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Original Article

Heterologous Materials Are Really Better than Autologous in Tympanoplasty Mastoid Obliteration? A Systematic Review with Meta-Analysis

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BACKGROUND: The aim is to analyze Literature concerning mastoid obliteration in adults with either autologous or heterologous grafts in the last 10 years.

Data Source: Databases such as NIH PubMed, Bookshelf, NLM Catalog, Cochrane Library, and Embase were consulted.

METHODS: Thirty-seven studies were selected (22 concerning autologous materials, 15 about heterologous ones). Only studies with more than 12 months of follow-up were considered. A statistical analysis with random-effects models was performed to allow the true effect sizes to differ from study to study.

RESULTS: The present literature review and meta-analysis does not allow to establish the supremacy of one technique over the other, but underlines the advantages of each reconstructive choice and the importance of mastoid obliteration in cholesteatoma surgery. The total number of obliterated ears was 2882. Overall otorrhea rate was 5% (5.2% for heterologous grafts; 4.9% for autologous materials; $P < .05$). Recurrent and residual cholesteatoma rate was 4.5% (3.4% in heterologous materials; 5.2% in autologous grafts; $P < .05$). Recurrent cholesteatoma rate was 1.8% (1.6% when using heterologous grafts, 1.9% with autologous; $P < .05$). Residual cholesteatoma rate was 1.5% (1.6% with heterologous materials, 1.5% with autologous; $P < .05$). TM (tympanic membrane) retraction pockets rate was 5.3% (3.6% with heterologous materials; $P > .05$; 7% with autologous materials; $P < .05$). TM perforations rate was 2.9% (4.3% with heterologous materials, 2.5% with autologous; $P < .05$). Infection rate was 2.3% (2.3% with heterologous materials, 2.2% with autologous; $P < .05$).

CONCLUSION: Heterologous materials are associated with significantly lower rates of recurrent and residual cholesteatoma and retraction pockets development, although they are associated with higher rates of otorrhea and TM perforation.

KEYWORDS: Mastoid obliteration, residual cholesteatoma, recurrent cholesteatoma, otorrhea

INTRODUCTION

Mastoid obliteration in cholesteatoma surgery is necessary to avoid complications related to large mastoid cavities following canal wall down (CWD) tympanoplasty, such as otorrhea, recurrent vertigo, several ear infections due to the difficulty to have a self-cleansing cavity, difficulty or impossibility in wearing conventional hearing aids, and soaking the ear and improving the patient's quality of life.[1-4]

There are 2 main groups of materials that can be applied to rebuild the external auditory canal (EAC) and obliterate the mastoid cavity. The first group is represented by autologous materials, such as bone paté, bone chips, fat, cartilage, muscular flap,

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or fascia. They are harvested directly from the patient, with virtually no risk of adverse effects or rejection, though they might lead to donor site morbidity, resorption and atrophy.[5] Recently, new surgical techniques adopting heterologous grafts have been developed. They involve different materials such as bioactive glass (BAG), bioactive glass-ceramic, or hydroxyapatite granules (HG). They have the advantage of being endlessly available, easy to use, uncontaminated and allow better aesthetical and functional results; the main disadvantage is the possible inflammatory response due to foreign body reaction.[5]

Currently, both kind of materials are commonly used in clinical practice and numerous articles regarding the 2 have been published, although the advantages of using one or another are still unclear. The aim of this study is to evaluate the prevalence of several outcomes to establish whether there is a best kind of graft for mastoid obliteration.

METHODS

Items designated by the PRISMA Statement were followed by the authors.[6] PICOS was designed as follows: population included only adult patients affected by cholesteatoma and the intervention concerned mastoid obliteration to improve control disease and patients quality of life. Mastoid cavities obliterated with heterologous materials were compared with the ones obliterated with autologous materials (C - comparison), the outcomes were the rates of long-term otorrhea, recurrent cholesteatoma, residual cholesteatoma, infections, recurrent and residual disease together, tympanic membrane perforations or retractions, and infections. Considering that the aim of the study was to analyze objective results, parameters concerning hearing improvement were excluded due to the high variability observed in ossiculoplasty methods.

This paper is a study of prevalence, since a metanalysis could not be performed, due to the low number of randomized control trials comparing heterologous and autologous materials that can be found in literature.

Databases such as NIH PubMed, Bookshelf, NLM Catalog, Cochrane Library, and Embase were consulted. The search was ((mastoid) AND (obliteration)) AND (cholesteatoma) and included all articles published after 2010. Eligibility criteria for the studies were English language and human population.

Three different reviewers read separately all the studies and then compared their results.

With regard to Embase, NIH Bookshelf, and NLM Catalog Databases all the articles found were excluded because concerning other outcomes. The research on Cochrane Library showed some relevant papers that were published also on PubMed.

The research on PubMed provided 308 articles, but only 144 studies that met the eligibility criteria (English, Humans, publication date after 2010). After duplicates elimination, 140 papers were screened. Twenty-six papers were excluded because not concerning exclusively mastoid obliteration and cholesteatoma surgery. Seven papers were not considered because they were literature reviews. Two were excluded because they were case reports. Fifteen were discarded because they were dealing with other outcomes. Five studies were not analyzed because they were not pertinent grafts. Eighty-five articles contained exhaustive information to be analyzed. Seven were discarded because they included pediatric population. Six were not included in the study because mixed autologous and heterologous materials were used for mastoid obliteration. Eighteen were discarded because dealing with other outcomes. Two were excluded because of unclear time of follow-up and other 2 because of a too short follow-up. Following qualitative analysis of the selected articles, 13 other studies concerning autologous materials were discarded to reduce the heterogeneity of the population, since the use of heterologous materials for mastoid obliteration has been developed mainly in the last 10 years. A total number of 38 articles was suitable for the systematic review: 23 dealing with autologous materials and 15 with heterologous materials (Figure 1; Table 1).

