VILNIUS UNIVERSITY
FACULTY OF MEDICINE

Medicine

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INTEGRATED STUDY MASTER'S THESIS

Riebalų persodinimo būdai injekcinei balso raukšlių medializacijai

Fat Grafting Techniques for Injection Medialization of Vocal Folds

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Vilnius, 2026.

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ABBREVIATIONS

ADRCs – Adipose-derived regenerative cells

ASCs – Adipose-derived stem cells

bFGF – Basic fibroblast growth factor

CAF – Centrifuged autologous fat

CaHA – Calcium hydroxylapatite

CT – Computed tomography

DOI – Digital object identifier

F0 – Fundamental frequency

GI – Glottic insufficiency

GRBAS – Grade, Roughness, Breathiness, Asthenia, Strain

HA – Hyaluronic acid

HNR – Harmonic-to-noise ratio

IL – Injection laryngoplasty

MeSH – Medical Subject Headings

MFR – Mean flow rate

MPT – Maximum phonation time

MT – Medialization thyroplasty

MTD – Muscle tension dysphonia

NHR – Noise-to-harmonic ratio

NR – Not reported

PDGF – Platelet-derived growth factor

PDMS – Polydimethylsiloxane

PICO – Population, Intervention, Comparison, Outcome

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PRP – Platelet-rich plasma

RCT – Randomized controlled trial

RLN – Recurrent laryngeal nerve

SVF – Stromal vascular fraction

TGF-β – Transforming growth factor beta

UVFP – Unilateral vocal fold paralysis

VEGF – Vascular endothelial growth factor

VHI – Voice Handicap Index

SUMMARY

Glottic insufficiency due to vocal fold paralysis, atrophy, sulcus vocalis, or post-resection scarring leads to significant voice impairment and may result in aspiration. Autologous fat injection laryngoplasty is an established minimally invasive technique for vocal fold medialization. However, no standardized protocol exists for fat harvesting, processing, or injection. This review evaluates how variations in autologous fat grafting techniques influence voice outcomes, graft longevity, and complication rates. A PRISMA-compliant review with narrative synthesis was conducted. PubMed, Cochrane Library (CENTRAL), and Scopus were searched in January 2026 for studies published between 2016 and 2026. Eight studies comprising 243 patients met the inclusion criteria. Due to substantial heterogeneity, a narrative synthesis was performed. Most studies reported improvement in subjective, perceptual, acoustic, and aerodynamic measures. Outcomes were more favorable in paralytic and atrophic conditions than in structurally altered vocal folds. Injection volume emerged as the most relevant modifiable factor, with higher volumes associated with improved outcomes and lower revision rates. In contrast, fat processing techniques showed no clear superiority, while correct placement within the thyroarytenoid muscle was essential. Adjunctive strategies, including platelet-rich plasma and scaffold-based approaches, showed variable and preliminary effects. Complication rates were low, and revision was primarily related to insufficient or declining medialization. Overall, autologous fat injection laryngoplasty is a safe and effective intervention. Injection volume and accurate placement appear to be an important modifiable factor of outcome, whereas no optimal processing technique can currently be identified. Further standardized, adequately powered studies with objective assessment of graft survival are required.

KEYWORDS

vocal fold medialization, injection laryngoplasty, autologous fat grafting, glottic insufficiency, voice outcomes, fat processing techniques

SUMMARY IN LITHUANIAN

Glottinis nepakankamumas dėl balso raukšlės paralyžiaus, atrofijos, sulcus vocalis ar popoperacinių randų sukelia ryškius balso sutrikimus ir gali lemti aspiracijos riziką. Autologinių riebalų injekcinė laringoplastika yra įtvirtinta minimali invazinė balso raukšlių medializacijos technika; tačiau nėra standartizuoto riebalų paėmimo, apdorojimo ar injekcijos protokolo. Ši apžvalga vertina, kaip autologinių riebalų transplantavimo technikų variacijos veikia balso rezultatus, transplantato ilgaamžiškumą ir komplikacijų dažnį. Atlikta PRISMA reikalavimus atitinkanti sisteminė apžvalga su naratyvinės sintezės metodu. 2026 m. sausio mėnesį buvo ieškoma tyrimų duomenų bazėse PubMed, Cochrane Library (CENTRAL) ir Scopus; atrinkti 2016–2026 m. paskelbti straipsniai. Įtraukimo kriterijus atitiko aštuoni tyrimai, apimantys 243 pacientus. Dėl ryškios heterogeniškumo buvo taikyta naratyvinė sintezė. Visuose įtrauktuose tyrimuose nustatytas kliniškai reikšmingas balso funkcijos pagerėjimas pagal subjektyvius, percepcijos, akustikos ir aerodinamikos rodiklius. Rezultatai buvo palankesni paralyžiaus ir atrofinės patologijos grupėse nei struktūriškai pakitusių balso raukšlių atvejais. Injekcijos tūris išryškėjo kaip svarbiausias keičiamas veiksnys: didesnis tūris siejamas su geresniais rezultatais ir mažesniu pakartotinių intervencijų dažniu. Riebalų apdorojimo technikos aiškaus pranašumo viena prieš kitą neparodė, tuo tarpu tikslus transplantato padėjimas į tiroaritenoidinį raumenį buvo esminis reikalavimas. Papildomosios strategijos, įskaitant turtingąją trombocitų plazmą ir karkasų pagrindu veikiančius metodus, davė kintamų ir preliminarių rezultatų. Komplikacijų dažnis buvo mažas, o pakartotinės intervencijos pirmiausia buvo susijusios su nepakankama arba mažėjančia medializacija. Apibendrinant, autologinių riebalų injekcinė laringoplastika yra saugi ir efektyvi intervencija. Injekcijos tūris ir tikslus transplantato padėjimas yra svarbiausi rezultatų veiksniai, tuo tarpu optimalaus apdorojimo metodo šiuo metu nustatyti nepavyksta. Reikalingi tolimesni standartizuoti, pakankamai didelės apimties tyrimai su objektyviu transplantato išgyvenamumo vertinimu.

1. INTRODUCTION

1.1. BACKGROUND AND CLINICAL RELEVANCE

The vocal folds are crucial structures in the larynx that are essential for phonation, swallowing, airway protection, and respiratory regulation (1,2). During phonation, the vocal folds are brought into close apposition, and airflow from the lungs sets them into oscillation to generate sound. This highly coordinated process relies on sufficient glottal closure, proper vocal fold tension, and neuromuscular symmetry (2,3).

Disruption of any component, particularly due to nerve injury or structural damage, can lead to incomplete glottic closure (4,5). Glottic insufficiency can be caused by a variety of structural, neurological, and functional pathologies. The most prevalent etiologies include unilateral vocal fold paralysis and unilateral or bilateral vocal fold paresis. Additional contributing factors comprise vocal fold atrophy, fibrosis, sulcus vocalis, and systemic neuromuscular disorders such as Parkinson's disease. Mechanical obstructions, such as benign or malignant masses and dysfunction of the cricoarytenoid joint may also contribute to impaired glottic closure.

These alterations may result in varying degrees of glottic gap formation, correlating with vocal function impairment. Consequently, patients may present with symptoms such as vocal fatigue, dyspnea during phonation, compensatory muscle tension dysphonia, odynophonia, or aspiration (4,6,7).

