A Meta-Analysis of Human Acellular Dermis and Submuscular Tissue Expander Breast Reconstruction

John Y. S. Kim, M.D.
Armando A. Davila, B.S.
Scott Persing, B.A., M.P.H.
Caitlin M. Connor, B.A.
Borko Jovanovic, Ph.D.
Seema A. Khan, M.D.
Neil Fine, M.D.
Vinay Rawlani, M.D.

Chicago and Maywood, Ill.

Background: Human acellular dermal matrix has become an increasingly used adjunct to traditional submuscular tissue expander/implant breast reconstruction, but there is no strong consensus regarding complication outcomes. This study stratified outcomes based on a meta-analysis of complications.
Methods: A query of the MEDLINE database for articles on human acellular dermal matrix and submuscular tissue expander breast reconstruction yielded 901 citations. Two levels of screening identified 48 relevant studies. The DerSimonian and Laird random-effects model was used to perform the meta-analysis. Risk ratios and pooled complication rates were calculated for each outcome of interest.
Results: Nineteen studies reporting human acellular dermal matrix ($n = 2037$) and 35 reporting submuscular outcomes ($n = 12,847$) were used to estimate complication rates. Rates were generally higher in acellular dermis patients: total complications, 15.4 versus 14.0 percent; seroma, 4.8 versus 3.5 percent; infection, 5.3 versus 4.7 percent; and flap necrosis, 6.9 versus 4.9 percent. Six studies reporting both acellular dermis and submuscular outcomes were used to estimate relative risks. There was an increased risk of total complications (relative risk, 2.05; 95 percent CI, 1.55 to 2.70), seroma (relative risk, 2.73; 95 percent CI, 1.67 to 4.46), infection (relative risk, 2.47; 95 percent CI, 1.71 to 3.57), and reconstructive failure (relative risk, 2.80; 95 percent CI, 1.76 to 4.45) in acellular dermis patients.
Conclusions: The meta-analysis suggests that the use of human acellular dermal matrix increases complication rates vis-à-vis submuscular expander/implant reconstruction. This must be weighed against its reported advantages in enhancing cosmesis and ameliorating contracture. (*Plast. Reconstr. Surg.* 129: 28, 2012.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, III.

In the United States, approximately 57,000 tissue expander/implant–based reconstructions are performed annually, representing approximately 65 percent of all breast reconstructions.[1] Acellular dermis has been an increasingly popular adjunct to traditional expander reconstruction with putative benefits including improved inframammary control, decreased incidence of migration, greater intraoperative fill (with decreased concomitant expansion time and number of postoperative visits), improved cosmesis, and amelioration of contracture.[2–8] The basic technique involves releasing the pectoralis muscle along its inferior border and using the acellular dermis to reconstruct the ensuing lower pole defect.

The technique of using human acellular dermal matrix for soft-tissue reconstruction has existed since the early 1990s, and its use has been described in a myriad of clinical contexts from

From the Division of Plastic and Reconstructive Surgery, the Department of Preventative Medicine, and the Lynn Sage Breast Center, Northwestern University, Feinberg School of Medicine, and Loyola University Chicago, Stritch School of Medicine.
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burn treatment and neourethra reconstruction to ameliorating contracture in hand and breast surgery.[2,4,9–11] However, universal acceptance in these varying clinical indications has been tempered by concerns about surgical complications including seromas, infections, and loss of mechanical integrity.[12–14] The complication profile of human acellular dermal matrix in breast reconstruction ranges widely throughout the 6 years of published reports (range, 3.2 to 48.7 percent), making it difficult to develop generalized outcomes from study to study.[2,3,5,7,12,15–18] The central unknown remains regarding how outcomes of human acellular dermal matrix–assisted breast reconstruction compare with outcomes of traditional submuscular breast reconstruction. Our study attempts to collate recent studies in *both* treatment arms and determine general complication profiles and patterns by means of standard meta-analysis methodology.

PATIENTS AND METHODS

Search Methods

A literature search was performed using PubMed to query the MEDLINE database (January 1, 2000, to February 6, 2011). Search terms included "tissue expander," "implant," "acellular dermis," "acellular dermal matrix," "AlloDerm" or "acellular matrix," and "breast reconstruction." Additional search methods included a manual review of reference lists of relevant studies.

Selection Criteria

Selection criteria were defined a priori. Eligible studies were limited to English-only and had to examine breast reconstruction in human patients. Study selection underwent two levels of review by two independent researchers (Fig. 1). Each study was required to clearly indicate the number of reconstructions performed. Studies reporting fewer than 25 tissue expander/implant reconstructions in at least one cohort were excluded. Titles and abstracts were screened for the following exclusion criteria: publications of brief communications, correspondence, discussions, letters, conference/lecture manuscripts, case reports, and reviews; publications containing only abstracts; novel modifications of surgical technique; outcomes related to breast augmentation; outcomes related solely to autogenous reconstruction; and outcomes about only a specific high-risk population.

Full articles were then retrieved for all studies that met the first level of criteria. Studies needed to report or provide data to calculate a total complication rate and report or provide data to calculate at least one of the following postoperative complications: seroma, hematoma, infection, and flap necrosis. In any studies that reported similar or overlapping cohorts, the publication with the greatest number of reconstructions was included.

Data Collection and Analysis

Data collection and analysis was performed following the guidelines set forth by the *Cochrane Handbook for Systematic Reviews of Interventions* and the "Meta-Analysis of Observational Studies in Epidemiology."[19,20] Two independent reviewers extracted data from all selected studies by using a standardized data abstraction form. This electronic data form included the lead author, publication year, type of reconstructive procedure, number of patients, number of reconstructions, number of unilateral and bilateral reconstructions, average patient age and body mass index, percentage of smokers and diabetic patients, percentage of patients who received radiation therapy before surgery, percentage of patients who received postoperative radiation therapy, percentage of patients who received chemotherapy, average tissue expander intraoperative fill, and average follow-up. Complication data included number of reconstructions with seromas, hematomas, infection, flap necrosis, and explantation.