Data concerning the following were extracted: type of graft (autologous/heterologous), the total number of obliterated ears, mean age of the population in the study, sex of the analyzed population, number of months of follow-up, rates of otorrhea, recurrent cholesteatoma, residual cholesteatoma, recurrent and residual disease, and tympanic membrane perforation or retractions.

Statistical analyses were performed employing CMA v3 and SPSS-IBM. To avoid the possible bias due to the characteristics of the population included, we used random-effects models which allow the true effect sizes to differ from study to study.[7] Seven meta-analyses were computed, to estimate the prevalence of these clinical outcomes: otorrhea, recurrent cholesteatoma, residual cholesteatoma and the combination of recurrent and residual cholesteatoma, retraction pockets, perforations rate, infections. The effect sizes were estimated by adopting a 95% confidence interval computed for a proportion.

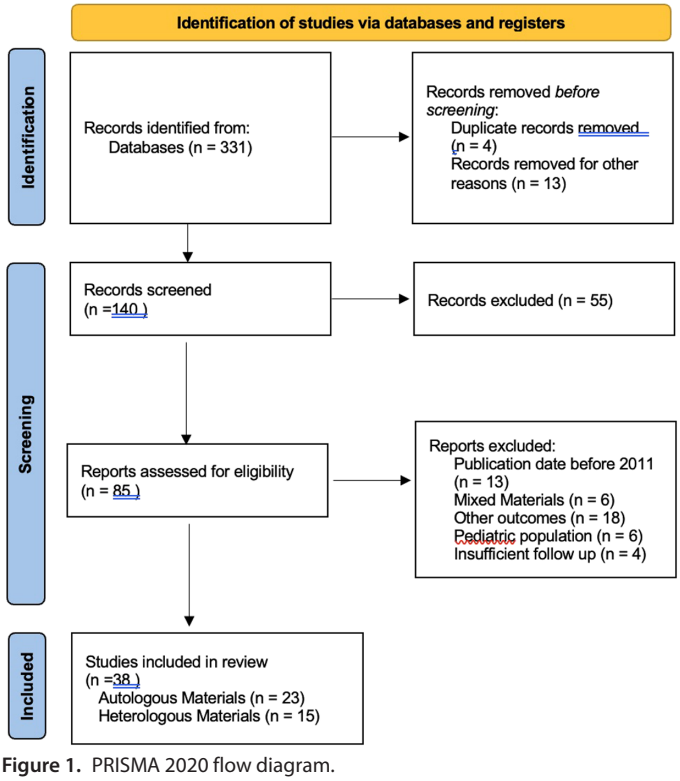

Figure 1. PRISMA 2020 flow diagram.

Table 1. Articles Selected for the Review

Author	Year	Place	Material	Total ears	Age	Sex	Otorrhea (%)	TM perforation	TM retraction pockets	Recurrent disease (%)	Residual disease (%)	Recurrent & residual disease (%)	% of secondary procedures	Infections	Follow-up (months)
Edfeldt et al[21] Retrospective	2012	Uppsala University Hospital, Sweden	Autologous bone paté, cartilage	330	38	195 M 135 F	0.3			10	3	13	47		72
Fischer et al[22] Retrospective	2020	Walter Reed National Military Medical Center, Maryland	Autologous bone paté	79 (78 pat)	35.8	54M 25F	10	9		0	8.2 (in long- term follow- up: 5/61 ears)	8.2	36.7	0	37 (18 pat did not have 12 months follow-up)
Fouad et al[23] Prospective *Considered only autologous patients (exclusion of eighteen pat with GIBC)*	2020	Zagazig University, Egypt	Autologous	7	31,9	4 M 3 F	28,5 (0% after surgery)	14.28		14.28					24
Harun et al[24] Retrospective	2015	Johns Hopkins Hospital, USA	Autologous bone paté + muscoloperiosteal flap	45	37.3	31M 14	8.9				1.6		28.9	3.2	30.5
Heo et al[25] Restrospective	2014	Inje University College of Medicine, Korea	Autologous	132	46,4	55 M 77 F	4.5	4.5	2.23	0.7	1.5	2.25		2.3	56.3
Kim et al[26] Retrospective	2019	Soonchunhyang University, Korea	Autologous bone paté	76	49.9	29 M 47 F		2.6		0	0	0			64
Kim et al[27] Retrospective	2012	Hallym University, Seoul, Republic of Korea	Autologous Muscular flap	113	47	60 M 53 F	17	0	3.5	2.6 5,3 epitelial pearl			29.2		38
Kurien et al[4] Retrospective	2013	University of Alberta, Canada	Autologous bone paté	58	40	31M 27F				6.8% (0% in obliterated area)			20.7	8.6	At least 12 months
Mishra et al[28] Randomized parallel groups study	2020	Army College od Medical Sciences and Base Hospital, Delhi, India	Autologous bone paté	35	30.6	14 M 21 F	5.71	5.71	8.57			5.71			15.67
Mokbel et al[29] Retroospective	2011	Mansoura University, Egypt	Autologous bone paté Muscular Flap	100	36	55 M 45 F	12	10							12
Roche et al[30] Retrospective	2011	Beaumont Hospital, Ireland	Autologous bone pat é Muscular Flap	45 42 pat	36	21 M 21F	0		6.8% shallow retraction pocket	0			78,5	8,8	17