To restore sufficient vocal fold closure, medialization techniques aim to reposition or augment the affected vocal fold toward the midline, thereby improving glottal competence and voice quality (8). While established surgical interventions such as type I thyroplasty and arytenoid adduction provide durable solutions for vocal fold medialization, injection laryngoplasty represents a minimally invasive and repeatable alternative that has gained increasing clinical relevance (4,9–11).

In particular, early injection laryngoplasty within six months of paralysis onset has been shown to reduce the risk of subsequent permanent thyroplasty by approximately 75% compared to conservative management (12). In injection medialization specifically, a filling material is deposited into the lateral aspect of the thyroarytenoid muscle or the paraglottic space, increasing vocal fold bulk and displacing the medial surface toward the midline without disrupting the overlying lamina propria (13,14).

Precise material placement is critical to treatment outcomes, as superficial injection causes improper biomaterial localization, tissue stiffening, and impeded vibration (11,14). In the literature, the terms 'vocal fold augmentation' and 'vocal fold medialization' are often used interchangeably, although augmentation refers specifically to increasing vocal fold volume, while medialization describes the repositioning of the vocal fold toward the midline. In this review, both terms are considered within the broader context of restoring glottic competence via injection laryngoplasty.

A variety of injectable materials have been investigated for this purpose, ranging from temporary agents such as hyaluronic acid and carboxymethylcellulose to longer-lasting materials such as calcium hydroxyapatite, which provides more durable volumization. Several substances including Teflon, silicone oil, and paraffin oil are considered obsolete due to their association with granuloma formation, tissue migration, or chronic inflammation (11,13,15,16).

Emerging materials under investigation include hydrogel composites, platelet-rich plasma, and stem cell-enriched fat preparations, which are being studied for their regenerative and cell-stimulatory potential (7,17). Among the available materials, autologous fat has been widely used for vocal fold augmentation since the early 1990s, owing to its favorable biocompatibility, cost-effectiveness, low risk of rejection, and viscoelastic characteristics similar to those of the vocal fold's lamina propria (18,19).

Systematic reviews have confirmed that no standardized technique exists for fat harvesting, processing, or injection, and that the existing literature does not allow for a direct comparison of processing methods in terms of vocal outcomes (16,20). This variability in technique and outcome forms the basis for the PRISMA-compliant review with a narrative synthesis presented in this thesis.

1.2. JUSTIFICATION FOR THE REVIEW AND RESEARCH QUESTION

Despite the widespread clinical use of autologous fat in injection laryngoplasty, considerable variability exists in the techniques applied for fat processing and injection. These procedural differences may significantly influence graft survival, voice quality, and complication rates. However, the current literature provides limited and often conflicting evidence regarding the comparative effectiveness of these approaches, with no established consensus on optimal fat grafting protocols (16,21).

This lack of standardization is further compounded by small sample sizes, heterogeneous study designs, and inconsistent follow-up periods across existing studies, limiting the generalizability of their findings and the ability to draw evidence-based conclusions for clinical practice (13,16,19).

The objective of this review is not to compare autologous fat with alternative injectable materials, but to examine differences within autologous fat grafting techniques, including variations in processing methods, injection approaches, and injection volume. Studies evaluating adjunctive biologic therapies, such as PRP and collagen in combination with autologous fat grafting, were also considered eligible, if outcomes attributable to the fat grafting component could be assessed independently.

Given this uncertainty in the literature, a PRISMA-compliant literature review with a narrative synthesis is warranted to evaluate the available evidence regarding the effectiveness, safety, and long-term graft stability of different autologous fat grafting techniques in vocal fold medialization.

To structure the research focus and define eligibility criteria, the PICO framework was applied. The population consists of patients undergoing vocal fold medialization due to glottic insufficiency. The

intervention of interest is autologous fat injection, with attention to the fat processing, preparation and injection technique. The comparison includes alternative approaches within autologous fat grafting, such as differences in preparation methods or injection strategies. The primary outcomes are voice quality improvement, graft longevity, complication rates, and revision rates. An overview is provided in Annex 1.

This review aims to answer the following key question: "In patients undergoing vocal fold medialization, what technical factors in autologous fat grafting are associated with favorable voice outcomes, graft longevity, and complication rates?"

1.3. OBJECTIVES AND STRUCTURE OF THE THESIS

The aim of this thesis is to evaluate the effects of different autologous fat grafting techniques on voice outcomes, graft longevity, and complication rates in patients undergoing vocal fold medialization via injection laryngoplasty.

To achieve this, the thesis seeks to identify and describe technical variations in autologous fat grafting, including differences in processing, and injection techniques, and to compare clinical outcomes across the included studies. Furthermore, the methodological quality of the available evidence is assessed and gaps in the current literature are identified, with the aim of providing evidence-based recommendations for clinical practice and future research.

The structure of the thesis is as follows: Chapter 1 introduces the clinical background and relevance of autologous fat injection laryngoplasty, presents the justification for the review and the research question, and outlines the objectives and structure of the thesis. Chapter 2 outlines the methodology of the review, including the search strategy, inclusion and exclusion criteria, study selection process, data extraction, and quality assessment.

Chapter 3 provides the theoretical background of autologous fat grafting in vocal fold medialization, encompassing the anatomy and histology of the vocal fold, the clinical rationale for injection laryngoplasty, the procedural principles of fat injection, and technical variations in fat harvesting, processing, and adjunctive strategies. Chapter 4 presents the results of the review, structured according to the characteristics of the included studies, technical variability across studies, clinical outcome domains, graft longevity, complication and revision rates, and an appraisal of evidence quality.

Chapter 5 discusses the findings in the context of current clinical practice and methodological limitations, and Chapter 6 concludes the thesis with a summary of key findings and recommendations for future research and clinical application.

2. METHODOLOGY

2.1. DESIGN AND PROTOCOL

Due to anticipated heterogeneity in study design, interventions, and outcome measures, a quantitative synthesis was not considered appropriate. Therefore, a PRISMA-compliant review with a narrative synthesis was intentionally chosen to assess the effects of different autologous fat grafting techniques in injection laryngoplasty for vocal fold medialization.

The review was conducted in accordance with the PRISMA 2020 guidelines to ensure methodological transparency, and reproducibility (22). The methodological approach was defined prior to initiating the literature search and includes a structured search strategy, predefined eligibility criteria, systematic study selection, data extraction, and quality assessment.

All relevant steps of the review process are described in detail in the following sections. The aim of this design is to ensure a comprehensive and unbiased synthesis of current evidence on how variations in fat processing, preparations and injection techniques influence clinical outcomes such as voice improvement, graft longevity, and complication rates in patients with glottic insufficiency.

2.2. SEARCH STRATEGY

A comprehensive literature search was conducted to identify clinical studies evaluating autologous fat grafting techniques for vocal fold medialization via injection laryngoplasty. Three databases were searched: PubMed, Cochrane Library (CENTRAL), and Scopus. These were selected to ensure broad coverage of clinical, surgical, and biomedical literature relevant to the topic.

The search strategy was constructed using a combination of Medical Subject Headings (MeSH) and free-text keywords, organized around three core concepts: patients undergoing vocal fold medialization for glottic insufficiency, the procedural context of injection laryngoplasty, and autologous fat as the injected graft material.