All rates used in the analysis were based on the number of reconstructions in each study. Two levels of analysis were performed. Cumulative pooled estimates were calculated from the standard error of complication rates based on the binomial distribution.[21] In instances where a study specified a zero occurrence rate of an outcome, the standard error was estimated using a constant continuity correction.[22] If a study did not specifically report an outcome, no correction was used, and the study was not included in the analysis of that outcome. Total complications for both analyses were retrieved for only defined postoperative complications (i.e., seroma, hematoma, infection/cellulitis, and flap necrosis). Relative risks were calculated from studies that examined complications in both human acellular dermal matrix and submuscular cohorts specifically. For both analyses, the DerSimonian and Laird random-effects method was used based on interstudy heterogeneity.[23,24] Heterogeneity was assessed using the Q statistic and the I^2 statistic.[25] Small Q statistic p values are indicative of statistically significant heterogeneity, whereas I^2 percentages indicate the amount of heterogeneity be-

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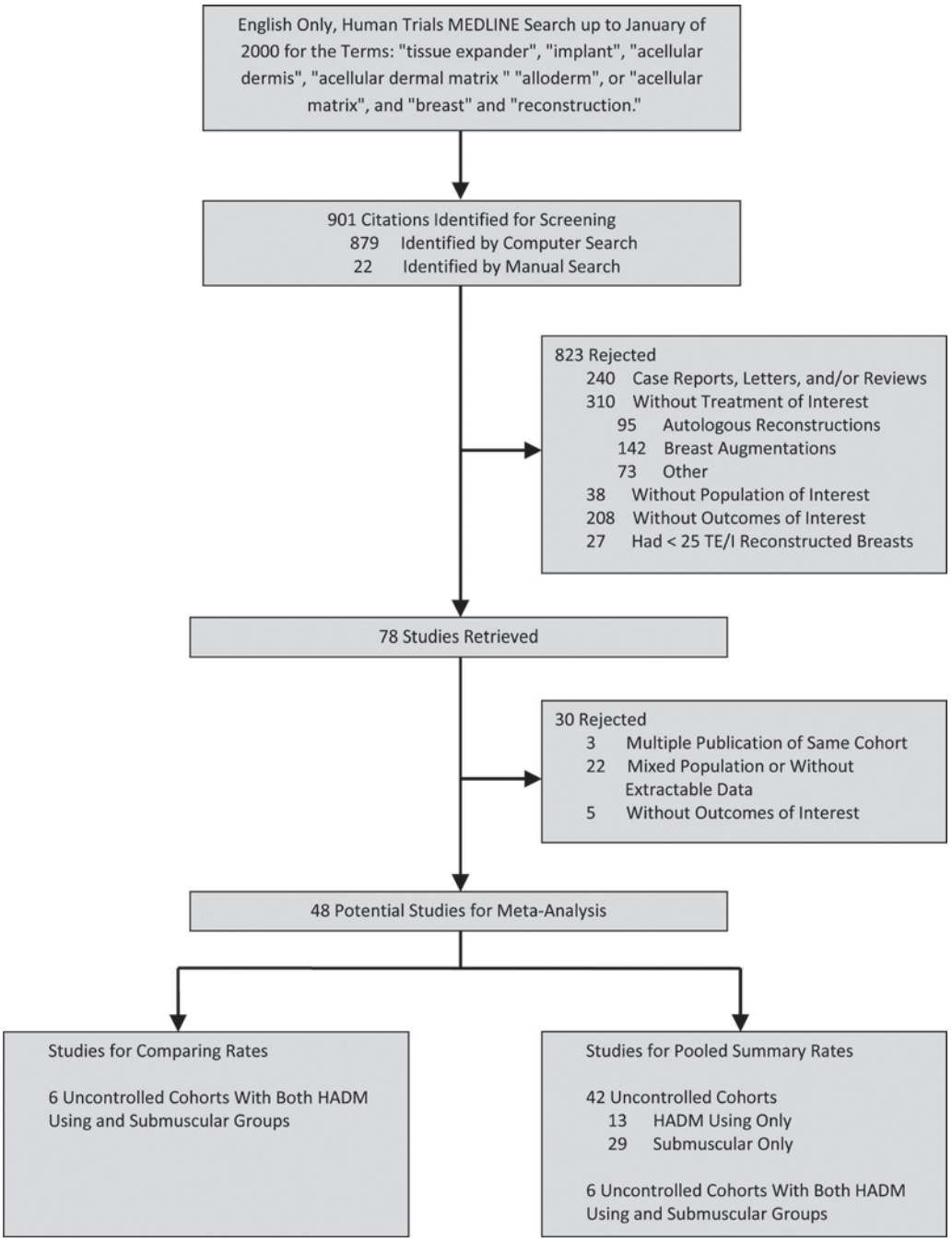

Fig. 1. Study attrition diagram. *TE/I*, tissue expander/implant; *HADM*, human acellular dermal matrix.

tween studies. For any heterogeneity of statistical significance, sources of heterogeneity were explored by means of an exclusion sensitivity analysis. Funnel plots, Egger's regression test, and Begg's rank correlation test were used to assess publication bias.[26,27] Statistical analysis was performed using MIX 2.0, Professional Software for Meta-analysis plug-in for Microsoft Excel, version 2.0.1.2 (BiostatXL, Sunnyvale, Calif.), and corroborated with RevMan5.0 (Cochrane Collaboration Information Management System, Oxford, United Kingdom).[28,29]

RESULTS

Study Characteristics

An English-language PubMed search of MEDLINE identified 879 articles that were eligible for screening. An additional 22 articles were identified through a manual bibliography search,

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resulting in a total of 901 citations. Of these, 823 were rejected after a review of titles and abstracts (Fig. 1). After full-text review of the remaining 78 articles, 30 were rejected. All 48 articles that were included were uncontrolled cohort studies. These 48 studies were used to develop pooled summary complication rates. Thirteen studies had information only on human acellular dermal matrix–based reconstructions.[2,3,5–7,15,18,30–35] Twenty-nine studies had information only on submuscular-based reconstructions.[36–64] Six studies reported complications for both human acellular dermal matrix and submuscular techniques.[12,13,16,17,65,66] In total, 2037 human acellular dermal matrix reconstructions and 12,847 submuscular reconstructions were included in the meta-analysis (Tables 1 and 2). Both cohorts had similar population demographics (Table 3). Human acellular dermal matrix reconstructions trended toward a higher average intraoperative fill (264.9 ml versus 187.1 ml; $p = 0.10$) when compared with submuscular reconstructions. The six studies used to calculate relative risks represented 877 human acellular dermal matrix reconstructions and 3464 submuscular reconstructions (Table 4).