(*Continued*)

Table 1. Articles Selected for the Review (*Continued*)

Author	Year	Place	Material	Total ears	Age	Sex	Otorrhea (%)	TM perforation	TM retraction pockets	Recurrent disease (%)	Residual disease (%)	Recurrent & residual disease (%)	% of secondary procedures	Infections	Follow-up (months)
Shah et al[31] Retrospective	2017	Government Medical College and Hospital, India	Autologous Periosteal Muscolar Flap	100	28,4	49M 51F	4			0	0	0		5% wound gaping	12
Stevens et al[32] Retrospective	2019	Arizona Otolaryngology Consultant, USA	Autologous bone paté	71	41,1	40M 31F		0%	32			8	36.6	1	35
Suzuki et al[33] Retrospective	2014	University of Occupational and Environmental Health, Japan	Autologous bone paté	73	49	42M 27F				1.4	9.6	11			27.8
Van Waegeningh et al[34] Retrospective	2020	European Institute for ORL-HNS, Belgium	Autologous Cortical bone chips and bone paté	61 (60 pat)			0			3,27	0	3,27	27.87		45
Vercruysse et al[35] Retrospective	2016	European Institute for ORL-HNS, Netherlands	Autologous bone paté + muscoloperiosteal flap	50	44.7	34M 16F	6	6	8	2	2	4	100		101.8
Yamamoto et al[36] Retrospective	2014	Niigata University, Niigata, Japan.	Autologous (bone patè)	118	48,4	60 M 58 F	2.5			0	7,6% 0% in obliterated area	7,6			83
Sioshansi et al[37] Retrospective	2021	Standford University, California	Autologous (bone patè)	43 ears (42 pat)	44,2	25 M 17 F	5			5			56		29
Westerberg et al[38] Retrospective	2018	Linkoping University, Sweden	Autologous (bone pate, cartilage, muscular flap)	230 (224 pat)		124 M 106 F		0.43		8% 4% eardrum origin 4% ear canal origin	1	9	100		36 (for 87% of patients)
Tan et al[39] Retrospective	2021	Singapore General Hospital	Autologous (middle temporal artery and inferior muscoloperiosteal flaps)	75	47	42 M 33 F	1.3			0			6.7		29
Ghiasi[40] Prospective	2015	Tabriz University of Medical Sciences, Tabriz, Iran	Autologous (mixed)	56 (48 pat)	28	21 M 27 F	13					12.5% residual keratin pearl in middle ear	30	7	28
Maniu et al[41] Retrospective	2012	Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania	Autologous (mixed)	56	41	34 M 22 F	12			0	0	0	26.79		32

(*Continued*)

Table 1. Articles Selected for the Review (*Continued*)

Author	Year	Place	Material	Total ears	Age	Sex	Otorrhea (%)	TM perforation	TM retraction pockets	Recurrent disease (%)	Residual disease (%)	Recurrent & residual disease (%)	% of secondary procedures	Infections	Follow-up (months)
Wilkie et al[42] Comparative study	2019	Royal Liverpool and Broadgreen University Hospitals, Liverpool, UK	Autologous (mixed)	55	59		7.3			7.3					30
Bernardeschi et al[43] Retrospective	2013	PItiè-Salpetriere, Paris, France	Heterologous Biphasic Ceramics (TricOs)	59 (57 pat)	47	31 M 26 F	5.08% 10% uncovered granules without signs200 of infections	6.77		0	0		93.2		14
Franco-Vidal et al[44] Prospective, multicentric	2014	Bordeaux 2 University Hospital, France	Heterologous TricOs/MBCP Prospective	57	46.1	36M 21F	12.28		1.75	3.5% 0% in mastoid obliteration area	0	3.5	14	3.5	12 (only 41 patients with full follow- up)
Geerse et al[45] Retrospective	2017	Academic Medical Center, Netherlands	Heterologous Hydroxyapatite granules	122		76M 46F	7	3.27		0	2.5	2.5	100		44
Geerse et al[46] Retrospective	2020	Academic Medical Center, Amsterdam	Heterologous hydroxyapathite granules	249	45	148 M 101 F	5			3.2	1.6 (0% in obliterated area)	4.8			52
Roux et al Prospective	2015	University Hospital of Tours, France	Heterologous Hydroxyapathite granules (MBCP)	36	46	24 M 12 F	(17% transient aseptic)			3.1 (retraction pocket)	6.2	9.3	69.4	5.5	24
Weiss et al[47] Cross sectional cohort study	2020	University Hospital Zurich, Switzerland	Heterologous Hydroxyapathite Matrix Material (HMM) Nanobone	23	56.9	7M 16F	30	4.3		17.4		43.5	0	9	88.3
Al Tamami et al[48] Retrospective	2020	Centre Hospitalier Lyon Sud, France	Heterologous BAG (45S5)	42	49.8	23M 19F	4.8% (7.1 after surgery)			0	0		64.3	2.38 (infected wound)	12
Bernardeschi et al[49] Prospective	2017	PItiè-Salpetriere, Paris, France	Heterologous BAG S53P4	41 (39 pat)	46	22M 17F	0		0	0	0	0	88		12
De Veij Mestdagh et al[50] Retrospective	2017	Diakonessenhius Utrecht, Netherlands	Heterologous BAG (S53P4)	49 (paed excluded)	34.2		2			2	0	2	67	0	22
Krol et al[51] Prospective	2021	Poland	Heterologous BAG (S53P4)	11	50.6	9F 2M	0% (at 6 months; 82% at thirty days after surgery)			0	0	0	100	0	6
Leonard et al[52] Retrospective	2021	Royal Victoria Hospital, Northern Ireland	Heterologous BAG (S53P4)	90	38	45M 45F	8		7% retraction of the attic	0		2% recidivism	38.9	2	22