The MeSH terms applied were "Vocal Cords", "Vocal Cord Paralysis", "Laryngoplasty", "Injections, Intralesional", and "Adipose Tissue". Free-text terms included "vocal fold", "vocal cord", "glottic insufficiency", "injection laryngoplasty", "vocal fold injection", "fat graft*", "fat injection", "autologous fat", "fat augmentation", and "fat transfer".

The terms 'vocal fold medialization' and 'vocal fold augmentation' were both considered, as they are frequently used interchangeably in the literature to describe the same clinical procedure. Boolean operators (AND, OR) and truncation symbols were applied to enhance sensitivity and precision (23–25).

Specific preparation methods and adjunctive biologic therapies were deliberately excluded as search terms, as these details are inconsistently reported in titles and abstracts. These variables were instead extracted during the data extraction phase. A detailed overview of all search terms grouped by concept is provided in Annex 2.

PubMed was searched on 11 January 2026, with filters applied to restrict results to English-language studies involving human participants published between January 2016 and January 2026. The Cochrane Library (CENTRAL) was searched on 11 January 2026 using the same conceptual structure. Scopus was searched on 12 January 2026 via the Advanced Search interface, with equivalent date and language restrictions applied. No restrictions on article type were applied during database searching to avoid premature exclusion of relevant studies.

The complete search strategies for each database are provided in Annexes 4, 5, and 6.

2.3. INCLUSION AND EXCLUSION CRITERIA

To ensure methodological rigor and transparency, predefined inclusion and exclusion criteria were established prior to the screening process, based on the PICO framework and aligned with the research objectives of this review.

Studies were considered eligible if they examined autologous fat injection for vocal fold medialization and reported at least one relevant clinical outcome, including voice improvement, graft longevity, complication rates, or revision rates. In addition, the eligible studies should describe at least one technical aspect of the fat transfer procedure, such as the preparation method or the injection technique.

Studies evaluating adjunctive biologic therapies including PRP or collagen in combination with autologous fat grafting were also considered eligible. Comparative analyses, where applicable, were restricted to comparisons within autologous fat grafting techniques. Studies directly comparing fat to non-biological materials or to surgical medialization procedures were excluded.

Regarding study design, accepted types comprised randomized controlled trials (RCTs), prospective and retrospective cohort studies, comparative and non-comparative clinical studies, and single-arm interventional studies. The inclusion of single-arm studies was considered appropriate given the limited and heterogeneous evidence base.

All studies were required to involve human participants, report a minimum follow-up period of six months, and include at least ten participants to ensure adequate data quality and clinical relevance. Only publications in English, published between January 2016 and January 2026, were considered.

Studies were excluded if they focused exclusively on surgical medialization techniques such as thyroplasty, employed non-fat injectable materials without an autologous fat component, or did not report any relevant clinical outcomes. Animal studies, cadaveric studies, in vitro experiments, narrative reviews, editorials, letters to the editor, and conference abstracts without full-text availability were likewise excluded.

A comprehensive overview of all inclusion and exclusion criteria is provided in Annex 3.

2.4. STUDY SELECTION PROCESS

Database searches of PubMed, Scopus, and the Cochrane Library yielded a total of 97 records (PubMed: n = 34, Scopus: n = 51, Cochrane Library: n = 12).

All records were imported into Zotero for initial deduplication using the built-in duplicate detection function. As automated deduplication algorithms may not consistently identify all duplicates, an additional manual deduplication step was subsequently performed in Microsoft Excel, with records compared based on DOI, title, and publication year.

A total of 35 duplicate records were removed, resulting in 62 unique records available for title and abstract screening. Titles and abstracts of all 62 records were screened against the predefined inclusion and exclusion criteria outlined in Section 2.3. Studies that clearly did not meet the eligibility criteria were excluded at this stage, resulting in 40 records being excluded and 22 records proceeding to full-text assessment.

All 22 full-text articles were successfully retrieved. Full-text articles were assessed for eligibility, and 14 records were excluded for the following reasons: insufficient reporting of fat grafting technique (n = 5), use of non-fat injectable material as the primary intervention (n = 3), insufficient follow-up period of less than six months (n = 2), sample size below ten participants (n = 2), wrong indication or population (n = 1), and animal study (n = 1).

Reasons for exclusion were documented using a predefined list of exclusion categories applied as a standardized classification during the screening process.

Following full-text assessment, eight studies met all eligibility criteria and were included in the final review. The complete study selection process is summarized in the PRISMA flow diagram provided in Annex 7.

2.5. DATA EXTRACTION AND QUALITY ASSESSMENT

Data extraction was performed systematically using a predefined extraction template developed prior to the screening process. For each included study, the following information was extracted: study design, sample size, fat harvesting and processing technique, use of adjunctive biologic therapies, injection approach and volume, and reported clinical outcomes including objective voice parameters and Voice Handicap Index (VHI) scores, graft longevity, complication rates, and revision rates.

The VHI is a validated patient-reported outcome measure assessing the functional, physical, and emotional impact of voice disorders on daily life. The GRBAS scale was used as a clinician-rated perceptual assessment tool, evaluating grade, roughness, breathiness, asthenia, and strain.

Maximum phonation time (MPT) and mean flow rate (MFR) were recorded as measures of glottic efficiency. Acoustic parameters extracted, where available, included jitter, shimmer, and noise-to-harmonic ratio (NHR), reflecting the regularity and stability of vocal fold vibration.

Fundamental frequency was not consistently reported across studies and was therefore not included in the comparative analysis. In addition, videostroboscopic findings were recorded when reported; however, as mucosal wave characteristics and vibratory symmetry were inconsistently quantified across studies, the analysis focused primarily on glottic closure as the most uniformly reported stroboscopic parameter.

A formal risk-of-bias tool was not applied, as the heterogeneity in study designs, including single-arm and non-comparative studies, would have limited the validity and comparability of such scoring systems.

Instead, a structured qualitative assessment was deliberately chosen, based on key domains including study design, sample size, blinding procedures, allocation methods where applicable, completeness of outcome reporting, and potential sources of bias. This qualitative approach enabled identification of consistent methodological limitations across studies and informed the critical appraisal presented in Section 4.6..

2.6. METHODOLOGICAL LIMITATIONS

Several methodological limitations of this review must be considered when interpreting the findings. First, due to substantial heterogeneity in study design, patient populations, interventions, and outcome measures, a quantitative synthesis was not appropriate. A narrative synthesis was therefore employed as the most suitable method to integrate the available evidence, although this limits the ability to derive pooled effect estimates.

Second, the review was conducted by a single author. Study selection, data extraction, and quality assessment were performed independently without duplicate screening or external validation, which may introduce a risk of selection bias. However, predefined inclusion criteria and a structured data extraction framework were applied to enhance consistency and transparency.

Third, a formal risk-of-bias tool was not applied. Given the heterogeneity in study designs, including non-comparative and single-arm studies, the use of standardized scoring systems would have been of limited validity. Instead, methodological quality was assessed qualitatively across key domains.

Fourth, the review was restricted to studies published in English between January 2016 and January 2026, introducing a potential risk of language and publication bias.

Fifth, although a comprehensive search strategy was applied across multiple databases, relevant studies may have been missed. Grey literature was not systematically searched, which may contribute to an overrepresentation of positive findings. The limitations of the primary literature are discussed in detail in Section 5.3.

