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Breast

Biologic Response With and Without Acellular Dermal Matrix in Breast Reconstruction

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Background: Acellular dermal matrices (ADMs) are biologic meshes commonly used in implant-based breast reconstruction (IBBR) procedures to provide implant support and coverage. Although the etiology is not well understood, increasing preclinical and clinical evidence suggest that ADMs may help prevent capsular contracture, a frequent complication of IBBR, by modulating the inflammatory response in the tissue surrounding breast implants. The objective of this narrative review is to discuss the evidence supporting the role of inflammation in capsular contracture following IBBR without ADM, and to characterize the potential mechanism(s) by which ADMs may reduce the incidence of capsular contracture in IBBR.

Methods: Relevant studies in English published up to December 31, 2023, were identified from 4 databases (BIOSIS Previews, Embase, MEDLINE, and Northern Light Life Sciences Conference Abstracts) using search terms such as "breast" and "capsular contracture."

Results: This review discusses the potential factors (eg, expander-to-implant reconstruction, diminished collagen integrity, postmastectomy radiation therapy, surface of implant, plane of placement, incision type, hematoma, seroma, postoperative infection, and biofilm) and emerging biomarkers (eg, *NRG1*, *IL-8*, TIMP-1, TIMP-2, *TIMP-4*, MMP2, *MMP12*, *ACAN*, *SAA1*, *TNFSF11*, and hyaluronan) that may be able to predict capsular contracture. The available evidence that tissue integration of ADMs modulates the wound healing process and inflammation, and the available clinical evidence, which indicates that ADMs may decrease rates of capsular contracture following postmastectomy radiation therapy, are summarized.

Conclusions: The studies summarized in this review suggest that ADMs may reduce the likelihood of capsular contracture in IBRR compared with no ADM use. *(Plast Reconstr Surg Glob Open 2025;13:e6671; doi: 10.1097/GOX.0000000000006671; Published online 2 April 2025.)*

INTRODUCTION

Acellular dermal matrices (ADMs) are commonly used in breast reconstruction procedures.[1] ADMs are biologic meshes developed from human or animal skin (eg, porcine or bovine)[2,3] that are processed to remove the cells, leaving the extracellular matrix, which acts as a support structure and a natural scaffold for soft tissue repair.[4,5] A biologic ADM scaffold can integrate into the host tissue, potentially modulating its response to infectious or inflammatory processes, factors that delay wound healing, and may impact other surgical complications.[6,7] ADMs may help stabilize the breast implant or tissue expander, provide an alternative to recruitment of adjacent muscles and fascia for support, decrease donor-site morbidity, and improve speed of recovery from surgical procedures.[8,9] A growing body of evidence demonstrates other benefits of the use of ADMs, including improvement in aesthetic outcomes by supporting contour and symmetry,[10–12] surgical wound healing,[13] and a possible reduction in capsular contracture, one of the more common complications associated with implant-based breast reconstruction (IBBR).[14–17] Preclinical and clinical evidence suggests that ADMs may mitigate capsular contracture by modulating the acute

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inflammatory factors within the tissue that surrounds the breast implants.[18,19]

The objectives of this review are to discuss evidence supporting the role of inflammation in capsular contracture following IBBR without ADM, characterize the mechanism by which ADMs may reduce the incidence of capsular contracture, and describe how modulation of the wound healing process and inflammatory mechanisms may facilitate the integration of ADMs and reduce the likelihood of capsular contracture.

SEARCH STRATEGY

In this narrative review, we selected relevant literature from 4 databases (BIOSIS Previews, Embase, MEDLINE, and Northern Light Life Sciences Conference Abstracts) using search terms such as "breast" and "capsular contracture" to provide an overview of capsular contracture in breast surgery. More detailed search criteria are reported in Table 1; relevant studies in English published up to December 31, 2023, were included in this review.