(*Continued*)

Table 1. Articles Selected for the Review (*Continued*)

Author	Year	Place	Material	Total ears	Age	Sex	Otorrhea (%)	TM perforation	TM retraction pockets	Recurrent disease (%)	Residual disease (%)	Recurrent & residual disease (%)	% of secondary procedures	Infections	Follow-up (months)
Mishra et al[28] Randomized parallel groups study	2020	Army College od Medical Sciences and Base Hospital, Delhi, India	Heterologous BAG (S53P4)	33	28.84	19M 14 F	3.03	3.03	6.06			3.03			15.57
Sarin et al[17] Prospective	2012	Turku University Hospital, Finland	Heterologous BAG (S53P4)	26	47.9	12 M 14 F	4	19.23	3.8	0	0	0	76.9		42.5
Silvola et al[16] Prospective	2012	Päijät-Häme Central Hospital, Lahti, Finland	Heterologous BAG (S53P4)	16	51.5	6 M 9 F	0						100		27
Sorour et al[53] Prospective	2017	Zagazig University, Egypt	Heterologous BAG	20	29.5	11M 9F	(10% after surgery)			0					12-36

Forest plots were created, and heterogeneity analysis of the effect sizes was performed by calculating the Higgins's I^2 statistic[8] and the Cochrane's *Q* index. A Cochrane's *Q* *P*-value <.1 and an $I^2 > 40\%$ were considered markers of heterogeneity.

Publication bias was explored through the inspection of the funnel plot and the Egger test. The funnel plot appears asymmetrical if publication bias is detected, whereas a non-statistically significant result of the *t*-value of the Egger's regression intercept allows us to discard publication bias.

A sub-group analysis was performed for each clinical outcome, comparing the effect sizes resulting from mastoid obliteration with autologous or heterologous materials. The significance of the *Q*-value in the mixed-effects analysis was used to assess significant differences between autologous or heterologous materials.

The level of significance was set at $P < .05$.

RESULTS

The included publications included 25 retrospective studies, 9 prospective studies, 1 randomized parallel groups study, 1 comparative study, and 1 cross-sectional cohort study. Mastoid obliteration with autologous materials was performed with bone patè, autologous remodeled cartilage, muscular flap individually or mixed together. Regarding heterologous materials, 9 studies dealt with BioActive Glass (BAG), S54P4 or 45S5. The others used hydroxyapatite granules: MBCP (byphasic calcium phosphate), HMM (Matrix Material Nanobone), or biphasic ceramics (TricOs). The studies were grouped in 2 categories, autologous or heterologous materials, assuming that bone paté, cartilage, and muscular flap (autologous materials) have the same behavior, with the same possibilities of being contaminated, limited availability, atrophy or resorption, while heterologous materials such as BAG or hydroxyapatite granules might have the same problems of osseointegration and tolerability.

The total number of obliterated ears was 2882: 2008 were obliterated with autologous materials, whereas 874 were treated with heterologous materials.

The mean follow-up was 2.4 ± 22.84 ± 22.8 months; 43.9 ± 23.4 for the autologous group; and 33.9 ± 21.4 for the heterologous group.

Otorrhea

The overall rate of otorrhea was 5% (SE = 0.007; $Z = 6.788$, $P = .000$), in mastoid cavities obliterated with heterologous materials was 5.2% (SE = 0.012; $Z = 4.394$, $P = .000$), in the ones obliterated with autologous grafts was 4.9% (SE = 0.010; $Z = 5.176$, $P = .000$) (Figure 2). The effect sizes comparison between autologous or heterologous materials was not significant ($Q = 0.024$; $P = .876$). Thirty-two studies were considered (18 for autologous materials, 14 for heterologous materials).

It is important to remark that all the studies were highly heterogeneous, especially for those concerning autologous materials ($Q = 77.804$, $P = .000$; $I^2 = 78.150$ vs $Q = 19.261$, $P = .115$; $I^2 = 32.507$). Overall I^2 value was 74.984 ($Q = 123.923$, $P = .000$). Furthermore, there was a publication bias, as demonstrated by Egger's regression intercept and funnel plot ($t = 10.277$, 1-tailed $P = .000$).