Pooled Complication Rates

There was an increased rate of total complications, 15.4 percent (95 percent confidence interval, 9.3 to 21.4 percent) versus 14.0 percent (95 percent confidence interval, 11.7 to 16.3 percent); seroma, 4.8 percent (95 percent confidence interval, 2.8 to 6.9 percent) versus 3.5 percent (95 percent confidence interval, 2.6 to 4.4 percent); infection, 5.3 percent (95 percent confidence interval, 3.1 to 7.4 percent) versus 4.7 percent (95 percent confidence interval, 3.8 to 5.7 percent); and flap necrosis, 6.9 percent (95 percent confidence interval, 3.6 to 10.2 percent) versus 4.9 percent (95 percent confidence interval, 3.7 to 6.2 percent) in human acellular dermal matrix when compared with submuscular reconstructions (Fig. 2 and Table 5). However, the rate of hematoma was greater in the submuscular cohort (1.5 percent; 95 percent confidence interval, 1.0 to 2.0 percent) than in the human acellular dermal matrix cohort (1.0 percent; 95 percent confidence interval, 0.5 to 1.5 percent), and the rate of reconstructive failure was very similar in both cohorts, 3.8 percent (95 percent confidence interval, 2.3 to 5.4 percent) versus 3.8 percent (95 percent confidence interval, 2.9 to 4.7 percent).

Meta-Analysis of Comparative Studies

There was an increase in the risk of total complications (relative risk, 2.05; 95 percent confidence interval, 1.55 to 2.70), seroma (relative risk, 2.73; 95 percent confidence interval, 1.67 to 4.46), infection (relative risk, 2.47; 95 percent confidence interval, 1.71 to 3.57), and reconstructive failure (relative risk, 2.80; 95 percent confidence interval, 1.76 to 4.45) in the human acellular dermal matrix cohort (Figs. 3 through 5 and Table 6). There was a trend toward increased risk of hematoma (relative risk, 2.06; 95 percent confidence interval, 0.86 to 4.95) and flap necrosis (relative risk, 1.56; 95 percent confidence interval, 0.85 to 2.85) in the human acellular dermal matrix cohort, but the results were not statistically significant.

Study Heterogeneity

The majority of pooled complication analyses showed significant heterogeneity (Table 5). Heterogeneity values of the 19 studies in the human acellular dermal matrix cohort (Q statistic, $p < 0.01$; $I^2 = 95.4$ percent) were similar to those of the submuscular cohort (Q statistic, $p < 0.01$; $I^2 = 94.0$ percent). Relative risk analyses were generally more homogeneous, with only total complications and flap necrosis reporting statistically significant heterogeneity (Q statistic, $p = 0.08$; $I^2 = 49.0$ percent; and $p = 0.02$; $I^2 = 68.3$ percent). In analyses of seroma (Q statistic, $p = 0.22$; $I^2 = 29.3$ percent), infection (Q statistic, $p = 0.72$; $I^2 = 0.0$ percent), hematoma (Q statistic, $p = 0.98$; $I^2 = 0.0$ percent), and reconstructive failure (Q statistic, $p = 0.53$; $I^2 = 0.0$ percent), heterogeneity was not significant (Table 6).

Publication Bias

The funnel plot generated to test for publication bias in the relative risk analysis of total complications showed relative symmetry (Fig. 6). Egger's weighted regression and Begg's rank correlation test showed minimal evidence of bias (bias = 0.30; 95 percent confidence interval, –5.96 to 6.57; $p = 0.90$, and Kendall's tau-b = –0.06; $p = 0.85$).

DISCUSSION

The advent of any new technology—and specifically, its integration with a new technique—generates uncertainty about outcomes and questions about benefits vis-à-vis risks. With human acellular dermal matrix–assisted tissue expander breast reconstruction, the potential for improvement in cosmetic and reconstructive outcomes has been promulgated with little consensus on cumula-

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Table 1. Characteristics of Study Populations Reporting Human Acellular Dermal Matrix Reconstruction Outcomes