BIOLOGICAL PROCESSES AND FACTORS CONTRIBUTING TO CAPSULAR CONTRACTURE

Capsular contracture occurs in 2.8%–20.4% of implant-based breast augmentation procedures[20] and up to 30% of breast reconstructions.[21] It is globally accepted that capsular contracture remains the most common complication following implant-based breast surgery.[20,22] Following IBBR, a fibrous capsule composed of myofibrils and collagen encircles the implant as part of the typical healing process. However, under pathologic conditions, this capsule thickens and causes firmness and pain in the breast.[23]

Evidence suggests that excessive peri-implant fibrosis and abnormal capsular formation may play a key role in pathogenesis of capsular contracture.[24] Histologic analysis of silicone breast implant capsules showed distinct tissue organization within the capsule characterized by an avascular layer of scar tissue or bundles of collagen, the presence of macrophages, and synovial-like metaplasia. This distinct tissue organization within the capsule suggests a potential role for an inflammatory response.[25,26]

Table 1. Search Criteria

	Search Criteria
Search terms	Breast; capsular contracture; capsular fibrosis; acellular dermal matrix; ADM; AlloDerm; FlexHD; Dermacell; Cortiva; GalaFlex; Durasorb; Surgimend; Ovitex PRS; Allomax; Allomend; Simpliderm; AlloPatch; EGIS N/5 acellular dermal matrix; Epiflex; PriMatrix; SureDerm; Xe-Derma; granulat*; regenerat*; inflammat*; immun*; host; reactivity; respons*; vascul*; capillary; fibroblast; MMP; metallo*; collagenase; vascular*; revascular*; cytokine; interleukin*; foreign*; macrophage*; growth factor; antibod*
Inclusion/exclusion criteria	• Articles were limited to those published in English • Preclinical studies, phase 1–4 studies, systematic reviews, meta-analyses, and case reports/case series were included
Publication dates	Articles published up to December 31, 2023, were included

Takeaways

Question: Do acellular dermal matrices (ADMs) have a role in prevention of capsular contracture following implant-based breast reconstruction (IBBR)?

Findings: This narrative review summarizes evidence supporting the role of inflammation in capsular contracture following IBBR, potential mechanisms by which ADMs reduce the incidence of capsular contracture, factors and biomarkers that may predict capsular contracture, and the potential for ADMs to be protective against capsular contracture following postmastectomy radiation therapy.

Meaning: The studies included in this review suggest that the use of ADMs in IBBR may reduce the likelihood of capsular contracture compared with no ADM use, indicating an important area for further clinical study and development.

The Role of Inflammation

The etiology of capsular contracture is multifactorial, and various factors that increase inflammation may ultimately result in this negative outcome.[27] Factors that can lead to capsular contracture include the introduction of bacteria, biofilm, or blood, tissue trauma, silicone gel bleed, radiation therapy, hematoma, and seroma (Fig. 1).[22,27–29] Efforts to identify potential factors and biomarkers of capsular contracture have been made (Table 2). One clinical study (N = 10 patients) demonstrated a positive correlation between the histopathologic score, a semiquantitative score ranging from a minimum of 0 to a maximum of 18 (higher score indicates more severe cellular fibrosis and capsule inflammation), of an ADM capsule biopsy and the 6-month postoperative Baker grade (P = 0.009).[39] In this study, the mean (SD) histopathologic scores for the ADM capsules and subpectoral capsules were 7.9 (3.4) and 11.4 (3.4), respectively, with lower scores indicating less cellular fibrosis and capsule inflammation.[39]

To identify potential biomarkers of capsular contracture, a data mining study identified 8 genes that may be related to capsular contracture: matrix metalloproteinase 2 (*MMP2*), transforming growth factor beta 1, *MMP9*, tumor necrosis factor alpha, estrogen receptor 11, insulin-like grown factor 1, interleukin *(IL)-10*, and *MMP1* (Table 2).[40] Additionally, 1 study determined that the gene *NRG1* was upregulated in patients with capsular contracture and may contribute to capsular contracture pathogenesis by increasing scar tissue formation via excess extracellular matrix deposition.[36] Identification of potential biomarkers of capsular contracture is a new area of research, and additional preclinical and clinical studies are needed to elucidate the role these factors may play in capsular contracture.