3. THEORETICAL BACKGROUND

3.1. ANATOMY AND HISTOLOGY OF THE VOCAL FOLD

The vocal folds are paired soft tissue structures located within the larynx, each composed of a layered mucosal architecture that provides the unique mechanical properties required to withstand the high-frequency oscillatory demands of phonation (1,14). Each vocal fold spans the distance between the anterior commissure of the thyroid cartilage and the vocal process of the arytenoid cartilage, forming the lateral boundaries of the glottis (2).

During phonation, the vocal folds are adducted toward the midline, and subglottic airflow sets them into vibration at frequencies typically ranging from 100 to 300 Hz in conversational speech, imposing repeated cycles of mechanical deformation that require both structural resilience and viscoelastic compliance (14).

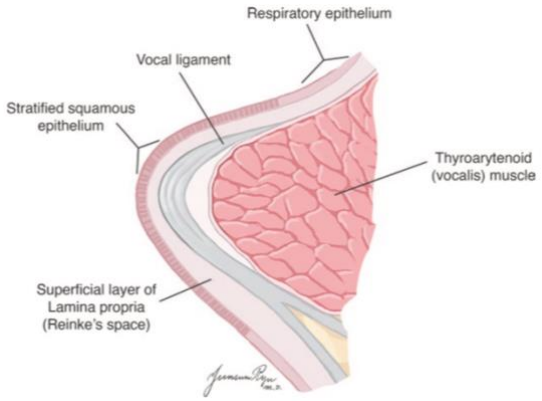

Figure 3-1. Cross section of the vocal cords
Adapted from (9)

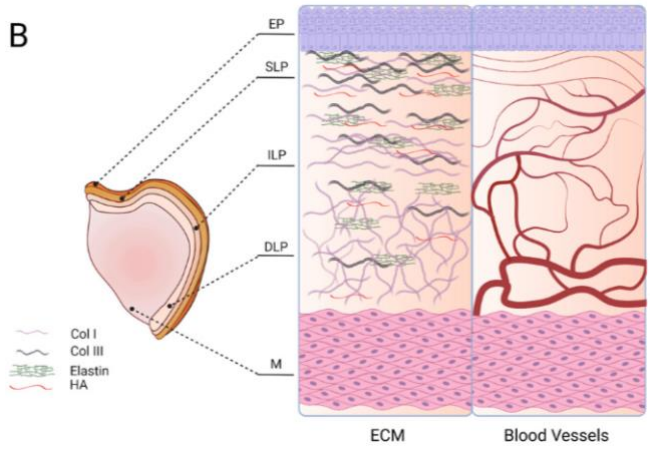

Figure 3-2. Layers of the vocal folds
Adapted from (14)

The histological organization of the vocal fold is best understood through Hirano's cover-body theory, which describes the vocal fold as a layered vibrator (26). The body comprises the thyroarytenoid muscle and the vocal ligament, which together provide structural tension and determine the overall stiffness of the vocal fold.

The cover consists of the superficial layer of the lamina propria and the overlying stratified squamous epithelium, which move as a vibratory unit during phonation, generating the characteristic mucosal wave that travels from the inferior to the superior aspect of the medial vocal fold surface (26).

Hirano further subdivided the lamina propria into three distinct layers with progressively different fiber compositions and mechanical properties (14,26). The superficial layer of the lamina propria, also known as Reinke's space, consists of loosely interwoven elastic and collagen fibers forming an acellular gelatinous layer, which accounts for the exceptional pliability of the vocal fold cover during phonation (2,27).

However, this loose architecture also renders it particularly susceptible to aberrant material deposition and inadvertent injection into Reinke’s space, which has an approximate thickness of 0.3 mm. Such

misplacement can disrupt the mucosal wave and may ultimately lead to permanent stiffening of the vocal fold cover (2,9,11,14).

The extracellular matrix of the lamina propria is primarily composed of collagen type I, which provides structural integrity, and collagen type III, which contributes to tissue resilience. Elastin fibers, which confer viscoelastic recoil, are concentrated predominantly in the intermediate layer of the lamina propria, while collagen fibers are more densely distributed in the deep layer. Hyaluronan is present throughout all layers and dampens mechanical stress during phonation (14).

From a surgical perspective, this layered architecture has direct implications for injection laryngoplasty. The medial fibers of the thyroarytenoid muscle, run parallel to the vocal ligament and constitute the primary target for augmentation injections, allowing effective medial displacement of the vocal fold while preserving vibratory function (9).

In cases of larger glottic gaps, additional augmentation of the paraglottic space may be utilized to enhance medialization (9,11). Injections placed at this depth increase vocal fold bulk and displace the medial surface toward the midline without disrupting the overlying cover layers.

The viscoelastic properties of any injectable material are therefore of critical importance: materials that closely match the mechanical properties of the native vocal fold cover produce more favorable phonatory outcomes than those with significant viscoelastic mismatch, even when placed deep to the lamina propria (11,14).

Autologous fat, with its viscosity closely resembling that of the lamina propria, is therefore considered particularly well-suited for vocal fold augmentation from a biomechanical standpoint (13,20).

3.2. INDICATIONS AND CLINICAL RATIONALE

Glottic insufficiency is the overarching clinical indication for vocal fold fat injection laryngoplasty. It describes an incomplete closure of the vocal folds during phonation and can result from a variety of underlying pathologies, including vocal fold paralysis, paresis, age-related atrophy (presbyphonia), scarring, and sulcus vocalis (11,20).

Irrespective of its etiology, GI manifests through a characteristic symptom complex comprising vocal breathiness, reduced vocal intensity, fatigue, and in more severe cases dysphagia and aspiration risk (20). Up to 9% of the general population has some form of voice abnormality, and 29% will develop a voice disorder during their lifetime (27).

Treatment for cases that do not respond to voice therapy includes injection laryngoplasty or medialization laryngoplasty, with the choice depending on the size of the glottic gap, the underlying cause, and the patient's overall condition (18, 25).

Among the many causes of GI, unilateral vocal fold paralysis (UVFP) represents one of the most clinically relevant and frequently treated entities, with an estimated incidence of approximately 5.13

per 100,000 adults annually (28,29). It arises most commonly from iatrogenic injury to the recurrent laryngeal nerve (RLN) or the vagus nerve and results in characteristic dysphonia with hoarseness and breathiness. Causes can be thyroid surgery, cervical or thoracic procedures, and neoplastic infiltration, idiopathic causes, trauma, or stroke (28,30). Due to its longer and more convoluted anatomical course, the left RLN is injured more frequently than the right (31).

The degree of impairment correlates directly with the neurophysiological extent of RLN injury, ranging from transient neuropraxia to complete nerve resection. On laryngoscopic examination, impaired cord motion, bowing, and inadequate glottic closure are observed (28).

Patients with UVFP additionally face an elevated risk of liquid aspiration, and weakened cough reflex, which can result in pulmonary complications including aspiration pneumonia (32).

The timing of intervention carries prognostic significance beyond the acute phase. Early medialization during the window of synkinetic reinnervation has been shown to favor a more advantageous final vocal fold resting position and to reduce the subsequent need for open-neck phonosurgical reconstruction (33). In contrast, prolonged untreated GI, predisposes patients to muscle tension dysphonia (MTD), a maladaptive hyperkinetic compensation pattern that may persist even after successful surgical correction, underscoring the importance of early intervention (34).

