in this endeavor.

Prof.dr. S.E.R. Hovius, thank you for giving me this amazing opportunity to collaborate with your prestigious institution and apply this work toward such an esteemed degree. This has been one of my life-long ambitions and I cannot be more grateful to you for agreeing to take me under your wing.

Dr. M.A.M. Mureau, I feel extremely lucky to have worked under your guidance and supervision and cannot imagine having to undertake this massive effort with anyone else. You have always been one to motivate me, and provide me with honest feedback. You conduct yourself in a manner that is inspirational to all aspiring plastic surgeons; always fair and professional. In you, I have not only gained a mentor but a friend as well.

S.J. Lin, MD, FACS, words alone cannot express my gratitude for everything that you have done for me. You have given me the opportunity to work at one of the best research institutes in the world. You show an eternal optimism toward teaching and have instilled in me a driving force that propels me to push harder and give all of what I have to everything that I undertake. The fact that I look forward to going to work every day and always want to give my best speaks volumes to how you inspire me to be a better person, a better researcher, and a better doctor. You bring out the best in me and for that I will be eternally grateful.

B.T. Lee, MD, MBA, FACS, I have sincerely enjoyed the time that I have spent in the Division of Plastic Surgery at the Beth Israel Deaconess Medical Center under your leadership. I am very gracious to you for always taking the time out of your busy schedule to provide me with guidance and support. I have learned a great deal from you. Your mentorship has helped to be successful not only in research, but has enabled me to have a promising future as a surgeon. My gratitude for your contribution is immeasurable.

Plastic surgery faculty at the Beth Israel Deaconess Medical Center (J. Upton, MD, S.A. Slavin, MD, FACS, D.J. Morris, MD, FACS, A.M. Tobias, MD, and P.S. Kim, MD), thank you for all of your support, mentorship and council. You have helped me to flourish and grow into a better researcher and physician, a person that I have long aspired to become. This has propelled my career to the next level and garnered me respect among my peers and for that I will forever be thankful.

Plastic surgery research team (Drs. P.G.L. Koolen and Drs. K. Kim), or as I like to call us, the tripod; the entity from which all research in the Division of Plastic Surgery at BIDMC emanates. I could not have hand-picked more brilliant people to work with. You are not just colleagues but life-long friends. I have no doubt that each of us will embark on successful careers in our chosen specialty. I cannot begin to describe how much you two mean to me and the debt of gratitude that I owe you for helping me to get through the tough times. The tripod will never break, and we will always be there to support one another.

Dr. A.N. Rabie, the man who taught me how to do research, and one of the kindest and most genuine individuals that I have had the honor of knowing in my life time. I have always considered you my older brother and I hope that I can become half the person and surgeon that you are.

Carin Oostdijk, without your help this degree would not have come to fruition. I am extremely thankful for all that you have done to help make this happen.

Geoffrey Brahmer, a truly special person. People like you are few and far between. You have taught me so much and helped me to evolve as an individual; to see the world in a different light. I will never forget the lessons learned from the many conversations that we have had over the years.

My lifelong friends (Drs. A.A.M. Hassan, Drs. A.B. Bayoumi, Drs. A.M.A. Alashry, Drs. A.T. Abu-Serewa, Drs. M.M. Ibrahim, Drs. Mustafa S. Zayed, M. Shaltout, and M.A. Attia), my brothers and dearest companions. I find myself speechless when trying to express how much you all mean to me. Together we form a bond that can never be broken; we survived medical school and persevered in the end. We have always pushed one another to become better, and it is this motivation that has urged me to try and go after my dreams and achieve all that I can.

My dear parents, Prof.dr. M.S.I. El Sayed and Dr. A.F.F. Ali, you have sacrificed so much for my brothers and I, and have always been there when we needed you the most. Thank you for everything that you have done for me. Without your guidance, love and support I would not be the person that I am today.

My biggest supporters, T.J. Fries, D.B. Sollecito, P. McGovern, B. Boyle, and M.K. Fries, thank you for everything that you have done for me.