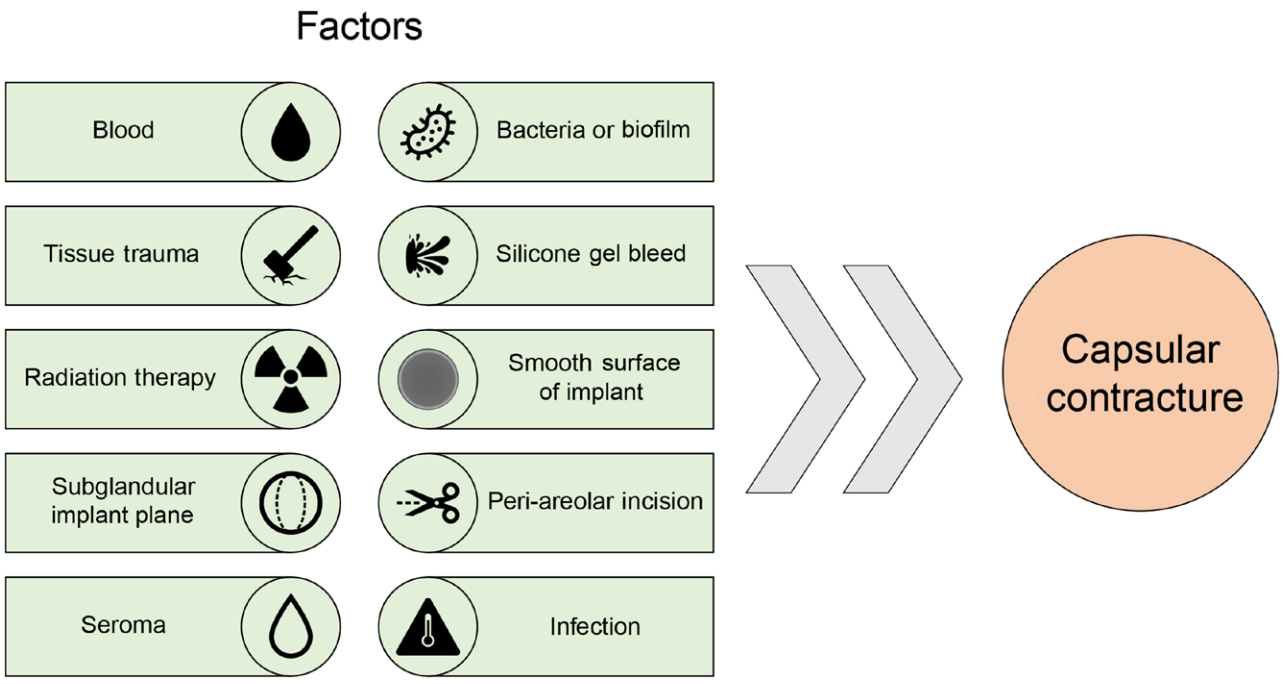

Fig. 1. Factors that may be responsible for the development of capsular contracture following implant-based breast reconstruction (IBBR).[22,27]

However, data from preclinical studies support that capsular contracture is a consequence of inflammatory processes.[41] Studies of biopsies obtained from contracted breast capsules have demonstrated the association of inflammation with the formation of capsular contracture.[26,37,42–45] Contracted breast capsules showed the presence of numerous inflammatory cells, such as macrophages and myofibroblasts,[26,46,47] and inflammatory molecules, such as toll-like receptor 4, tissue inhibitors of metalloproteinase (*TIMP-4*), *IL-1β, IL-8, IL-6, IL-10*, interferon γ, transforming growth factor beta, tumor necrosis factor alpha, and *CD248*.[37,42–46] Coating the surface of implants with a biocompatible anti-inflammatory agent (Met-Z2-Y12) reduced capsule thickness and attenuated capsular contracture in a murine model,[48] further supporting that inflammatory processes are a factor in the development of capsular contracture.