	Patient Characteristics							Complications					
Reference	No. of Reconstructions	Mean Age (yr)	Mean BMI	Previous XRT (%)	Postoperative XRT (%)	Mean Intraoperative Fill (ml)	Mean Follow-Up (mo)	Total Complications	Seroma	Hematoma	Infection	Flap Necrosis	Reconstructive Failure
Antony et al., 2010[16]	153	44.5	23.8	10.5	9.2	NA	NA	32	11	3	11	7	9
Becker et al., 2009[30]	50	50.9	26.3	0.0	NA	40.0	14.3	2	1	NA	1	NA	NA
Bindingnavele et al., 2007[31]	65	50.0	NA	NA	12.2	NA	10.0	6	3	1	2	NA	1
Breuing and Colwell, 2007[15]	67	46.0	NA	7.4	7.4	NA	16.1	2	NA	NA	2	NA	1
Buck et al., 2010[3]	58	53.3	NA	4.0	10.0	213.5	4.6	5	1	1	2	1	2
Chun et al., 2010[12]	269	47.0	25.5	8.7	6.5	322.7	NA	131	38	6	24	63	16
Lanier et al., 2010[65]	52	51.0	29.8	5.8	5.8	256.0	6.7	31	8	0	15	8	10
Liu et al., 2011[17]	266	NA	24.9	NA	9.8	187.8	NA	75	19	1	18	37	13
Losken, 2009[7]	31	48.0	26.7	NA	25.8	NA	10.2	1	0	NA	0	1	0
Margulies et al., 2005[32]	50	46.0	NA	NA	NA	NA	7.9	2	NA	NA	1	1	NA
Nahabedian, 2009[6]	100	48.2	NA	11.8	18.4	NA	17.0	13	5	NA	5	3	2
Namnoum, 2009[33]	29	NA	NA	NA	3.4	170.0	21.0	3	1	NA	1	1	NA
Preminger et al., 2008[66]	45	NA	NA	NA	NA	223.8	NA	7	3	1	3	NA	NA
Rawlani et al., 2011[2]	121	50.2	NA	2.5	19.0	256.6	10.2	19	2	0	9	8	11
Salzberg et al., 2011[18]	466	NA	NA	2.4	2.1	412.8	28.9	11	NA	5	1	5	6
Sbitany et al., 2009[13]	92	48.6	26.4	NA	12.0	412.5	NA	11	3	NA	8	NA	4
Spear et al., 2008[5]	58	50.3	NA	5.2	13.8	242.0	18.1	7	1	NA	4	2	1
Topol et al., 2008[34]	35	NA	NA	NA	NA	NA	9.5	3	NA	NA	3	NA	2
Zienowicz and Karacaoglu, 2007[35]	30	NA	NA	NA	NA	441.0	18.0	6	NA	NA	NA	6	NA

NA, not applicable; XRT, radiotherapy.

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Table 2. Characteristics of Study Populations Reporting Submuscular Reconstruction Outcomes

	Patient Characteristics							Complications					
Reference	No. of Reconstructions	Mean Age (yr)	Mean BMI	Previous XRT (%)	Postoperative XRT (%)	Mean Intraoperative Fill (ml)	Mean Follow-Up (mo)	Total Complications	Seroma	Hematoma	Infection	Flap Necrosis	Reconstructive Failure
Alderman et al., 2002[36]	79	47.9	NA	NA	NA	NA	NA	33	NA	NA	28	5	3
Antony et al., 2010[16]	2910	48.1	26.3	11.1	11.4	NA	NA	341	47	26	79	189	55
Ascherman et al., 2006[37]	123	52.5	NA	6.5	15.4	NA	15.5	16	11	NA	2	3	9
Berry et al., 2010[38]	733	50.8	NA	3.7	9.5	NA	NA	107	NA	18	74	15	64
Caffo et al., 2000[39]	108	48.9	NA	6.8	5.8	NA	NA	10	8	NA	1	1	0
Castello et al., 2000[40]	56	44.0	NA	NA	17.9	127.0	31.0	10	2	NA	7	1	4
Chang et al., 2008[41]	776	NA	NA	4.3	5.0	NA	NA	39	NA	NA	39	NA	92
Cicchetti et al., 2006[42]	107	48.0	NA	NA	26.2	NA	60.0	18	10	NA	8	NA	NA
Clough et al., 2001[43]	360	47.0	NA	2.7	5.0	NA	50.4	33	8	7	7	11	6
Chun et al., 2010[12]	146	46.2	23.8	5.2	8.2	131.2	NA	22	4	2	3	13	1
Cordeiro and McCarthy, 2006[44]	1522	NA	NA	5.6	15.3	NA	NA	118	5	10	58	45	33
Collis and Sharpe, 2000[45]	197	48.0	NA	NA	NA	NA	NA	25	NA	2	20	3	12
Delgado et al., 2010[46]	400	50.0	26.9	NA	30.5	NA	32.4	18	NA	9	4	5	16
Eriksen and Stark, 2006[47]	70	49.0	NA	NA	17.1	NA	8.0	5	NA	NA	5	NA	NA
Goodwin et al., 2005[48]	691	54.7	24.8	9.3	11.6	NA	NA	95	17	8	23	47	13
Lanier et al., 2010[65]	75	50.0	24.7	9.3	10.7	74.0	7.8	18	5	0	9	4	4
Liu et al., 2011[17]	204	NA	24.8	NA	10.4	74.9	NA	35	8	0	5	22	5
Losken et al., 2010[49]	34	58.7	34.0	3.7	11.1	328.0	16.0	15	6	NA	4	5	3
McCarthy et al., 2008[50]	1170	46.0	NA	9.6	9.5	NA	NA	197	38*	NA	57	102	22
Nano et al., 2005[51]	83	NA	NA	NA	NA	NA	NA	6	NA	3	3	NA	2
Padubidri et al., 2001[52]	481	NA	NA	NA	NA	NA	NA	58	17	4	23	14	NA
Pinsolle et al., 2006[53]	65	NA	NA	NA	NA	NA	NA	11	NA	1	5	5	5
Preminger et al., 2008[66]	45	NA	NA	NA	NA	201.1	2.1	3	2	0	1	NA	NA
Pusic and Cordeiro, 2003[54]	370	48.0	NA	NA	8.6	271.0	NA	15	5*	NA	10	NA	8
Radovanovic et al., 2010[55]	214	47.0	NA	13.1	NA	340.0	NA	33	6	2	9	16	12
Saint-Cyr et al., 2010[56]	31	52.0	26.1	9.7	NA	NA	6.5	7	2	0	1	4	1
Salgarello et al., 2011[57]	256	47.5	NA	NA	4.5	NA	26.2	39	3	6	13	17	2
Sandelin et al., 2004[58]	188	NA	NA	NA	NA	NA	NA	7	NA	2	5	0	3
Sbitany et al., 2009[13]	84	51.7	28.2	NA	6.0	130.0	NA	9	3	NA	6	NA	3
Scuderi et al., 2011[59]	248	47.5	NA	0.0	0.0	NA	NA	28	12	14	2	NA	2
Strock, 2009[60]	246	NA	NA	0.0	NA	NA	NA	7	NA	NA	7	NA	4
Tallet et al., 2003[61]	77	51.5	NA	10.4	61.0	NA	25.0	17	9*	NA	4	4	9
Vandeweyer et al., 2000[62]	124	46.9	NA	NA	4.8	NA	65.0	10	NA	3	4	3	1
Woerdeman et al., 2007[63]	174	44.0	23.6	8.3	4.2	138.0	73.4	62	21	4	24	13†	19
Woerdeman et al., 2006[64]	400	43.0	24.0	6.1	NA	183.0	28.6	168	20	31	61	56†	72

NA, not applicable; XRT, radiotherapy.
*Seroma and hematoma combined.
†Reported as skin problems.