My siblings, Omar and Yousef, life has no meaning without the two of you in it. We have always been there for one another. Nothing in this world can break the link that exists between us.

My wife, Julia, without your patience, love and care I would not have been able to make it this far in my career. You bring out the very best in me. Thank you for tolerating my idiosyncrasies and for being there during the good times and the bad. You are the glue that keeps our family together. We have a long life ahead of us, and the best is yet to come.

My daughter, Chloe, the light of my life, the reason I look forward to waking up every morning. A smile, a kiss, and a hug from you are all I need to make my day.

Curriculum Vitae

Ahmed Mohamed Said Ibrahim was born on March 11th, 1986 in London, England, United Kingdom. At the age of 1 year his family moved to Egypt, then at the age of 5 they relocated to Saudi Arabia, and finally at the age of 9 to Kuwait. There he attended the British School of Kuwait. After graduating in 2002, he was accepted into medical school at Ain Shams University in Cairo, Egypt. Throughout the course of his medical education, he routinely visited the United States of America where he completed several clinical clerkships, notably achieving "High Honors" during his month in Plastic and Reconstructive Surgery at the Beth Israel Deaconess Medical Center and Harvard Medical School in Boston, Massachusetts. He obtained his medical degree with honors in 2008, and started as an intern physician at the Ain Shams University Hospitals with a special focus on general plastic surgery and orthopedic trauma. Following the completion of his first year of training, he was invited to work as a research fellow in the Division of Plastic and Reconstructive Surgery at the Beth Israel Deaconess Medical Center and Harvard Medical School under the supervision of S.J. Lin, MD, FACS. During his time in Boston he became involved in the research described in this thesis under the direct supervision of Dr. M.A.M. Mureau and Prof.dr. S.E.R. Hovius. Upon completion of his research fellowship, he hopes to continue his specialist training in Plastic and Reconstructive Surgery in the United States of America. Ahmed is married to Julia Fries-Ibrahim; they have one daughter, Chloe, and a second child on the way.

List of Publications

PUBLICATIONS INCLUDED IN THIS THESIS:

Ayeni OA, **Ibrahim AM**, Lin SJ, Slavin SA. Acellular dermal matrices in breast surgery: tips and pearls. ***Clin Plast Surg*** 2012; 39:177-186. PMID: 22482359

Ibrahim AM, Ayeni OA, Hughes KB, Lee BT, Slavin SA, Lin SJ. Acellular Dermal Matrices in Breast Surgery: A Comprehensive Review. ***Ann Plast Surg.*** Feb 12 2013. PMID: 23407245

Ibrahim AM, Shuster M, Koolen PG, Kim K, Taghinia AH, Sinno HH, Lee BT, Lin SJ. Analysis of the NSQIP Database in 19, 100 Patients Undergoing Implant Based Breast Reconstruction: Complication Rates with Acellular Dermal Matrix. ***Plast Reconstr Surg.*** Nov 2013. PMID: 24165587

Ibrahim AM, Koolen PG, Ashraf AA, Mureau MA, Lee BT, Lin SJ. Current Use of Acellular Dermal Matrix in Reconstructive Breast Surgery: A Survey of Current Practice among Plastic Surgeons. **Accepted, *Plast Reconstr Surg Global Open***

Ibrahim AM, Koolen PG, Chuang DJ, Markarian M, Ganor O, Tobias AM, Lee BT, Lin SJ, Mureau MA. Does Acellular Dermal Matrix Really Improve Aesthetic Outcome in Tissue Expander/Implant Based Breast Reconstruction? **Submitted for publication**

OTHER PUBLICATIONS DURING PHD PERIOD:

Rabie A, **Ibrahim AM**, Lee BT, Lin SJ. Use of intraoperative computed tomography in complex facial fracture reduction and fixation. ***J Craniofac Surg*** 2011 Jul; 22(4):1466-1467. PMID: 21772153

Ibrahim AM, Rabie AN, Lee BT, Lin SJ. Intraoperative CT: A teaching tool for the management of complex facial fracture fixation in surgical training. ***J Surg Educ*** 2011 Sep-Oct; 68(5):437-441. PMID: 22135829