Additionally, significantly higher levels of bacterial colonization in high-grade contracted patient samples (66.7%) compared with low-grade samples (0%; $P < 0.001$) suggest that bacterial infection may result in increased inflammation and fibrosis, leading to capsular contracture. The most common bacterial contaminants identified were coagulase-negative staphylococci (33.3% of patients), *Propionibacterium acnes* (21.8%), *Staphylococcus aureus* (8.3%), and *Escherichia coli*/β-hemolyzing streptococci co-colonies (4.2%).[49] The potential link between bacterial presence, increased inflammation, and capsular contracture was demonstrated when repeated injection of lipoteichoic acid, a component of the cell wall of gram-positive bacteria, induced capsular contracture in a preclinical murine model through activation of the *IL-6/STAT3* signaling pathway.[43]

A study investigating molecular phenotypic descriptors of capsular contracture using whole genome arrays of biopsy samples from control (Baker I–II) and contracted (Baker III–IV) tissue showed that the key inflammatory target genes *IL-8*, *TIMP-4*, aggrecan, *MMP12*, serum amyloid A1, and tissue necrosis factor superfamily member 11 were dysregulated in contracted capsules and therefore may serve as biomarkers for capsular contracture.[37] Histologic evaluation of contracted capsules from another study (N = 17 patients) demonstrated a significant correlation between capsular contracture and increased serum concentrations of *TIMP-1*, *TIMP-2*, *MMP2*, and hyaluronan. A decreased ratio of *MMP* to *TIMP*, potentially indicating increased degradation of the extracellular matrix, was also correlated with capsular contracture.[38] Further studies are needed to elucidate the roles that these factors and biomarkers may have in capsular contracture.

CLINICAL EVIDENCE SUGGESTING THAT ADM USE MITIGATES CAPSULAR CONTRACTURE

Numerous studies support lower rates of capsular contracture with the use of ADM in breast reconstruction. In a large study that compared 5-year outcomes in more than 9500 women who underwent breast reconstruction with or without ADM (product not specified), the rate of capsular contracture in patients undergoing revision-reconstruction with ADM was 1.4% compared with 8.9% without ADM.[4] Additionally, immediate IBBR with and without the ADM AlloDerm (Allergan Plc, Bridgewater, NJ) in 203 patients demonstrated a capsular contracture rate of 3.8% with up to 4 years of AlloDerm use, versus

Table 2. Factors and Biomarkers for Capsular Contracture

Factor	Potential Role in Capsular Contracture	
Expander-to-implant reconstruction (vs direct-to-implant reconstruction)[15]	Capsular contracture may occur due to: • ADM and overlying skin poorly interfaced due to skin redundancy and dead space • ADM placement over inflamed surface • Decreased mastectomy flap perfusion	
Diminished collagen integrity[30]	Increases inflammation, leading to capsular contracture	
Postmastectomy radiation therapy[9,31–33]	• Increase in myofibroblasts is correlated with Baker score (a measure of capsular contracture) • Ionizing radiation results in myofibroblast dysregulation and sustained fibrogenesis, leading to capsular contracture	
Surface of implant[34]	• Textured implants are associated with lower rate of occurrence of capsular contracture • Surface pores may induce a collagenous fiber orientation that is multidirectional, which limits the fibrous capsule from contracting	
Plane of placement[34]	• Submuscular implant placement is associated with lower incidence of capsular contracture compared with subglandular implants • The pectoralis muscles provide a vascularized tissue layer that acts as a barrier to endogenous bacteria found in the glandular tissues	
Incision type[34]	Periareolar incisions are associated with higher rates of capsular contracture compared with inframammary and transaxillary incisions, potentially due to endogenous bacteria release from the glandular tissue as the implant pocket is developed	
Hematoma[34]	Increases inflammation, which may lead to capsular contracture	
Seroma[34,35]	May contribute to infection and/or capsular contracture	
Postoperative infection[34]	Increases inflammation, which may lead to capsular contracture	
Biofilm[34]	Extends the proinflammatory phase, which may lead to excess capsular fibrosis	
Biomarker	**Increased or decreased capsular contracture?**	**Potential role in capsular contracture**
NRG1[36]	Increased	Increases deposition of the extracellular matrix and scar tissue formation
IL-8[37]	Increased	Recruits neutrophils to the implant and results in phagocytosis of the implant
TIMP-1[38]	Increased	Elevated *TIMP-1* contributes to scar formation
TIMP-2[38]	Increased	Less inhibition of *MMP2*, leading to extracellular matrix degradation
TIMP-4[37]	Decreased	Less inhibition of *MMPs*, leading to extracellular matrix degradation
MMP2[38]	Increased	Role in extracellular matrix degradation and remodeling
MMP12[37]	Increased	Role in extracellular matrix degradation and remodeling
ACAN[37]	Decreased	Structural component of the extracellular matrix
SAA1[37]	Decreased	Expressed due to increased inflammation
TNFSF11[37]	Decreased	Involved in T-cell activation
Hyaluronan[38]	Increased	Marker of inflammation and fibrosis