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Table 3. Average Demographic Data

	HADM	Submuscular	*p*
Mean age, yr	48.8	48.8	0.97
Mean BMI	26.2	26.1	0.94
Smokers, %	11.3	17.6	0.10
Diabetes, %	4.1	2.6	0.21
Previous radiotherapy, %	5.8	6.5	0.64
Postoperative radiotherapy, %	11.1	13.3	0.50
Chemotherapy, %	39.8	43.0	0.67
Mean intraoperative fill, ml	264.9	187.1	0.10
Mean follow-up, mo	13.8	29.9	0.02

HADM, human acellular dermal matrix.

tive risks. The variance in total complication profiles reported in the literature (range, 3.2 to 48.7 percent) suggests the need for pooled analysis.[2,3,5,7,12,15–18] The aim of our meta-analysis was to focus on complication profiles and perform both a risk analysis and pooled summary estimates using the most recent literature. We did not specifically address the underlying rationale for using human acellular dermal matrix or validate the potential advantages of this technique, as these topics have been discussed elsewhere in the literature.[2,4,5,6,15]

An important question associated with the use of human acellular dermal matrix is whether or not there is an enhanced infection rate. Our meta-analysis shows that the risk of infection is more than doubled when using human acellular dermal matrix (relative risk, 2.47; 95 percent confidence interval, 1.71 to 3.57). This risk is corroborated by the difference in pooled rates between human acellular dermal matrix and submuscular reconstruction, 5.3 percent (95 percent confidence interval, 3.1 to 7.4 percent) versus 4.7 percent (95 percent confidence interval, 3.8 to 5.7 percent), respectively. This may not be surprising considering that the initial state of the human acellular dermal matrix is that of a pre-revascularization biological material and, as such, another potential foreign body added to the stressed hypovascular milieu of mastectomy flaps. Another concern with human acellular dermal matrix has been the potential for enhanced seroma formation—the rationale being that the biological material may incite an inflammatory response that manifests as seroma (or, alternatively, as the cellulitic mimic termed "red breast syndrome").[2,67,68] Indeed, our meta-analysis suggests this to be the case in both the risk analysis and pooled rates (relative risk, 2.73; 95 percent confidence interval, 1.67 to 4.46; and 4.8 percent; 95 percent confidence interval, 2.8 to 6.9 percent, versus 3.5 percent; 95 percent confidence interval, 2.6 to 4.4 percent).

Another complication associated with tissue expander reconstruction is hematoma. The relative similarity in tissue plane dissection and technique between the human acellular dermal matrix and submuscular cohort would presuppose a hypothesis that hematoma rates would be similar. Indeed, both the meta-analysis and the pooled complication analysis indicate that hematoma rates themselves are not affected by the incorporation of human acellular dermal matrix into the standard submuscular technique.

The rates of mastectomy flap necrosis and human acellular dermal matrix use may be related by intraoperative expansion. With the anatomical constraints of an intact pectoralis major muscle eliminated, the human acellular dermal matrix–based tissue expander reconstruction may allow for greater intraoperative fill as suggested by our analysis (264.9 ml versus 187.1 ml; $p = 0.10$). However, this must be counterbalanced by the possibility of added vascular insult to already compromised mastectomy flaps and the attendant risk of necrosis. Thus, our pooled complication rates suggested a higher rate of flap necrosis in the human acellular dermal matrix cohort, 6.9 percent (95 percent confidence interval, 3.6 to 10.2 percent) versus 4.9 percent (95 percent confidence interval, 3.7 to 6.2 percent). However, the risk analysis did not connote a significant relative risk with this variable (relative risk, 1.56; 95 percent confidence interval, 0.85 to 2.85). Moreover, intraoperative fill showed no apparent correlation with flap necrosis in studies that reported both of these values ($p = 0.56$). Part of the reason for this lack of correlation may be the degree of clinical judgment that factors into expansion—wholesale expansion of prostheses is limited by surgical assessment of mastectomy flaps, which will vary from patient to patient. Finally, with the meta-analysis reflecting an increased total complication profile and relative risk, it is perhaps not surprising that the risk of reconstructive failure or removal of the expander is higher in the human acellular dermal matrix cohort (relative risk, 2.80; 95 percent confidence interval, 1.76 to 4.45). Reducing the incidence of these complications has been discussed by various authors in the literature.[2,12,16,18] Specifically, strategies that have been used by the senior author (J.Y.S.K.) include judicious intraoperative expansion, careful patient selection based on an intraoperative assessment of flap vascularity, dead space management with the use of quilting sutures, and aggressive irrigation of the breast pocket.