Song YA, Melik R, Rabie AN, **Ibrahim AM**, Moses D, Tan A, Han J, Lin SJ. Electrochemical activation and inhibition of neuromuscular systems through modulation of ion concentrations with ion-selective membranes. ***Nature Materials*** 2011 Oct 23; 10(12):980-986. PMID: 22019944

Patel PP, **Ibrahim AM**, Zhang J, Nguyen JT, Lin SJ, Lee BT. Accessory breast tissue. ***Eplasty*** 2012; 12:ic5. Epub 2012 Apr 23 PMID: 22536461

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Nguyen JT, Ashitate Y, Buchanan IA, **Ibrahim AM**, Gioux S, Patel PP, Frangioni JV, Lee BT. Face transplant perfusion assessment using near-infrared fluorescence imaging. ***J Surg Res*** 2012 Oct; 177(2): e83-8. PMID: 22572616

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Ibrahim AM, Gerstle TL, Rabie AN, Song YA, Melik R, Han J, Lin SJ. Nanotechnology in Plastic Surgery. ***Plast Reconstr Surg.*** 2012 Dec; 130(6); 879e-887e. PMID: 22878482

Ibrahim AM, Rabie AN, Kim PS, Medina M, Upton J, Lee BT, Lin SJ. Static Treatment Modalities in Facial Paralysis: A Review. ***J Reconstr Microsurg.*** 2013 May; 29(4): 223-32. PMID: 23303519

Hadad I, **Ibrahim AM**, Lin SJ, Lee BT. Augmented SIEA flap after ligation of bilateral inferior epigastric arteries and DIEP vessels. ***J Plast Reconstr Aesthet Surg.*** 2013 Jun; 66(6): 845-7.PMID: 23047181

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Ashraf AA, Colakoglu S, Nguyen JT, Anastasopoulos A, **Ibrahim AM,** Yeuh J, Lin SJ, Tobias AM, Lee BT. Patient Involvement in The Decision Making Process Improves Satisfaction

And Quality of Life in Postmastectomy Breast Reconstruction. ***J Surg Res.*** 2013 Sep; 184(1): 665-70. PMID: 23706394

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Kim PS, Malin E, Kirkham JC, Helliwell LA, **Ibrahim AM,** Tobias AM, Upton J, Lee BT, Lin SJ. The Boston Marathon Bombings: The Early Plastic Surgery Experience of One Boston Hospital. ***Plast Reconstr Surg.*** 2013 Nov; 132(5): 1351-63. PMID: 24165616

Kim K, **Ibrahim AM**, Koolen PG, Frankenthaler RA, Lin SJ. Analysis of the NSQIP Database in 676 Patients Undergoing Laryngopharyngectomy: Does Flap Reconstruction Make a Difference in Complications? ***Otolaryngol Head Neck Surg.*** 2014 Jan; 150(1); 87-94. PMID: 24240767

Ibrahim AM, Rabie AN, Tobias A, Lee BT, Lin SJ. Common Patterns of Reconstruction for Mohs Defects in the Head and Neck. ***J Craniofac Surg.*** 2014 Jan; 25(1): 87-92. PMID: 24240767

Ibrahim AM, Gerstle TL, Kim PS, Lee BT, Lin SJ. A Plastic Surgery Technique in Evolution: 3-Dimensional Printing. ***Plast Reconstr Surg***. 2014 Feb; 133(2); 446-51. PMID: 24469175

Sinno HH, Izadpanah A, Vorstenbosch J, Dionisopoulos T, **Ibrahim AM**, Tobias AM, Lee BT, Lin SJ. Living with Unilateral Mastectomy Defect: An Objective Assessment and Outcomes Study. ***J Reconstr Microsurg***. 2014 Feb 17. PMID: 24535675

De Blacam C, Colakoglu S, Ogunleye AA, Nguyen JT, **Ibrahim AM,** Lin SJ, Kim PS, Lee BT. Risk Factors Associated with Complications in Lower Extremity Reconstruction with the Distally-Based Sural Flap: A Systematic Review and Pooled Analysis. ***J Plast Reconstr Aesthet Surg***. 2014 Feb 7. PMID: 24662152