The psychosocial burden of untreated UVFP reinforces this rationale: qualitative research demonstrates substantial effects on emotional well-being, professional identity, and social participation, with greater voice-related handicap in patients who have not yet accommodated to their altered voice (35).

A clinically increasingly relevant subgroup is represented by patients with age-related vocal fold atrophy, termed presbyphonia, which results from progressive loss of vocal fold muscle mass and leads to incomplete glottic closure (7). It is important to note that approximately 50% of all UVFP patients may not ultimately require any rehabilitative procedure (36). Nevertheless, when aspiration, severe dysphonia, or debilitating voice impairment is present, active treatment is required. Surgical intervention becomes necessary when spontaneous recovery with speech therapy fails to occur, when functional impairment is significant, or when the RLN has been completely transected (37).

Compared to synthetic or semi-synthetic injectables, autologous fat carries a lower risk of foreign body reaction or allergic response, can be generously injected, and is readily removable in revision procedures (11,20). It offers a potential long-lasting augmentation when graft survival is achieved. This is an advantage over hyaluronic acid, which requires repeated injections due to its limited duration (13,38). Furthermore, fat grafts contain adipose-derived stem and endothelial cells, endowing them with regenerative potential beyond simple volumization, a property not shared by any currently available synthetic injectable (7,14).

However, the effectiveness of fat injection is fundamentally constrained by the natural process of resorption, which can lead to a gradual reduction in volume and a potential decline in the achieved clinical outcome over time (16,20).

3.3. PRINCIPLES AND MECHANISMS

Both medialization thyroplasty (MT) and injection laryngoplasty (IL) are based on the same fundamental principle: medial displacement of the paralyzed vocal fold toward the contralateral healthy fold to restore competent glottic closure during phonation. While MT achieves this through structural repositioning using an implant, IL relies on volumetric augmentation (28). Injection laryngoplasty achieves medialization by delivering injectable material into the thyroarytenoid muscle and/or paraglottic space, thereby displacing the vocal fold medially while avoiding direct disruption of the lamina propria (13,28).

Preservation of the layered microarchitecture of the vocal fold is critical, as the viscoelastic properties of the lamina propria are essential for maintaining a functional mucosal wave. Because the injection is performed deep to Reinke's space, the superficial lamina propria remains functionally preserved, allowing maintenance of the mucosal wave provided the material is accurately placed (13,14). Several injection approaches exist, each with specific technical characteristics and indications. The trans-oral approach, the only non-percutaneous awake technique, uses a curved needle via the oral cavity under endoscopic visualization and offers the highest precision, but requires considerable operator experience and favorable anatomy (39). The trans-cricothyroid approach introduces the needle through the cricothyroid membrane along a short extramucosal path, making it faster and better tolerated, although the needle tip is not directly visible and depth must be estimated (40). The trans-thyrohyoid approach inserts the needle through the thyrohyoid membrane, while the trans-cartilaginous approach involves direct puncture of the thyroid cartilage at the level of the vocal folds (41).

The choice among approaches is guided by patient anatomy, surgeon experience, and the specific augmentation target. Autologous fat, due to its higher viscosity compared to synthetic fillers, is frequently administered under general anesthesia via microlaryngoscopy, which allows for direct visualization and more controlled injection volumes.

Material selection and injection technique are governed by biomechanical constraints. Substances with viscoelastic properties similar to the native vocal fold cover, such as hyaluronic acid, yield more favorable phonatory outcomes, whereas stiffer materials may impair mucosal wave propagation and alter vibratory energy dynamics (37,38). The use of autologous fat as an injectable material carries several inherent advantages. It is biocompatible, non-toxic, easily obtainable, cost-effective, and rarely triggers foreign body reactions (20). In addition to its volumetric effect, it contains adipose-

derived stem cells and endothelial components that may promote angiogenesis and tissue remodeling, suggesting regenerative potential (27).

Despite these advantages, autologous fat is associated with several clinically relevant limitations. Postoperative resorption remains unpredictable, with reported rates ranging from 20% to 60%, making overcorrection necessary (13,16). The survival of injected adipose tissue is fundamentally limited by the balance between graft volume and available vascular supply: each fat droplet must be in close contact with surrounding capillaries to ensure adequate oxygenation. If the amount of injected fat exceeds the capacity of the recipient site to provide sufficient vascular ingrowth, neovascularization remains inadequate, leading to progressive adipocyte necrosis and subsequent fibrosis.

Variability in local tissue vascularity and injection technique further contributes to the difficulty in predicting the extent of resorption on an individual basis (44). Furthermore, excessive injection can alter vocal fold biomechanics and lead to clinically relevant dysphonia, occasionally requiring revision procedures (14,27).

Timing is a key clinical consideration. In the early phase after recurrent laryngeal nerve injury, spontaneous reinnervation may occur within approximately six months. Therefore, temporary materials such as hyaluronic acid or carboxymethylcellulose are often preferred initially, to avoid premature commitment to long-lasting augmentation (31,45). Autologous fat, although not fully permanent, provides a more durable effect and is typically reserved for cases in which recovery is unlikely (37).

3.4. TECHNICAL ASPECTS OF FAT HARVESTING

Despite decades of clinical experience with fat injection laryngoplasty, there remains no standardized protocol governing fat harvesting, processing, or injection technique (16). Consequently, considerable variability persists across clinical practice, reflecting differences in surgeon preference, available resources, and institutional protocols.

The most commonly used donor site is the periumbilical or infraumbilical subcutaneous region, chosen for its reliable abundance of subcutaneous fat and ease of access (20). Alternative harvesting sites include the peritrochanteric region, the inner knee, the submental region, and the buccal fat (46).

There are two principal harvesting techniques, liposuction and open surgical excision. Liposuction is performed after subcutaneous infiltration of a lidocaine-based tumescent solution, with fat typically aspirated using an 18-gauge needle attached to a 20 mL syringe under approximately 1 atm of negative pressure, or alternatively via a 10 mL Luer-Lock syringe connected to a 2–3 mm blunt-tipped cannula.

The harvested volume varies considerably, generally ranging from 5 mL to 30–40 mL depending on the intended injection volume and degree of planned overcorrection (13). Because lipoaspirate

contains blood, tumescent fluid, and cellular debris, further processing steps, including washing, sedimentation, or centrifugation, are required to isolate the injectable fat fraction prior to use (47).

In contrast, open surgical excision involves removing adipose tissue as a single intact block through a small incision. Approximately 3–5 cm^3 of tissue is manually excised, followed by primary closure of the skin or mucosa (13). Because tissue is obtained without aspiration, shear forces on adipocytes are minimized, and exposure to concentrated local anesthetic infiltrate and ambient air, both of which have been shown to significantly impair adipocyte viability, are substantially reduced (48,49).

The excised tissue remains structurally intact and contains less tumescent and irrigation fluid than lipoaspirate. However, it typically has a higher proportion of connective tissue septa, requiring careful mechanical fragmentation into small, injectable pieces prior to use (50). The tissue should be transferred immediately into sterile closed containers, as even brief air exposure of 15 to 30 minutes results in measurable reductions in cell viability (49). Processing requires careful washing with isotonic saline or Ringer's lactate and decanting to remove oil and blood components.