ACAN, aggrecan gene; *NRG1*, neuregulin-1 gene; *SAA1*, serum amyloid A 1 gene; *TNFSF*, tumor necrosis factor superfamily (ligand) member 11 gene.

19.4% without.[50] There was no evidence of capsular contracture in an analysis of 10 cases of ADM-assisted prepectoral breast reconstruction (ADM: Braxon; Decomed Srl, Venice, Italy; median follow-up period: 49.2 mo; follow-up range: 48–50 mo; age range: 34–63 y; nipple-sparing mastectomy: 7 patients; skin-sparing mastectomy: 3 patients).[51] Capsular contracture was not observed in a 1.5-year retrospective study comparing soaking Artia Reconstructive Tissue Matrix (Allergan Plc) in povidone-iodine versus triple-antibiotic rinse for mitigating surgical site infection in 257 ADM-assisted breast reconstructions.[52]

A 3.1% rate of occurrence of capsular contracture with the use of ADM (either DermACELL [LifeNet Health, Virginia Beach, VA] or MegaDerm [L&C Bio Corp., Seoul, Korea]) in 159 patients who underwent direct-to-implant breast reconstruction was also reported in a 2-year retrospective study.[53] A retrospective study that included more than 1500 ADM-assisted breast reconstructions from December 2001 to May 2014 reported that the cumulative incidence of capsular contracture was 0.8%. AlloDerm was the predominant ADM used (93%), followed by Strattice (Allergan Aesthetics, an AbbVie Company, Branchburg, NJ; 6.9%) and FlexHD (MTF/Ethicon, Inc., Somerville, NJ; 0.1%).[54]

Few clinical studies have compared the type of ADM used and postoperative complications following IBBR. A retrospective study with a minimum follow-up of 3 months included 81 patients who underwent IBBR with ADM and found there were no significant differences in postoperative outcomes reported for patients treated with porcine ADM (Strattice) compared with bovine ADM (Surgimend; TEI Biosciences, Boston, MA).[55] No patients reported capsular contracture in this study.[55] A scoping review of clinical studies investigated complications associated with human, porcine, and bovine ADMs.[2] Capsular contracture rates were low for all ADM types.[2] Bovine ADM had the highest rate of capsular contracture (6.1%), followed by porcine ADM (2.2%), and human ADM (1.6%).[2]

Similarly, a retrospective study of 41 patients who underwent breast reconstruction with ADM with a median follow-up of 3 years reported that complication rates were lowest for human ADM (7%), followed by porcine ADM (19%), and bovine ADM (44%).[56] Prospective, clinical studies are needed to definitively demonstrate whether a link exists between the type of ADM used in IBBRs and postoperative outcomes.