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Kim K, **Ibrahim AM**, Koolen PG, Lee BT, Lin SJ. Trends in Facial Fractures Treatment Using the ACS-NSQIP Database. ***Plast Reconstr Surg.*** 2014 Mar; 133(3): 627-38. PMID: 24263396

Perrone GS, Leisk GG, Lo TJ, Moreau JE, Haas DS, Papenburg BJ, Golden EB, Partlow BP, Fox SE, **Ibrahim AM**, Lin SJ, Kaplan DL. The Use of Silk-Based Devices For Fracture Fixation. ***Nature Communications***. 2014 March 4; 5: 3385. PMID: 24594992

Silvestre, Bess CR, Nguyen JT, **Ibrahim AM**, Patel PP, Lee BT. Evaluation of Wait Times for Patients Seeking Cosmetic and Reconstructive Breast Surgery. **Accepted, *Ann Plast Surg***

Rabie AN, Chang J, **Ibrahim AM,** Lee BT, Lin SJ. Use of Tragal Cartilage Grafts in Rhinoplasty: An Anatomic Study and Review of the Literature. **Accepted**, ***Ear Nose Throat J***

Sinno HH, Markarian MK, **Ibrahim AM**, Lin SJ. The Ideal Nasolabial Angle in Rhinoplasty: A Preference Analysis of the General Population. **Accepted, *Plast Reconstr Surg***

Ibrahim AM, Vargas CR, Colakoglu S, Nguyen JT, Lin SJ, Lee BT. The Biomechanical Properties of Meshes used in Ventral Hernia Repair: A Comprehensive Review of Synthetic and Biologic Meshes. **Accepted, *J Reconstr Microsurg***

Ibrahim AM, Sinno HH, Izadpanah A, Vorstenbosch J, Dionisopoulos T, Lee BT, Lin SJ. Population Preferences of Undergoing Brachioplasty for Arm Laxity. **Accepted, *Ann Plast Surg***

Koolen, PG, **Ibrahim, AM,** Kim K, Sinno HH, Andrews RA, Schneider BE, Jones DB, Lin SJ. Patient Selection Optimization following Combined Abdominal Procedures: Analysis of 4,925 patients undergoing Panniculectomy/Abdominoplasty with and without Concurrent Hernia Repair. **Accepted, *Plast Reconstr Surg***

Sinno H, Dionisopoulos T, Slavin SA, **Ibrahim AM**, Chung KC, Lin SJ. The Utility of Outcomes Studies in Plastic Surgery. **Accepted, *Plast Reconstr Surg Global Open***

Ibrahim AM, Sinno HH, Izadpanah A, Vorstenbosch J, Dionisopoulos T, Mureau AM, Tobias AM, Lee BT, Lin SJ. Nipple-Areolar Complex Reconstruction Following Postmastectomy Breast Reconstruction: A Comparative Utility Assessment Study. **Accepted, *Plast Reconstr Surg Global Open***

Kim K, Mella J, **Ibrahim AM**, Koolen PG, Lin SJ. Is There an Association between Component Separation and Venous Thromboembolism? An Analysis of the NSQIP Database in 34,541 Patients Undergoing Incisional/Ventral Hernia Repair. **Submitted for publication**

Kim K, **Ibrahim AM**, Koolen PG, Seyidova N, Lin SJ. Analysis of Morbidity and Mortality in Patients Undergoing Skull Base Reconstruction: An Outcomes Review of a National Patient Population. **Submitted for publication**

Ibrahim AM, Vargas CR, Koolen PG, Chuang D, Lin SJ, Lee BT. Readability of Online Patient Resources for Melanoma. **Submitted for publication**

PhD Portfolio Summary

Summary of PhD training and teaching activities

Name of PhD student:	A.M.S. Ibrahim
Erasmus MC Department:	Plastic, Reconstructive and Hand Surgery
PhD period:	April 1st, 2010 - November 30th, 2014
Promoter:	Prof.dr. S.E.R. Hovius
Supervisor:	Dr. M.A.M. Mureau, S.J. Lin, MD, FACS