Mild centrifugation may additionally be employed to further purify the graft and prepare injectable micro-aliquots, and closed filtration systems can improve purity in a manner comparable to lipoaspirate processing (47,49). High-speed centrifugation is not routinely required given the reduced tumescent fluid content (47). The processed fat is subsequently transferred into small-volume syringes using minimal volume differential to reduce shear-induced cellular damage (49).

From a clinical perspective, lipoaspirate has demonstrated more favorable symmetry outcomes in head and neck reconstructive applications compared with en-bloc excised fat transplants, and injectability may be more limited following fragmentation of open excision specimens (46).

Current evidence found no significant difference between the two techniques with respect to postoperative voice parameters including maximum phonation time, jitter, and shimmer, suggesting that the choice of harvesting method may be based primarily on surgeon preference and clinical context (13).

3.5. VARIATIONS IN FAT PROCESSING TECHNIQUE

The processing of harvested fat prior to injection is a critical, yet highly variable, step that may significantly influence adipocyte viability and ultimately the durability of the graft (47). At the cellular level, lipoaspirate contains not only mature adipocytes but also a heterogeneous population of progenitor cells, most notably adipose-derived stem cells (ASCs) (47). These cells are believed to enhance graft survival by promoting revascularization of the implanted tissue and replacing dying adipocytes during the early post-transplantation phase (47,51).

Both adipocytes and ASCs are highly sensitive to mechanical trauma and ischemia, making the choice of processing technique biologically consequential (47). Despite this importance, no standardized

technique has been established for human vocal fold fat injection, and published studies differ considerably in their approaches.

A commonly applied initial step is washing of the lipoaspirate. Various solutions have been described, including saline, insulin-enriched solutions aimed at improving adipocyte preservation, and Ringer's lactate combined with corticosteroids as a washing and stabilization medium (16). By removing blood and contaminants, washing reduces the proportion of undesired cellular components while preserving a relatively high concentration of endothelial and mesenchymal adipose-derived stem cells within the usable fraction (52,53).

Following washing, different separation techniques are employed. One of the simplest methods is gravity separation also known as sedimentation or decantation, in which the lipoaspirate passively separates into an oil, fat, and aqueous layer. The unwanted layers are discarded, and the fat fraction is used for injection (49). While this technique preserves a relatively high number of viable adipocytes, it may also retain a higher proportion of unwanted components, including blood-derived CD45-positive cells, which may negatively affect graft quality (47,52).

In contrast, centrifugation actively separates the lipoaspirate based on density into an upper oil layer, a middle adipocyte-rich fraction, and a lower aqueous phase containing blood and tumescent fluid, with only the intermediate layer retained for injection (47). However, this benefit must be weighed against the risk of mechanically induced cellular damage.

Experimental data suggest that centrifugal forces exceeding 3,000 g significantly impair ASC viability and that high-speed centrifugation may be more harmful to adipose tissue than low-speed protocols (54,55). The most widely adopted centrifugation-based protocol is the Coleman technique, which consists of centrifugation at 3000 rpm for three minutes followed by manual removal of the oil and blood fractions (47). Although commonly used in reconstructive fat grafting, its direct applicability to vocal fold injection remains insufficiently validated (56).

Alternative low-trauma processing techniques have been proposed. Cotton gauze rolling, most performed using Telfa pads, involves placing harvested fat onto an absorbent surface and gently rolling it to remove excess fluid and oil, thereby minimizing mechanical stress on adipocytes and increasing stromal vascular fraction (SVF) content (47,57). Similarly, manual selection techniques, where adipose tissue is cut into small fragments and separated from surrounding connective tissue- have been described, particularly in settings where specialized equipment is unavailable (52).

Various forms of filtration have also been reported, ranging from sterile metal sieves to simpler methods using surgical gauze or tea strainers. While these approaches aim to remove debris and fluid components, some studies suggest that filtration using rigid strainers may be associated with increased tissue inflammation and less effective oil removal compared with gentler techniques such as gauze rolling, potentially compromising graft viability (52).

Beyond these conventional processing methods, biologically augmented approaches have emerged. One such technique involves the use of Stromal Vascular Fraction gel derived from lipoaspirate, which is enriched with regenerative cells including ASCs. Early clinical studies in patients with UVFP have reported promising outcomes, suggesting a potential advantage of cell-enriched grafts (17).

3.6. ADDITIVES AND ADJUNCTIVE THERAPIES

The durability of autologous fat injection in the vocal fold remains a key limitation, and multiple strategies have been investigated to enhance graft survival and prolong clinical benefit. These approaches primarily target angiogenesis, cell survival, and tissue integration, and can be broadly divided into biological additives, cell-based therapies, structural modifications of the graft, and adjunctive procedural strategies.

Biological additives focus on enhancing angiogenesis and reducing apoptosis of transplanted adipocytes. The addition of basic fibroblast growth factor (bFGF) has been associated with improved vocal fold repair and reduced fat and fascia resorption on imaging, likely due to its pro-angiogenic and anti-apoptotic effects (58,59). Similarly, platelet-rich plasma (PRP) represents a promising adjunct due to its high concentration of growth factors such as PDGF (platelet-derived growth factor), TGF-β (transforming growth factor-beta), VEGF (vascular endothelial growth factor), and bFGF, which are involved in mesenchymal cell recruitment, proliferation, and extracellular matrix synthesis. PRP has also been shown to accelerate re-epithelialization in injured vocal folds through upregulation of growth factor receptors. When used in combination with autologous fat, PRP has been reported to improve acoustic outcomes and reduce glottal gap recurrence compared to fat injection alone, suggesting an additional antifibrotic effect at the injection site (60–62).

Cell-based therapies represent a further development. Stromal vascular fraction, typically isolated via enzymatic processing of lipoaspirate, is a heterogeneous cell population containing adipose-derived regenerative cells (ADRCs), endothelial cells, pericytes, and immune cells, which collectively promote angiogenesis and tissue remodeling (63,64). The regenerative potential of these approaches is largely attributed to adipose-derived stem cells (ASCs), which demonstrate greater resistance to ischemia than mature adipocytes and contribute to graft survival through differentiation into adipocytes, secretion of pro-angiogenic cytokines, and immunomodulation (65).

Early clinical data from the first phase I/IIA trial on ADRC-enriched fat laryngoplasty indicate superior patient-reported vocal outcomes compared to conventional centrifuged fat, supporting the biological rationale for cell enrichment (64). A related strategy involves combining ASC-enriched grafts with growth factors such as bFGF, which has been shown to further augment vasculogenesis beyond what ASCs alone can achieve, addressing the limitation of insufficient early vascularization following fat grafting (66).

Modifications of the graft itself have also been explored. Nanofat, produced by mechanical emulsification of lipoaspirate, contains fewer viable adipocytes but is enriched in regenerative cell components, shifting its role from volumetric augmentation toward tissue regeneration (7).

Structural reinforcement through the combination of fat with autologous fascia lata represents a complementary strategy. The fascial component provides mechanical stability at the injection site, may reduce early volume loss by attenuating the inflammatory resorption response, and contributes a fibrous scaffold that supports longer-term structural integrity of the augmented fold (67,68).

This composite approach differs from fascia-only injection medialization, in which minced or processed fascia lata is injected without a volumetric filler component. While fascia-only injection has been shown to improve glottic closure and voice outcomes, and offers predictable structural support with low inflammatory response, it lacks the volumetric and regenerative capacity associated with the adipose component and may not fully replicate the viscoelastic properties required for optimal mucosal wave propagation (69,70).