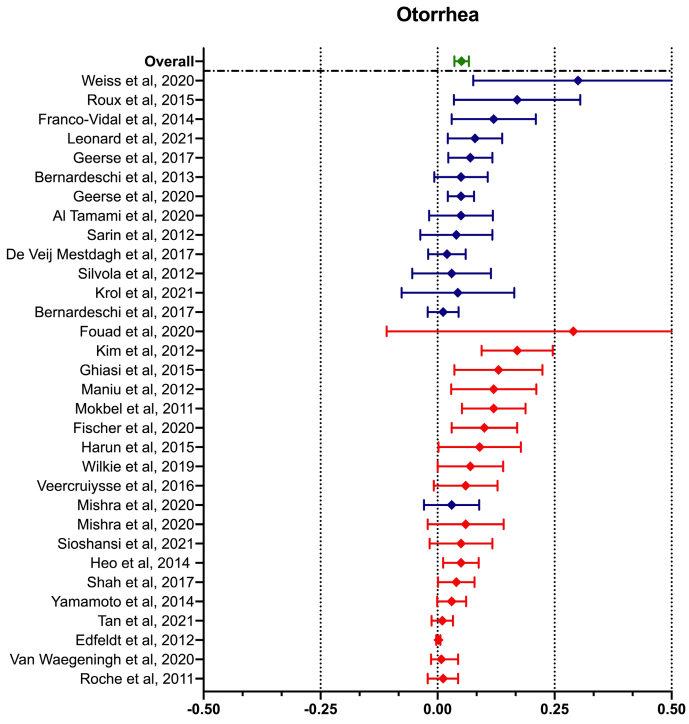

Figure 2. Otorrhea (Forrest Plot). The overall rate of otorrhea was 5%; in mastoid cavities obliterated with heterologous materials the rate was 5.2% while in the ones obliterated with autologous grafts was 4.9%. Red line: Studies concerning autologous materials; Blue line: Heterologous materials; Green line: Overall rate observed in all the studies.

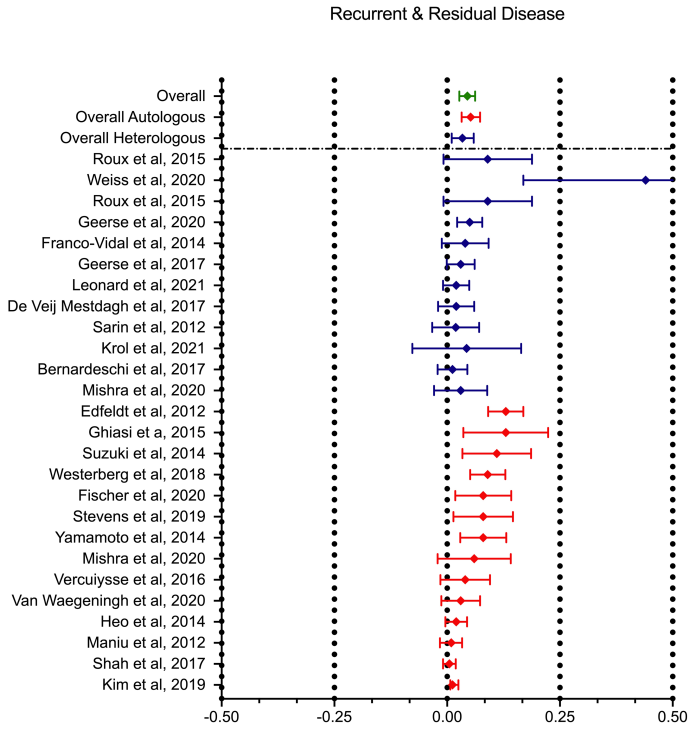

Figure 3. Recurrent and Residual Cholesteatoma (Forrest Plot). Overall recurrence and residual rates were 4.5, 5.2% in surgeries performed with autologous materials and 3.4% in obliterative surgeries with heterologous materials. Red line: Studies concerning autologous materials; Blue line: Heterologous materials; Green line: Overall rate observed in all the studies.

Recurrent and Residual Cholesteatoma

A total number of 25 studies was considered (14 for autologous, 11 for heterologous materials). Overall recurrence and residual rates were 4.5% (SE = 0.009; $Z = 5.042$, $P = .000$), 5.2% in surgeries performed with autologous materials (SE = 0.010; Z = 4.992, $P = .000$), and 3.4% in obliterative surgeries with heterologous materials (SE = 0.013; $Z = 2.732$, $P = .006$) (Figure 3).

Heterogeneity was observed in both autologous and heterologous categories, higher for the former ($Q = 73.427$, $P = .000$; I2=82.295 vs $Q = 14.378$, $P = .156$; $I^2 = 30.450$). Overall I^2 was 72.825 ($Q = 88.315$, $P = .000$). Egger's regression intercept was significant ($t = 4.694$, 2-tailed $P = .000$), showing publication bias for this outcome.

Recurrent Cholesteatoma

Twenty-two studies were evaluated for this outcome (17 for autologous, 5 for heterologous). Overall rate of recurrent disease was 1.8% (SE = 0.004; Z = 4.819, $P = .000$), 1.9% for autologous materials (SE = 0.004; Z = 4.130, $P = .000$), 1.6% for heterologous materials (SE = 0.006; Z = 2.513, $P = .012$). An heterogeneity of the studies could be observed for autologous materials ($Q = 53.308$ $P = .000$; $I^2 = 66.234$), but not for heterologous materials ($Q = 10.742$, $P = .552$, $I^2 = 0.000$). Overall heterogeneity was verified ($Q = 64.107$; $P = .000$; $I^2 = 51.643$). This outcome had publication bias ($t = 4.795$, 1-tailed $P = .000$).