Although beyond the scope of this study, the issue of cost-effectiveness is another important element to consider when performing human acellular dermal matrix–assisted breast reconstruc-

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Table 4. Characteristics of Study Populations Comparing Human Acellular Dermal Matrix and Submuscular Outcomes

Reference	No. of Reconstructions	Mean Age (yr)	Mean Intraoperative Fill (ml)	Total Complications	Seroma	Hematoma	Infection	Flap Necrosis	Reconstructive Failure
Antony et al., 2010[16]									
HADM	153	44.5	NA	32	11	3	11	7	9
Submuscular	2910	48.1	NA	341	47	26	79	189	55
Chun et al., 2010[12]									
HADM	269	47.0	322.7	131	38	6	24	63	16
Submuscular	146	46.2	131.2	22	4	2	3	13	1
Lanier et al., 2010[65]									
HADM	52	51.0	256.0	31	8	0	15	8	10
Submuscular	75	50.0	74.0	18	5	0	9	4	4
Liu et al., 2011[17]									
HADM	266	48.0	187.8	75	19	1	18	37	13
Submuscular	204	50.0	74.9	35	8	0	5	22	5
Preminger et al., 2008[66]									
HADM	45	NA	223.8	7	3	1	3	NA	NA
Submuscular	45	NA	201.1	3	2	0	1	NA	NA
Sbitany et al., 2009[13]									
HADM	92	48.6	412.5	11	3	NA	8	NA	4
Submuscular	84	51.7	130.0	9	3	NA	6	NA	3

HADM, human acellular dermal matrix; NA, not applicable.

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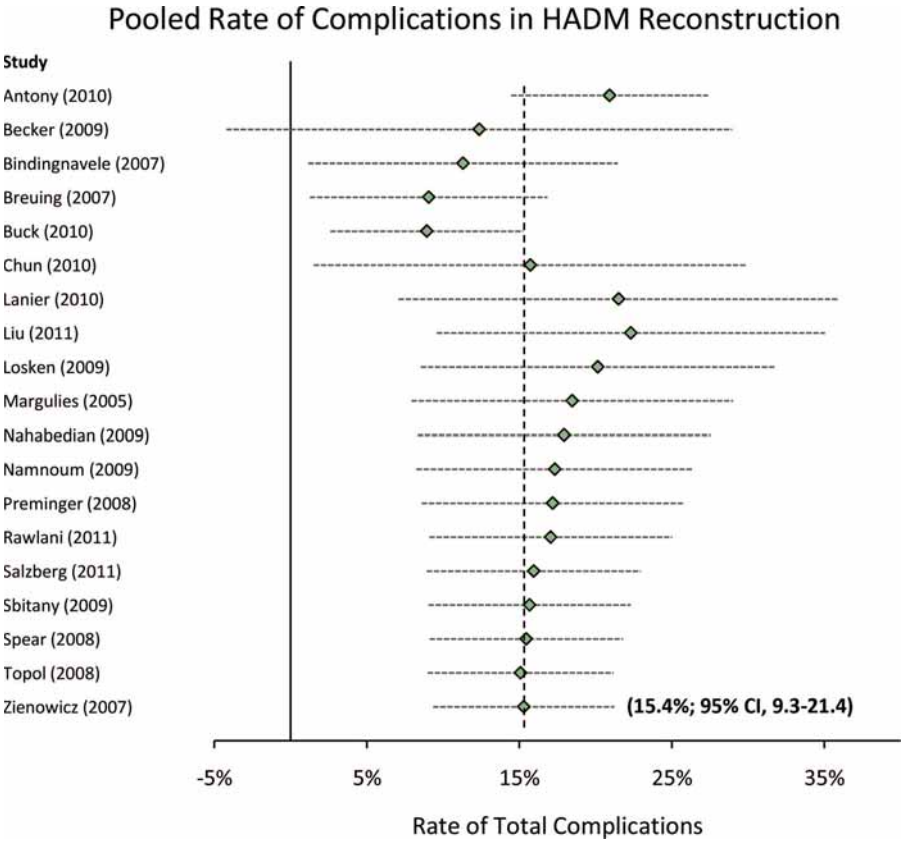

Fig. 2. Cumulative pooled rate of total complications in human acellular dermal matrix (*HADM*) reconstruction. *Diamonds* indicate the cumulative pooled rate of partial flap loss in individual studies. *Horizontal lines* represent the corresponding 95 percent confidence interval (*CI*). The *vertical dashed line* represents the cumulative rate estimate.

Table 5. Pooled Complication Rates for Human Acellular Dermal Matrix and Submuscular Patients

	No. of Studies	No. of Reconstructions	Pooled Complication Rate (%)	95% CI (%)	*Q* Statistic, *p*	I^2 (%)
HADM						
Total complications	19	2037	15.4	9.3–21.4	<0.01	95.4
Seroma	14	1389	4.8	2.8–6.9	<0.01	71.0
Hematoma	9	1495	1.0	0.5–1.5	0.68	0.0
Infection	18	2007	5.3	3.1–7.4	<0.01	83.9
Flap necrosis	13	1683	6.9	3.6–10.2	<0.01	90.0
Reconstructive failure	14	1833	3.8	2.3–5.4	<0.01	64.0
Submuscular						
Total complications	35	12,847	14.0	11.7–16.3	<0.01	94.0
Seroma	24	9886	3.5	2.6–4.4	<0.01	85.7
Hematoma	22	9547	1.5	1.0–2.0	<0.01	65.7
Infection	35	12,847	4.7	3.8–5.7	<0.01	85.8
Flap necrosis	26	10,818	4.9	3.7–6.2	<0.01	91.2
Reconstructive failure	31	12,144	3.8	2.9–4.7	<0.01	88.3

CI, confidence interval; HADM, human acellular dermal matrix.

tion. Our study does not specifically address this topic; however, each surgeon considering the potential benefits of human acellular dermal matrix must also consider the potential economic burden and aforementioned complication profile as well.