1. PhD training	
	Year
General academic skills	
• Biomedical English writing and communication	Self taught
Research skills	
• EndNote Essentials Workshop (Hands-On). Harvard Medical School Countway Library, Boston, MA	2010
• Searching with PubMed. Harvard Medical School Countway Library, Boston, MA	2010
• The New NIH Grant Format from the Reviewer's Perspective. Beth Israel Deaconess Medical Center, Boston, MA	2010
• Navigating the IRB. Beth Israel Deaconess Medical Center, Boston, MA	2011
• Introduction to Quantitative Methods: Study Design and Data Analysis. Harvard School of Public Health/Beth Israel Deaconess Medical Center, Boston, MA	2012
• Scientific Writing "How to Assemble a Manuscript for Publication". Beth Israel Deaconess Medical Center, Boston, MA	2013
In-depth courses	
• Head and Neck Cadaver Dissection Laboratory. Waltham, MA	2010
Oral Presentations	
• Neural Prosthetic Implant Device for Chemical and Electrical Stimulation. Presented at the 55th Annual Meeting of The Plastic Surgery Research Council. San Francisco, California	2010
• Vasopressors and Reconstructive Flap Perfusion. Presented at Anesthesia Grand Rounds, Beth Israel Deaconess Medical Center, Boston, Massachusetts	2010
• Tumors of The Parotid Gland/Head and Neck Cancer. Presented at Plastic Surgery Grand Rounds (Core Curriculum), Shriners Burn Hospital, Boston, Massachusetts	2011
• Graded Nerve Modulation Using a BioMEMS Device. Presented at the 56th Annual Meeting of The Plastic Surgery Research Council. Louisville, Kentucky	2011
• Orthopedic PGY-1's Minimal Goals and Objectives. Presented at Orthopedic Intern Orientation for Plastic Surgery. Massachusetts General Hospital, Boston, Massachusetts	2011
• Electrochemical Prosthesis Using a BioMEMS Device. Presented at Plastic Surgery Division Meeting, Beth Israel Deaconess Medical Center, Boston, Massachusetts	2011
• Development of a Facial Nerve Neuroprosthetic Device. Presented at Harvard Plastic Surgery Grand Rounds, Shriners Burn Hospital, Boston, Massachusetts	2011
• Advanced Nerve Stimulation and Inhibition by Ion Selective Membrane (ISM) Electrodes. Presented in Cellular Biophysics: Special Lecture, Massachusetts Institute of Technology (MIT), Cambridge, Massachusetts	2011