Residual Cholesteatoma

Twenty-three studies were considered for his outcome (13 for autologous materials, 10 for heterologous). The overall rate of residual disease was 1.5% (SE = 0.003; Z = 4.811, $P = .000$) and was similar both for autologous materials (1.5%; SE = 0.004; Z = 3.847, $P = .000$) and for heterologous materials (1.6%; SE = 0.005; Z = 2.896, $P = .004$).

Studies dealing with autologous materials accomplished more heterogeneity compared to heterologous materials ($Q = 23.890$, $P = .021$; $I^2 = 49.769$ vs $Q = 3.414$, $P = .946$; $I^2 = 0.000$). Overall I^2 was 20.255 ($Q = 27.588$, $P = .190$). Publication bias was observed in this outcome only for autologous materials ($t = 4.067$, 2-tailed $P = .000$).

Tympanic Membrane Perforations

Fifteen studies were considered (10 for autologous materials,5 for heterologous). The overall rate of TM perforations was 2.9% (SE = 0.008; Z = 3.802, $P = .000$), 2.5% for autologous materials (SE = 0.008; Z = 3.101, $P = .002$), and 4.3% for heterologous materials (SE = 0.016; Z = 2.765, $P = .006$) (Figure 4).

Studies dealing with autologous materials accomplished more heterogeneity compared to heterologous materials ($Q = 28.263$, $P = .001$; $I^2 = 68.156$ vs $Q = 4.349$, $P = .361$; $I^2 = 8.027$). Overall I^2 was 64.738 ($Q = 39.703$, $P = .000$). Publication bias was observed in this outcome ($t = 7.852$, 2-tailed $P = .000$).

Tympanic Membrane Retraction Pockets

Eleven studies were considered for this outcome (6 for autologous materials, 5 for heterologous). The overall rate was 5.3% (SE = 0.017; Z = 3.157, $P = .002$), 7% in surgeries performed with autologous materials (SE = 0.021; Z = 3.393, $P = .001$) and 3.6% in obliterative surgeries with heterologous materials (SE = 0.021; Z = 1.751, $P = .080$) (Figure 5).

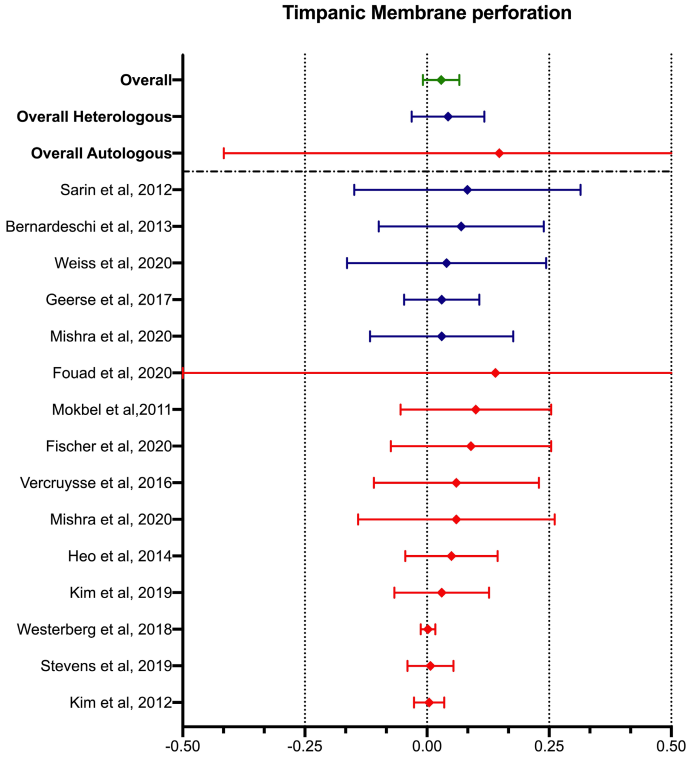

Figure 4. TM perforations (Forrest Plot). The overall rate of TM perforations was 2.9%, 2.5% for the ears obliterated with autologous materials, and 4.3% in those where heterologous materials were used. Red line: Studies concerning autologous materials; Blue line: Heterologous materials; Green line: Overall rate observed in all the studies.