CLINICAL EVIDENCE OF DECREASED INFLAMMATION WITH ADMS

Inflammation may be lessened in breast reconstruction with use of ADMs, according to clinical studies. A retrospective study of 20 patients demonstrated fewer inflammatory cell markers, such as macrophages and myofibroblasts, in implant capsules with AlloDerm compared with native implant capsules without ADM.[19] Another study included 20 patients who underwent immediate prepectoral breast reconstruction with tissue expanders totally covered with Braxon, a porcine ADM, and 30 patients who underwent submuscular breast reconstruction with tissue expanders without ADM. This study found statistically significantly fewer proinflammatory macrophages and myofibroblasts in the ADM group compared with the submuscular breast reconstruction group after 1 year.[57]

ADM TISSUE INTEGRATION AND MODULATED HOST RESPONSE

In addition to the factors discussed earlier, evidence suggests that human ADM is able to integrate into the host tissue and modulate its immune responses to pathogens and inflammatory stimuli, which may reduce the possibility of capsular contracture occurring after breast reconstruction.[58] Preclinical studies demonstrate that ADM tissue integration is characterized by vascular integration and infiltration of cells leading to host tissue remodeling,[59] which may facilitate this integration process. Additionally, a preclinical study in a nonhuman primate tissue expander model demonstrated that loss of collagen integrity may be predictive of inflammation and capsule formation.[30] Rat tissue specimens harvested at 3, 7, and 14 days after implantation of AlloDerm, analyzed using histologic methods, showed evidence of host myofibroblast and endothelial cell migration and proliferation through the ADM. This resulted in revascularization of the ADM and integration into the host tissue.[60] Through revascularization, infiltration with cells involved in inflammatory, proliferative, and remodeling phases of normal wound healing, and tissue integration, AlloDerm appeared to facilitate wound healing.[60] A study of 20 rabbits implanted with silicone membrane fragments in the left thoracodorsal region, 10 with implants wrapped in AlloDerm and 10 without, found a statistically significant decrease in myofibroblast and fibroblast cell counts and capsule thickness with AlloDerm-wrapped silicone implants compared with implants alone. The implants wrapped with AlloDerm also appeared more mobile, with less distinct borders with the surrounding tissue compared with the implants alone. The findings suggested that AlloDerm provided a biologic medium for tissue integration as well as migration and repopulation of host fibroblasts and endothelial cells, thereby facilitating healing and discouraging capsule formation.[61]

ADM appears to provide a biologic matrix scaffold that the body recognizes and, thus, through reduction of inflammatory signals and integration into patient tissues, may alter the wound healing cascade (Fig. 2).[60] An in vitro study in which human peripheral blood mononuclear cells from healthy volunteers were exposed to various biologic meshes, including AlloDerm, AlloMax (CR Bard/Davol, Inc., Cranston, RI), and FlexHD, found that cells exposed to AlloDerm produced statistically significantly lower levels of *IL-1β* and *IL-6* cytokines in addition to lower levels of *IL-8* and *VEGF* compared with the 2 other human ADMs studied, indicating limited immune activation.[62] After enclosure of a tissue expander with AlloDerm, there was significantly reduced *IL-6* production in nonhuman primates, fewer macrophages, and minimal capsule formation compared with the tissue expander alone or the tissue expander enclosed in AlloMax ADM.[63] Implantation of silicone prostheses with and without xenogenic ADM in a rodent model demonstrated reduced thickness of the myofibroblast tissue layer surrounding the implant and reduced inflammatory signals compared with the no-ADM cohort.[64]

In a long-term case study of a single patient, AlloDerm was fully integrated with no evidence of capsule or fibrotic response 12 years after breast reconstruction.[65] A histological and electron microscopic study in 22 patients found that an experimental human ADM derived from skin grafts obtained from a tissue bank was repopulated with fibroblasts, myofibroblasts, lymphocytes, macrophages, granulocytes, and mast cells, and was well vascularized several months after delayed-stage breast reconstruction,[66] indicating full tissue integration. A retrospective study of 68 patients who underwent 2-stage tissue expander/IBBR with AlloDerm using histologic analysis after expander placement (mean follow-up: 6 mo) reported the presence of neovascularization and cellular repopulation in the implant without chronic inflammation.[9] In a prospective cohort study of 10 patients, DermACELL, a human ADM, exhibited fibroblast infiltration and revascularization 6 weeks following breast reconstruction. In this study, AlloDerm and FlexHD showed less fibroblast infiltration and revascularization at this early postoperative timepoint, but the authors acknowledged that further studies comparing human ADMs are needed.[67]