The fat-fascia composite therefore attempts to combine volumetric augmentation and tissue regeneration with the mechanical durability of fascia, particularly in cases with significant tissue loss or fibrosis, where structural reinforcement and volume restoration are both required, though robust comparative outcome data between the two approaches remain limited. Minced auricular cartilage, when used as a structural carrier combined with fat, offers a further alternative: although chondrocyte viability is not maintained following implantation, the stability of the cartilage extracellular matrix confers long-term structural persistence (71).

Emerging and experimental approaches aim to further enhance regenerative outcomes. Autologous fibroblast injection, in which fibroblasts cultured from mucosal biopsies are reintroduced into the vocal fold, has demonstrated improvements in mucosal wave characteristics, likely reflecting partial restoration of the viscoelastic properties of the lamina propria (72).

Metabolic modifications of the graft have also been investigated, with insulin representing the most studied agent in this context. Its biological rationale is grounded in well-described pro-angiogenic properties: insulin promotes endothelial cell migration and tubular structure formation, upregulates VEGF expression, and supports pericyte survival and proliferation, collectively facilitating new vessel formation (73). Reported protocols in experimental studies have used insulin concentrations in the low micromolar range, typically applied as short-term pre-incubation prior to grafting.

However, these parameters are derived from heterogeneous preclinical models rather than standardized clinical protocols. A study compared lipoinjection with and without insulin in a canine model of unilateral vocal fold paralysis, measuring residual graft volume by MRI at twelve weeks. The addition of insulin did not result in a significant improvement in graft retention compared to injection without insulin (74). These findings are consistent with a rodent study in which pre-

implantation of fat grafts in insulin solution resulted in no significant improvement in graft weight or adipocyte viability at three months compared to untreated controls, despite evidence of increased vascular marker expression (75). No standardized clinical protocol for insulin-based fat preparation exists, and its use therefore remains experimental without sufficient evidence to support routine application.

Injection strategies themselves can be considered adjunctive. Overcorrection is commonly performed to compensate for anticipated partial resorption, with a mean overcorrection of approximately 30% reported in the literature. However, the optimal degree remains debated and is largely based on surgical experience rather than quantitative evidence (50). Staged or repeated injections represent an additional strategy, allowing progressive volume adjustment and adaptation to individual resorption patterns over time (21).

Scaffold-based approaches represent an additional strategy to improve fat graft survival by providing a supportive microenvironment for cell viability and tissue integration. Collagen-based matrices have been investigated for their ability to promote cell adhesion and mimic native extracellular matrix properties. Hydrogels can serve as injectable carriers that support uniform cell distribution and facilitate nutrient diffusion within the graft. Extracellular matrix-derived scaffolds aim to provide bioactive structural support while promoting angiogenesis and tissue remodeling (14,43,76). While promising in the context of tissue engineering, their application in vocal fold augmentation remains largely experimental, with limited clinical data available (14).

Beyond fat and its modifications, numerous other injectable materials are available, each with distinct viscoelastic properties and durability. Temporary agents such as carboxymethylcellulose persist for one to two months and are mainly used for trial injections (11,38). Hyaluronic acid (HA) is widely used for short- to mid-term augmentation from 6–12 months, particularly in acute unilateral vocal fold paralysis, presbyphonia, and sulcus vocalis (11,77).

Calcium hydroxylapatite (CaHA) provides longer-lasting effects from 12–24 months, but carries a risk of increased stiffness and unpredictable behavior (38). Polydimethylsiloxane (PDMS) is a permanent material associated with strong improvements in phonatory parameters, though its irreversibility necessitates careful patient selection (29).

A detailed discussion of alternative injectable materials is beyond the scope of this review, as the primary focus lies on strategies to optimize autologous fat graft survival rather than on comparative material selection.

4. RESULTS OF THE REVIEW

4.1. CHARACTERISTICS OF INCLUDED STUDIES

Eight studies published between 2017 and 2025 were included, comprising a total of 243 patients undergoing autologous fat injection laryngoplasty for glottic insufficiency of varying aetiologies.

Study designs were heterogeneous and included four randomized controlled trials (62,64,78,79), two retrospective studies (80,81), one retrospective cohort study (82) and one prospective cohort study (83).

The primary indications included unilateral vocal fold paralysis or immobility (64,78–81), scarred vocal folds following tumor resection and sulcus vocalis (83), type II sulcus vocalis (62), and bilateral vocal fold atrophy with or without sulcus (82). All procedures were performed under general anesthesia using direct suspension laryngoscopy.

Considerable variability was observed in fat harvesting and processing techniques, as well as in injected volumes, which ranged from 0.1 mL to 6.0 mL. Four studies investigated adjunctive approaches, including platelet-rich plasma (62,79), injectable collagen scaffolds (78), and adipose-derived regenerative cells (64).

Voice outcomes were assessed using different versions of the Voice Handicap Index (VHI-10, VHI-30) in seven studies and the GRBAS perceptual rating scale in six. Acoustic parameters were reported in six studies, most consistently maximum phonation time, jitter, shimmer, and noise-to-harmonic ratio. Additional imaging-based assessments were performed selectively, including computed tomography to quantify implant volume (78) and endoscopic measurements of vocal fold bowing and width ratios (81).

No serious adverse events were reported across the included studies. Minor complication rates were low and are detailed in Section 4.5. Revision rates ranged from 0% in the randomized controlled trials and in Pagano (80), to 23.8% in Salmerón-González (83). Mean follow-up ranged from six months (62) to a median of four years (81), with the remaining studies reporting follow-up periods between 12 and 24 months.

4.2. OVERVIEW OF TECHNICAL VARIABILITY ACROSS INCLUDED STUDIES

The techniques for autologous fat injection laryngoplasty varied substantially across studies. Harvest sites included the periumbilical region, lower abdomen, flank, and thigh. Techniques ranged from small-volume aspiration using 18-gauge needles (62,81), to conventional liposuction with 2.1–3 mm cannulas under manual negative pressure (79,82).

Jin (78) applied the Coleman technique, while Fawaz (79) harvested microlobular fat without specifying technical parameters. Lasso (64) represented a clear outlier, requiring a minimum of 180 cm^3 of abdominal fat due to the Celution system requirements for ADRC extraction.

Fat processing techniques also differed considerably. Centrifugation was most used but with variable parameters (300 g to 3000 rpm; 3–5 minutes), typically followed by three-layer separation and selection of the middle fraction (62,80,83). Salmerón-González (83) uniquely added an emulsification step to reduce particle size.

Alternative approaches included filtration without centrifugation (81), gravity sedimentation (78), and combined washing and enzymatic processing for ADRC isolation (64).

Adjunctive biological agents were incorporated in four studies. Platelet-rich plasma was used in two studies with differing preparation protocols (62,79). Jin (78) combined fat with an injectable collagen scaffold, while Lasso (64) enriched grafts with adipose-derived regenerative cells. Pagano (80) applied fibrin glue topically at the injection site rather than modifying the graft itself.