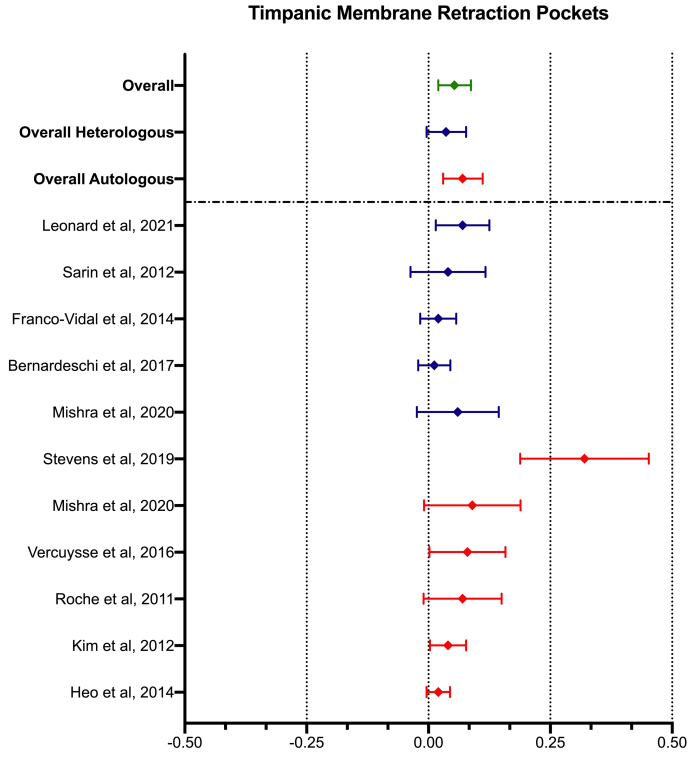

Figure 5. TM retraction pockets (Forrest Plot). The overall rate was 5.3%, 7% in surgeries performed with autologous materials, and 3.6% in obliterative surgeries with heterologous materials. Red line: Studies concerning autologous materials; Blue line: Heterologous materials; Green line: Overall rate observed in all the studies.

Heterogeneity was observed only for studies concerning autologous materials ($Q=22.542$, $P=.000$; $I^2=77.819$ vs $Q=3.983$, $P=.408$; $I^2=.000$). Overall I^2 was 63.153 ($Q=27.139$, $P=.002$). Egger's regression intercept was significant ($t=3.937$, 2-tailed $P=.003$), showing publication bias for this outcome.

Infections

Fifteen studies were considered for this outcome (8 for autologous materials, 7 for heterologous). The overall rate was 2.3% (SE = 0.006; Z = 3.990, $P=.000$), 2.2% in surgeries performed with autologous materials (SE = 0.007; Z = 3.151, $P=.002$), and 2.3% in obliterative surgeries with heterologous materials (SE = .010; Z = 2.450, $P=.014$).

Heterogeneity was observed only for studies concerning autologous materials ($Q=12.397$, $P=.008$; $I^2=43.535$ vs $Q=3.352$, $P=.764$; $I^2=.000$). Overall I^2 was 11.821 ($Q=15.877$, $P=.321$). Egger's regression intercept was significant ($t=6.957$, 2-tailed $P=.000$), so there was publication bias for this outcome.

DISCUSSION

This study is a systematic review with meta-analysis that considers prevalence of the abovementioned outcomes and it is addressed to oto-surgeons that deal with advanced cholesteatoma surgeries with the aim to help to decide whether to use autologous or heterologous materials for mastoid obliteration. In 2018 Van der Toom et al[9] observed lower rates of recurrent and residual disease in patients that underwent mastoid obliteration: in CWU tympanoplasty with mastoid obliteration, these rates were 0.28% and 4.2% respectively, and in CWD tympanoplasty with mastoid obliteration, 5.9% and 5.8%, respectively, suggesting that obliterative techniques can improve patient's quality of life with lower rates of second-look surgery.

In this meta-analysis, the rates of recurrent and residual cholesteatoma were statistically significantly lower in those mastoid cavities obliterated with heterologous materials: 3.4% vs 5.2%, as well as the only rate of recurrent disease. A lower rate of recurrence and residual cholesteatoma can be explained in different ways: autologous materials are more likely to be reabsorbed, leaving space to the possible development of cholesteatoma. Furthermore, in vitro study demonstrated that S53P4 BAG granules down-regulate the inflammatory cytokine release and exhibit antibacterial properties, probably reducing the recurrent disease.[10]

The rate of residual cholesteatoma and the infections were statistically significant, but did not show great differences between autologous and heterologous materials. The development of TM retraction pockets in those patients treated with autologous materials is significantly high (7%), while the rate in patients that underwent surgery with heterologous materials was not significant (3.6%). This may suggest that the progressive reabsorption of autologous materials can change the ear aeration, favoring the development of retraction pockets.[11]

On the other hand, TM perforations were significantly higher in the mastoid obliterated with heterologous materials (4.3% vs 2.5%). This finding may be associated with reduced trophism of the obliteration material and the longer time needed to integrate.

The significantly higher rate of otorrhea in obliterative techniques involving heterologous materials (5.2% vs 4.9%) was presumably due to a primary inflammatory response to a new biomaterial still not osteo-integrated; several studies described a transient, sterile otorrhea that resolved within 1 year.[12,13] Otorrhea can be a reaction of the dynamic interface between cellular response, biodegradation, or bioresorption of materials and their transformation from biphasic calcium phosphate ceramic to carbonate hydroxyapatite.[14] Bernardeschi et al demonstrated a good integration of biphasic ceramics granules in the ear, performing a CT, 1 year after surgery, showing well-integrated granules in the mastoid cavity, without any sign of surrounding osteitis.[15] Further advantages of bioactive glass S53P4 are the bacteriostatic and bactericidal properties due to the presence of silicon ions that increase pH: this might explain the definition of otorrhea as sterile and its capacity to lead to a reduction of ear infections.[13,16,17]

It is crucial to highlight that studies concerning autologous materials did not report the length of otorrhea, either sterile or not, therefore if not specified, we assumed that otorrhea was due to an infected ear. Two studies evaluating mastoid obliteration with heterologous materials reported higher rates of otorrhea, increasing the rate of this outcome: Stoor et al,[13] in their study regarding mastoid cavity obliteration with BioActive Glass (S53P4), observed an otorrhea rate of 14%; however, this was defined as transient, sterile and was specifically described as granulation healing tissue. Moreover, Roux et al[12] reported 17% of transient aseptic otorrhea in their study regarding hydroxyapatite granules.