The statistical tools used to analyze the studies were stratified to formal meta-analysis for studies with both human acellular dermal matrix and submuscular cohorts and to cumulative pooled complication summaries for studies with solely human

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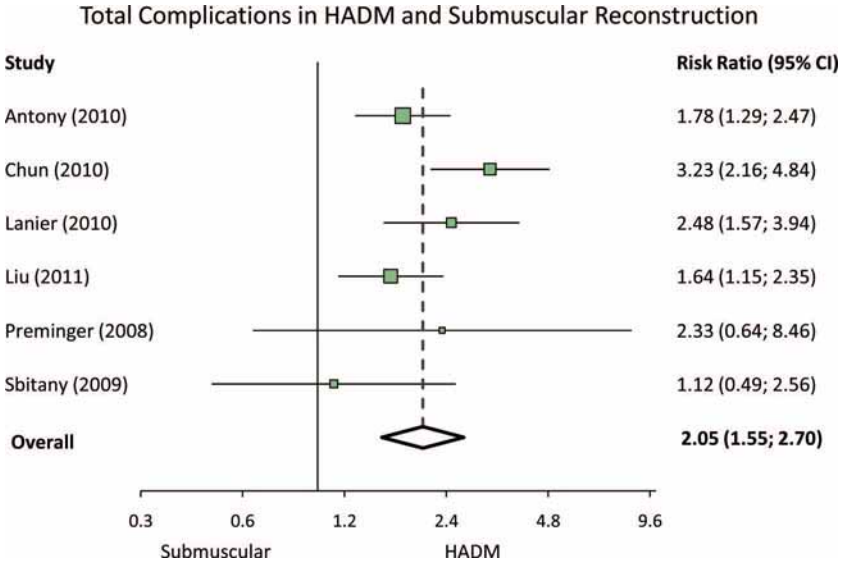

Fig. 3. Total complications in human acellular dermal matrix (*HADM*) and submuscular reconstruction. Size of the *solid squares* is inversely proportional to the variance of the study estimate. The *diamond* represents the random-effects relative risk and 95 percent confidence interval (*CI*). The *dashed line* represents the overall risk estimate.

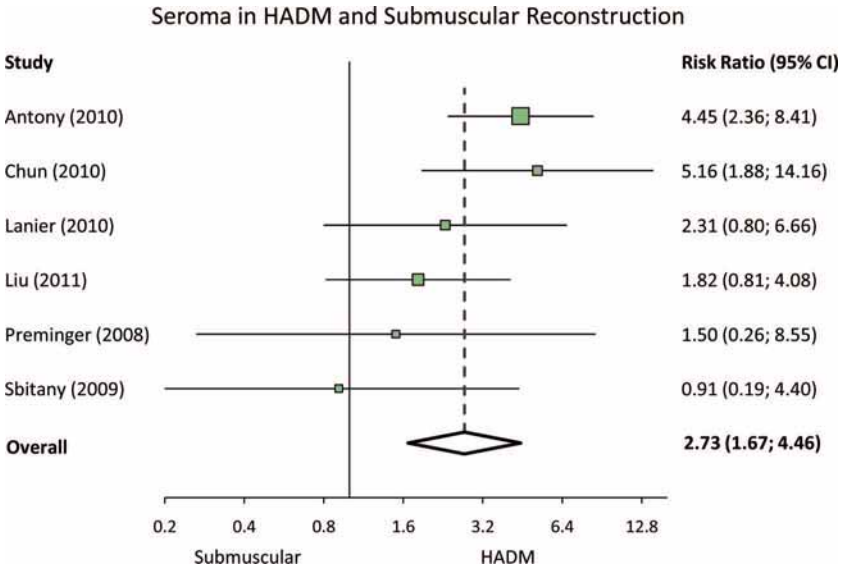

Fig. 4. Seroma in human acellular dermal matrix (*HADM*) and submuscular reconstruction. Size of the *solid squares* is inversely proportional to the variance of the study estimate. The *diamond* represents the random-effects relative risk and 95 percent confidence interval (*CI*). The *dashed line* represents the overall risk estimate.

acellular dermal matrix or submuscular cohorts. An earlier study performed a noncomparative complication summary (no submuscular cohort) with a similar range of human acellular dermal matrix complications as seen in our analysis, but our specific meta-analysis allows for an introduction of relative risk and a more up-to-date complication profile.[69] Even with the inclusion of a more robust analysis, the data are hampered by missingness because of the inconsistent reporting of variables in the literature. This may explain the lack of perfect concordance between the pooled complication rates and relative risk.

Our heterogeneity values for the pooled complications in both cohorts were significant. We explored causes of heterogeneity, which we hy-

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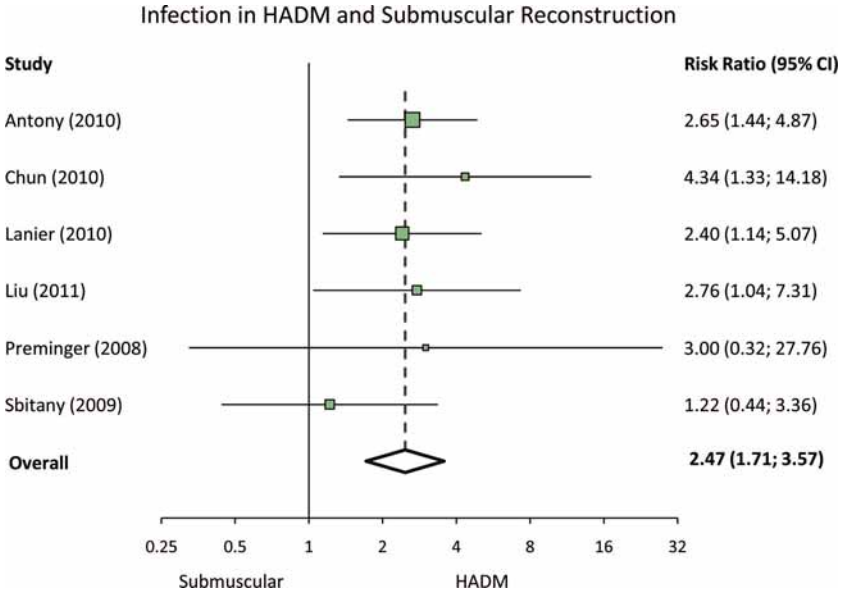

Fig. 5. Infection in human acellular dermal matrix (*HADM*) and submuscular reconstruction. Size of the *solid squares* is inversely proportional to the variance of the study estimate. The *diamond* represents the random-effects relative risk and 95 percent confidence interval (*CI*). The *dashed line* represents the overall risk estimate.