PROTECTIVE ROLE OF ADM IN RELATION TO RADIATION THERAPY

Several clinical studies have identified postmastectomy radiation therapy as a potential factor in the development of capsular contracture.[9,13,31–33] A retrospective study that included patients who underwent mastectomy with breast reconstruction found an 18.7% rate of capsular contracture after postmastectomy radiation therapy compared

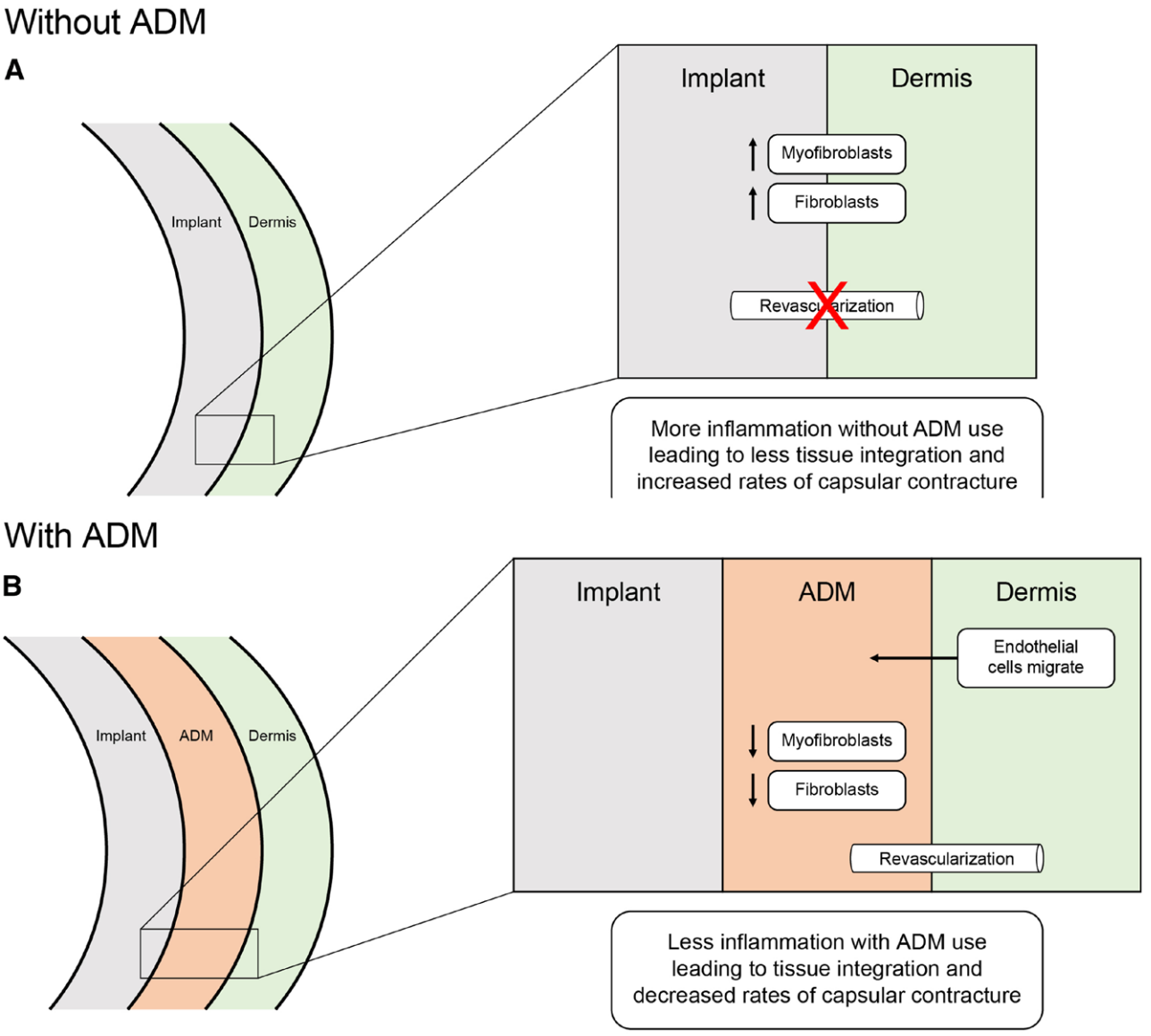

Fig. 2. Inflammatory host response to implant-based breast reconstruction (IBBR) after healing (A) without ADM and (B) with ADM.[18,60,61]

with 7.5% without postmastectomy radiation therapy.[32] Another retrospective study of 84 patients who received radiation therapy and then underwent breast reconstruction with ADM (86 breasts) reported a low occurrence (n = 5; 5.8%) of clinically significant capsular contracture (Baker's grade III or IV).[68]

Radiation therapy may stimulate inflammation via overproduction of proinflammatory cytokines and increased cellular infiltration.[69,70] It is postulated that the use of ADMs may be protective and decrease rates of capsular contracture–related reoperation and explantation for patients undergoing postmastectomy radiation therapy by modulating this inflammatory response.[13,71] In a clinical study, 30 patients underwent immediate 2-stage IBBR with, or without, the use of CG CryoDerm (CGBio, Seoul, Korea), a human ADM. In this study, the biopsies of irradiated and nonirradiated submuscular capsules with and without ADM were examined. There was decreased expression of inflammatory molecules, such as transforming growth factor beta-1, in irradiated capsules with ADM, as well as lower levels of myofibroblasts, fibroblasts, vascularity, and activated macrophages in both the irradiated and nonirradiated capsules with ADM overall.[72] In a study of patients treated with postmastectomy radiation therapy, breast reconstructions that utilized ADMs (AlloDerm or Surgimend) were associated with fewer expander failures and lower risk of reoperation/explantation than reconstructions that did not utilize ADMs.[13] A 4-year retrospective cohort study demonstrated a 6% rate of capsular contracture in nonirradiated capsules versus 13% in irradiated capsules with immediate IBBRs performed with porcine ADM.[73]