Safety and tolerability were assessed for heterologous materials by Bagot d'Arc and Daculsi,[18] in 2003, showing that a combination of biphasic calcium phosphate bioceramics with human fibrin sealant forms a moldable material easy to apply in mastoid cavities reconstruction, providing immediate mechanical stability and, thereafter, promoting osteoinduction, enhancing the process of wound healing. In a further study, Bernardeschi et al[19] analyzed cutaneous and labyrinthine tolerance of bioactive glass S53P4, suggesting it might be a valid alternative to reduce recurrent disease. Additionally, none of their patients reported vertigo, dizziness or skin intolerance to the materials.

Although heterologous materials proved to be safe, Roux et al[12] and Bernardeschi et al[19] reported some cases of hydroxyapatite granules extrusion in EAC, consequently treated either through clinical removal under microscopical guidance or through surgical management (reinforcement of the reconstructed canal with cartilage or autologous muscle). In both studies, the follow-up was longer than 1 year; however, further studies are required to analyze pathogenesis and risk factors underneath granules extrusion, to identify the unsuitable patients for this technique.

This meta-analysis has several limitations that could affect the interpretation of the results. All the autologous materials and heterologous ones were grouped together because of the need to maintain the study's statistical power. The authors are aware that different materials may have distinct characteristics but, as stated in the introduction, the grafts considered in the 2 groups shared among them some key-point feature that justify this statistical choice. Moreover, sometimes heterologous materials might be minimally associated with autologous grafts (e.g., cartilage to separate the heterologous materials from the mesotympanum), although the former was in overwhelming majority in the obliterated mastoid cavity. Furthermore, a publication bias has been observed for almost all the outcomes: this might be explained either by the author's choice not to publish studies showing a worse outcome compared to the published ones or by the insufficient sample size. Therefore, the study of prevalence is not able to reflect the daily oto-surgical scenario, which is characterized by great differences among centers. Considering the 2 outcomes together (recurrent and residual), we could overcome the publication bias, showing a more descriptive statistical analysis of cholesteatoma behavior in obliterative mastoidectomies. A publication bias has further been described by Moller et al, 2020:[20] in their review regarding cholesteatoma recurrence, they stated that low recurrence rates might be explained by the high experience of ear surgeons performing the operations included in the studies.

An additional limitation is that sometimes the differentiation between recurrent or residual cholesteatoma might be difficult. Hence prospective, randomized studies are needed to better understand the impact of autologous and heterologous materials on these 2 outcomes. Furthermore, only 1 randomized controlled study was found, therefore we were forced to perform an analysis of prevalence, and not of effectiveness.

Finally, an evaluation of auditory outcomes was not carried out, because of the high number of different reconstruction methods (cartilage, remodeled ossicles, titanium prosthesis such as TORP or PORP) and high variability among patients, which would not have allowed a good analysis.

CONCLUSION

The present Literature review and meta-analysis does not allow to establish the supremacy of one technique over the other, but underlines the advantages of each reconstructive choice. Heterologous materials seem to offer a slight but statistically significant advantage when compared to autologous obliteration tissue in terms of recurrent and residual cholesteatoma and in the development of retraction pockets and might be helpful in revision surgeries being virtually endlessly available. On the other hand, autologous materials showed lower rates of otorrhea and TM perforations.

Up to date, the only available therapy for cholesteatoma is surgery, however, despite all the techniques, it still is a recurrent disease, as other authors have already observed.[9] Mastoid obliteration is pivotal for the patient's quality of life, since it allows them to soak the ear and to wear hearing aids with social hearing improvement. Furthermore, it gives excellent results with low residual and recurrent rates, no matter what type of obliteration material is used. In obliterated ears, the residual and recurrent rates are comparable with the reported CWD results, yet without the morbidity caused by CWD, such as vertigo, dizziness, ear infections, and the need of closer follow-up.[1-4]

The key-points are the improvement of patients' quality of life, the reduction of cholesteatoma recidivism or the need of a second surgery. Otologists must deal with a chronic disease, with the tendency to recur and extend to surrounding structures. Further comparative

studies between autologous and heterologous materials should be designed. Also, a better evaluation of each of the heterologous materials is needed, to establish their safety, tolerability, and bio-compatibility.

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist Item	Location where Item Is Reported
Title			
Title	1	Identify the report as a systematic review.	Title page
Abstract			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
Introduction			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2
Methods			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	3,4
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	3,4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	3,4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	3,4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	3
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	3
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	4,5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	3,4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	3,4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	4,5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	4,5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	4,5
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	4,5
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	4,5

Results			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	3,4
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	6,7,8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	6,7,8
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	6,7,8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	6,7,8
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	6,7,8
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	6,7,8
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	6,7,8
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	6,7,8
Discussion			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	9
	23b	Discuss any limitations of the evidence included in the review.	10,11
	23c	Discuss any limitations of the review processes used.	11,12
	23d	Discuss implications of the results for practice, policy, and future research.	9-12
Other Information			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Not registered
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Title Page
Competing interests	26	Declare any competing interests of review authors.	Title Page
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Tables, figures, on request

PRISMA 2020 Checklist.