• Liposuction, Weight Reduction Surgery. Presented at the National Academies (Biomedical Engineering Materials and Applications (BEMA) Roundtable Meeting. Washington, DC	2012
• Near-Infrared Imaging For Intra-operative Assessment Of Perfusion In Vascularized Bone. Presented at the 7th Annual academic Surgical Congress. Las Vegas, Nevada	2012
• Assessment Of Perfusion In A Partial Face Transplantation Model With A Near-Infrared Imaging System. Presented at the 7th Annual academic Surgical Congress. Las Vegas, Nevada	2012
• Low-Power Nerve Activation and Inhibition By Ion Selective Electrodes. Presented at the Johnson & Johnson Corporate Office of Science and Technology (COSAT) Research Briefing, Massachusetts Institute of Technology. Cambridge, Massachusetts	2012
• Utilization of Spatial Frequency Domain Imaging to Monitor Composite Facial Transplantation with Microsurgical Vascular Anastomosis. Presented at the 53rd Annual Meeting of the New England Society of Plastic and Reconstructive Surgeons. Woodstock, Vermont	2012
• Professional Courtesy in Plastic Surgery. Presented at the 53rd Annual Meeting of the New England Society of Plastic and Reconstructive Surgeons. Woodstock, Vermont	2012
• BioMEMS for Electrochemical Prosthesis. Presented at Plastic Surgery Grand Rounds, University of Chicago Medical Center, Chicago, Illinois	2012
• Development of a Facial Neuroprosthetic Device. Presented at The Wellman Center for Photomedicine. Boston, Massachusetts	2012
• Use of the NSQIP Database for Comparison of Complication Rates in Tissue Expander/Implant Based Breast Reconstructions With and Without the Use of Acellular Dermal Matrix. Presented at the Clowes Research Symposium 2012, Beth Israel Deaconess Medical Center, Boston, Massachusetts	2012
• Common Patterns of Reconstruction for Mohs Defects in the Head and Neck. Presented at the 8th Annual Academic Surgical Congress. New Orleans, Louisiana	2013
• Patient Involvement in The Decision Making Process Improves Satisfaction And Quality of Life in Postmastectomy Breast Reconstruction. Presented at the 8th Annual Academic Surgical Congress. New Orleans, Louisiana	2013
• Epidemiologic Assessment of Facial Fractures Using the NSQIP Database. Presented at the Northeastern Society of Plastic Surgeons 30th Annual Meeting. Washington, DC	2013
• Does Flap Reconstruction Make a Difference in Complications Following Laryngopharyngectomy? Analysis of the NSQIP. Presented at the Northeastern Society of Plastic Surgeons 30th Annual Meeting. Washington, DC	2013
• Abdominal Contouring Surgery following Massive Weight Loss: Analysis of 4, 925 patients undergoing Abdominoplasty with and without Concurrent Hernia Repair. Presented at the Northeastern Society of Plastic Surgeons 30th Annual Meeting. Washington, DC	2013
• Population Preferences of Undergoing Brachioplasty for Arm Laxity. Presented at the Northeastern Society of Plastic Surgeons 30th Annual Meeting. Washington, DC	2013
• BioMEMS for Neuroprosthesis. Presented at Plastic Surgery Visiting Professor (Dr. Paul S. Cederna) Research Discussion Forum, Beth Israel Deaconess Medical Center, Boston, Massachusetts	2013
• 3D-Printing: A Plastic Surgery Application in Evolution. Presented at Plastic Surgery The Meeting 2013. San Diego, California	2013
• Analysis of the NSQIP Database in 19,100 Patients: How Does Acellular Dermal Matrix Affect Complication Rates in Implant Based Breast Reconstruction? Presented at Plastic Surgery The Meeting 2013. San Diego, California	2013
• Silk-Based Devices to Modulate Fracture Healing. Presented at Plastic Surgery The Meeting 2013. San Diego, California	2013
• Effects of Statins on Ischemia-reperfusion Complications in Autologous Free Flap Breast Reconstruction. Presented at the 8th Annual Academic Surgical Congress. San Diego, California	2014