LIMITATIONS

The goal of this narrative review is to provide an overview and synthesis of the literature, drawing from a

wide range of studies and sources. It aims to identify key themes, trends, and gaps in the existing scientific literature. Because it is not meant to be a formal systematic literature review, the potential for bias regarding the inclusion or exclusion of articles and the interpretation of the findings may be a limitation of the data and conclusions presented herein.

CONCLUSIONS

Preclinical and clinical studies suggest that inflammatory mechanisms play an important role in capsule formation and the development of capsular contracture. Discovering biomarkers of capsular contracture is an exciting, new area of research, and future studies are required to elucidate their roles in pathogenesis of capsular contracture. Evidence from these studies suggests that the use of ADM reduces the incidence of capsular contracture, potentially by modulating the host response to inflammatory processes following IBBR and/or postmastectomy radiation therapy. The use of ADM in IBBR may thus lower the likelihood of capsular contracture compared with no ADM use, indicating an important area for further clinical study and development.

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DISCLOSURES

Dr. Sbitany is a consultant for AbbVie, Inc. Dr. Mukhatyar is a former employee of AbbVie. Drs. Hammer, Hoonjan, Leung, and Gardocki-Sandor are full-time employees of AbbVie and may own stock in the company. Allergan Aesthetics, an AbbVie Company, funded this study. Medical writing support was provided by Lindsay Achzet, PhD and Regina Kelly, MA of Peloton Advantage, LLC, an OPEN Health company, and was funded by Allergan Aesthetics, an AbbVie Company.

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