Table 6. Relative Risks for Human Acellular Dermal Matrix versus Submuscular Reconstruction

	No. of Studies	Relative Risk	95% CI	*Q* Statistic, *p*	I^2 (%)
Total complications	6	2.05	1.55–2.70	0.08	49.0
Seroma	6	2.73	1.67–4.46	0.22	29.3
Hematoma	4	2.06	0.86–4.94	0.98	0.0
Infection	6	2.47	1.71–3.57	0.72	0.0
Flap necrosis	4	1.56	0.85–2.85	0.02	68.3
Reconstructive failure	5	2.80	1.76–4.45	0.53	0.0

CI, confidence interval.

pothesize stem from clinical and methodologic diversity between the studies. Rather than ignoring the heterogeneity present in our study by using a fixed-effects model, we incorporated the heterogeneity through the use of the random-effects model. We had similar results calculating relative risk when applying both models, and varying results for pooled complications. As a result, we chose the more conservative, random-effects estimate for both. In addition, when an exclusion sensitivity assessment was performed by removing study population outliers, there was little change in the statistical significance of the majority of our results. Nevertheless, the relative imbalance of cohort sample sizes in human acellular dermal matrix versus submuscular reconstruction ($n = 2037$ versus $n = 12{,}847$) introduces the possibility of heightened β error when combined with the missingness factor. Another limitation to this study was that the meta-analysis was based primarily on nonrandomized studies. Ideally, a more robust analysis would require level I evidence with randomized controlled trials. Nonrandomized studies tend to be more susceptible to selection bias because of the potential for greater systematic differences between cohorts as compared with randomized controlled trials, which use randomization and blinding to address this bias. The significant heterogeneity seen in our study (as with most meta-analyses including nonrandomized studies) was expected and is likely related to the increased interstudy methodologic diversity characteristic of nonrandomized study inclusion. The impact of this bias can be mitigated by using strong study inclusion criteria and the same random-effects model we used to draw statistical conclusions.

These limitations and assumptions notwithstanding, the pooled complication rates and risk analysis both demonstrate convergent patterns of increased complications in the human acellular

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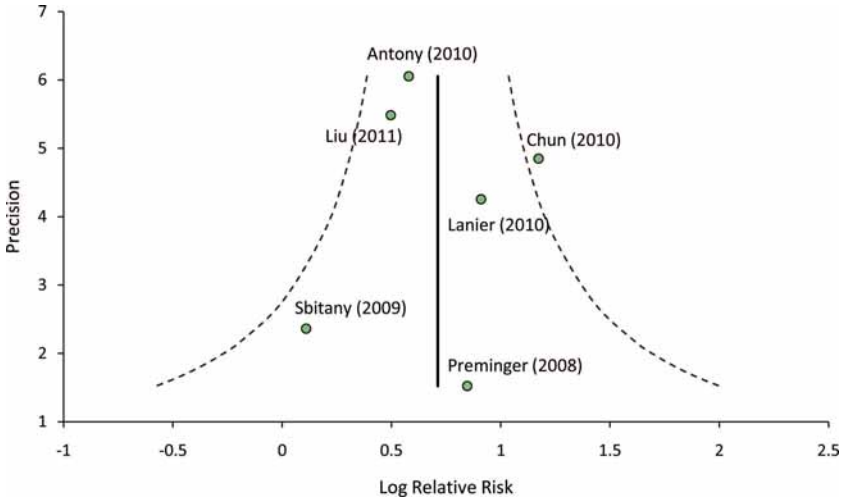

Fig. 6. Funnel plot of log relative risks according to their precision for total complications. The *vertical solid line* is drawn at the pooled log of relative risk for total complications, and the *dashed lines* represent the expected 95 percent confidence interval for a given standard error.

dermal matrix cohort. Given that the studies in the human acellular dermal matrix cohort represent the earliest data on a new technique modification, this may not be surprising because some of the reported data will reflect a learning curve phenomenon (whereas the submuscular cohort studies will reflect patient data from a more mature technique that is several decades old). Intrainstitutional data will thus vary from early adoption to later proficiency.[70] Interinstitutional data may differ according to diverse surgical practices, including the use of tumescent solution or the predilection for thinner mastectomy flaps. In total, there were five different acellular matrices used in the meta-analysis, with the majority of cases involving AlloDerm. However, with only one smaller scale matched study specifically analyzing outcomes related to use of differing human acellular dermal matrix technology, no conclusions can be drawn related to differences in human acellular dermal matrix—this would be a key direction for future studies. With respect to differentiating human acellular dermal matrix from submuscular reconstruction, these issues may or may not impact outcomes.

CONCLUSIONS

Human acellular dermal matrix–assisted breast reconstruction is a technique that continues to evolve. Its principal value proposition may be the potential enhancement in cosmesis and amelioration of late or irradiation-induced contracture.[2,5–7,15,18,71] In this analysis, the average follow-up time for the human acellular dermal matrix cohort was 13.8 months versus 28.3 months for the submuscular cohort. As more studies with longer follow-up are generated, a more robust meta-analysis will be possible with which to assess these long-term results. Specifically, issues related to revision surgery, capsular contracture, and patient satisfaction could be further elucidated.

Focusing specifically on comparing complication profiles of human acellular dermal matrix and traditional submuscular reconstruction by means of a meta-analysis and pooled summaries, our study demonstrates that human acellular dermal matrix seems to connote a higher complication profile than submuscular reconstruction. Although this may well be an artifact of communal inexperience with a new technique, it is nevertheless an important clinical finding to consider in communicating best practice information to patients. Moreover, future studies that directly link benefits with realized risk will help clarify the utility of this technique.

John Y. S. Kim, M.D.
Division of Plastic and Reconstructive Surgery
Northwestern University
Feinberg School of Medicine
675 North St. Clair Street
Galter Suite 19-250
Chicago, Ill. 60611
jokim@nmh.org

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