• Analyzing Patient Preference for Nipple-Areola Complex Reconstruction Using Utility Outcome Studies. Presented at the American Association of Plastic Surgeons 93rd Annual Meeting. Miami Beach, Florida	2014
• The Decision to Undergo Mastopexy for Breast Ptosis: Analysis of Patient Preferences Using Utility Outcome Scores. Presented at the 68th Annual Meeting of the Canadian Society of Plastic Surgeons. Montreal, Quebec	2014
Poster Presentations	
• Ion-Specific Membranes: A New Neuroprosthetic Device for the Treatment of Neurological Diseases. Presented at the Massachusetts Biotechnology Council (MassBio) Annual Meeting 2011, Cambridge, Massachusetts	2011
• A New Neuroprosthetic Device for Electrochemical Activation and Inhibition of Neuromuscular Systems. Presented at the 4th Massachusetts Life Sciences Innovation (MALSI) Day, Boston, Massachusetts	2011
• Microfabricated ion-selective micro electrodes for enhanced neuromuscular stimulation. Presented at the BioMethods Boston Conference, Boston, Massachusetts	2011
• Near-Infrared Imaging For Intra-operative Assessment Of Perfusion In Vascularized Bone. Presented at the 58th Annual Meeting, Massachusetts Chapter, American College of Surgeons, Boston, Massachusetts	2011
• Assessment Of Perfusion In A Partial Face Transplantation Model With A Near-Infrared Imaging System. Presented at the 58th Annual Meeting, Massachusetts Chapter, American College of Surgeons, Boston, Massachusetts	2011
• The Neurologic Dimmer Switch. Presented at Harvard Medical School Surgery Research Day, Boston, Massachusetts	2012
• Tissue Oximetry Free Flap Monitoring in the Head and Neck. Presented at the 2012 American Academy of Otolaryngology – Head and Neck Surgery Foundation Annual Meeting & OTO EXPO, Washington, DC	2012
• Intraoperative CT: A Teaching Tool for the Surgical Management of Complex Facial Fractures. Presented at Harvard Medical School Medical Education Day, Boston, Massachusetts	2012
• Use of the NSQIP Database for Comparison of Complication Rates in Tissue Expander/Implant Based Breast Reconstructions With and Without the Use of Acellular Dermal Matrix. Presented at Harvard Medical School Soma Weiss Student Research Day, Boston, Massachusetts	2013
• A Smart Fix: Silk Based Devices to Modulate Fracture Healing. Presented at Harvard Medical School Surgery Research Day, Boston, Massachusetts	2013
• The Ideal Nasolabial Angle in Aesthetic Rhinoplasty. Presented at the Northeastern Society of Plastic Surgeons 30th Annual Meeting. Washington, DC	2013
• High Impact Articles in Rhytidectomy. Presented at The Aesthetic Meeting 2014, San Francisco, California	2014
• High Impact Articles in Rhinoplasty. Presented at The Aesthetic Meeting 2014, San Francisco, California	2014
• Spray-on Bandage for Monitoring of Tissue Oxygenation. Presented at the Third Harvard Medical School Surgery Research Day, Boston, Massachusetts	2014
• Analysis of the NSQIP Database in 479 Patients Undergoing Skull Base Surgery: The Impact of Reconstruction. Presented at the Third Harvard Medical School Surgery Research Day, Boston, Massachusetts	2014
• Use of ADM in breast reconstruction: Analysis of the NSQIP database. Presented at the Third Harvard Medical School Surgery Research Day, Boston, Massachusetts	2014

National and International Conferences	
• 2010 American Academy Of Otolaryngology-Head And Neck Surgery Annual Meeting & OTO EXPO, Boston, Massachusetts	2010
• Massachusetts Biotechnology Council (MassBio) Annual Meeting 2011, Cambridge, Massachusetts	2011
• 56th Annual Meeting of the Plastic Surgery Research Council, Louisville, Kentucky	2011
• 4th Massachusetts Life Sciences Innovation (MALSI) Day, Boston, Massachusetts	2011
• 58th Annual Meeting, Massachusetts Chapter, American College of Surgeons, Boston, Massachusetts	2011
• Inaugural Harvard Medical School Surgery Research Day, Boston, Massachusetts	2012
• 53rd Annual Meeting of the New England Society of Plastic and Reconstructive Surgeons, Woodstock, Vermont	2012
• Harvard Medical School Medical Education Day, Boston, Massachusetts	2012
• Second Annual Harvard Medical School Surgery Research Day, Boston, Massachusetts	2013
• Northeastern Society of Plastic Surgeons 30th Annual Meeting. Washington, DC	2013
• Plastic Surgery The Meeting 2013. San Diego, California	2013
• Third Annual Harvard Medical School Surgery Research Day, Boston, Massachusetts	2014

2. Teaching activities	
	Year
Supervision of research students	
• Aldebarani Gonzalez (Carol Davila University of Pharmacy and Medicine, Bucharest Romania)	2011
• Daniel Gittings (Boston University School of Medicine, Boston, MA)	2012
• Marina Shuster (Harvard Medical School, Boston, MA)	2012-present
• Jason Silvestre (Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA)	2012
• Chen Zheng (Tufts University School of Medicine)	2013-present
• Jie Sun (Harvard School of Dental Medicine, Boston, MA)	2013-present