Injection targets were consistent across studies, with fat delivered into the thyroarytenoid muscle lateral to the vocal process and a general aim of 20–30% overcorrection. Variations included additional injections into the arytenoid region (81) or midcord (64,82). Correct placement into the deep thyroarytenoid muscle layer was consistently emphasized across studies, with superficial deposition into the lamina propria explicitly described as a technical complication to avoid, as it impairs mucosal wave propagation and vocal fold pliability (80,81).

Injection instruments varied according to graft properties and surgical approach. Brüning's syringes were used in several studies (62,78,82), while Pagano (80) used a modified 19-gauge butterfly needle with trimmed wings to allow microsurgical handling. 19-gauge needles were also used by Lasso (64) and Umeno (81), whereas finer 23-gauge needles were employed by Salmerón-González (83) and larger-bore instruments by Fawaz (79), depending on graft viscosity and intraoperative access.

Injected volumes varied widely. The smallest volumes were reported by Salmerón-González (0.1–0.6 mL) (83), followed by Pagano (mean 0.75 mL) (80). Tsou used a fixed volume of 1.5 mL (62), while Lasso reported mean volumes of approximately 1.8 mL (64), and Fawaz (79) and Jin (78) targeted up to 3 mL. Umeno reported the widest range (mean 2.7 mL, up to 6.0 mL) (81) and van den Broek did not report injected volumes (82).

Across all studies, intentional overcorrection of at least 20–30% beyond the desired final vocal fold position was applied as a compensatory strategy for anticipated early-phase resorption, though the degree of overcorrection was assessed visually by the operating surgeon in all cases and was not standardized or objectively quantified in any included study.

Perioperative management varied across studies. Voice rest ranged from 48 hours of complete restriction (80) to one week of partial restriction (83). Corticosteroids were used in selected studies (80), and prophylactic antibiotics in Jin (78) and Pagano (80). Lasso described the most complex protocol, involving a two-stage procedure with initial fat harvesting under local anesthesia followed by delayed injection under general anesthesia after ADRC processing (64).

A simplified overview of the key technical parameters across included studies is presented in the table below. Detailed summary table of comparative parameters across studies are presented in Annex 8 and Annex 9.

Table 4-1. Overview of the technical variability
NR = not reported; ADRC = adipose-derived regenerative cells; PRP = platelet-rich plasma.

Study	Harvest Site	Processing	Injection Instrument	Volume (mL)	Adjunct
Salmerón-González	Abdomen	Centrifugation + emulsification	23-G needle	0.1–0.6	—
Jin	Lower abdomen	Gravity sedimentation	Brüning's syringe	~3.0	Collagen scaffold
Lasso	Abdomen	Centrifugation / ADRC (Celution®)	19-G needle	~1.8	ADRCs
Tsou	Lower abdomen	Centrifugation 3000 rpm	Brüning's syringe	1.5	PRP (4:1)
Fawaz	Periumbilical	Centrifugation (microlobular)	12-G syringe	≤3.0	PRP (2:1)
Pagano	Periumbilical/flank	Centrifugation 1280 g	19-G butterfly needle	0.15–1.5	Fibrin glue (topical)
Umeno	Periumbilical	Tea filter filtration	19-G endolaryngeal needle	0.5–6.0	—
van den Broek	Abdomen	Centrifugation (NR)	Brüning's syringe	NR	—

4.3. COMPARISON OF CLINICAL OUTCOMES

Across all eight included studies, autologous fat injection laryngoplasty improved voice quality across subjective, perceptual, and objective domains. VHI improved in all seven reporting studies. The largest reductions were observed in paralytic and atrophic indications: Pagano (80) reported a reduction from a median of 64 to 29, while van den Broek (82) demonstrated a clinically relevant VHI-30 reduction of 19.4 points at 12 months, with comparable outcomes across subgroups. In contrast, Salmerón-González (83) reported a smaller reduction of 5.6 VHI-10 points in post-resection scarring.

Regarding adjunctive strategies, Lasso (64) observed improvement in both groups, with postoperative scores significantly lower in the ADRC group than in the fat-alone group ($p = 0.032$, Wilcoxon; $p = 0.042$, t-test), the only study showing between-group superiority for a cellular adjunct, although based on a small sample. Jin (78) reported superior VHI trajectories in the collagen scaffold group at 6, 12, and 24 months, whereas deterioration occurred in the fat-alone group after 6 months. Among PRP studies, Tsou (62) found lower VHI-10 scores in the PRP group at 1 month, while Fawaz (79) found no between-group differences.

GRBAS improved across all six reporting studies, particularly in grade and breathiness. Salmerón-González (83) demonstrated improvement across all subscales. These gains were generally maintained at follow-up. PRP studies showed superior early perceptual outcomes, with convergence by 12 months in Fawaz (79).

MPT improved in all six reporting studies. A volume-dependent effect was demonstrated by Umeno (81), with greater improvement in the high-volume group after adjustment, representing the clearest

dose–response relationship. Fawaz (79) reported higher MPT in the PRP group at both 1 and 12 months, the only parameter showing sustained between-group superiority.

Jitter decreased across all studies reporting it. Tsou (62) found superior values in the PRP group, whereas Fawaz (79) reported no between-group difference. Shimmer showed inconsistent results, with reductions in Salmerón-González (83) and Tsou (62), but no relevant change in Pagano (80). Noise-to-harmonic ratio NHR improved in Salmerón-González (83) and Tsou (62), with no between-group difference in Fawaz (79). Mean flow rate decreased in Pagano (80) and Umeno (81), with a non-significant trend toward greater reduction at higher volumes in the latter.

Lasso (64) assessed 14 biomechanical parameters using BioMet®Phon, a system to monitor phonation quality and most patients showed substantial qualitative improvement. The fat-alone group demonstrated more uniform moderate gains, whereas the ADRC group showed greater variability, including both the largest improvements and isolated functional setbacks. In both groups, improvements were mainly attributed to reduced vocal fold imbalance, consistent with a medialization mechanism.

Glottic closure improved in all five studies reporting stroboscopy. Pagano (80) reported sustained improvement in 16 of 18 patients at a median follow-up of 19 months. PRP studies demonstrated superior early closure, with convergence by 12 months in Fawaz (79) and persistent superiority at 6 months in Tsou (62). Van den Broek (82) identified dynamic range and VHI as the primary significantly improved parameters.

A simplified overview of the key clinical outcomes across included studies is presented in Table 4-3 below. A detailed summary of the clinical outcomes is provided in Annex 10.

Table 4-2. Overview of primary clinical outcomes

↑ = significant improvement; – = no significant improvement; NR = not reported; HV = high volume (≥3 mL); LV = low volume (<3 mL); mo. = months; CAF = centrifuged autologous fat

Study	VHI	GRBAS	MPT	Acoustic	Glottic Closure	Key Finding
Salmerón-González	↑	↑	↑	↑	NR	All outcomes improved; stable at 20.7 months
Jin	↑ scaffold > fat	NR	↑	↑ (trend)	↑	Scaffold group: sustained improvement; fat-alone deteriorated from 6 months
Lasso	↑ ADRC > CAF	NR	NR	↑	↑	ADRC: better patient-reported outcomes; no biomechanical between-group difference
Tsou	↑ PRP > fat at 1 mo.	↑	↑	↑ PRP > fat	↑ PRP > fat	PRP: consistent early advantage; sustained at 6 months
Fawaz	↑ (equal)	↑ PRP > fat at 1 mo.	↑ PRP > fat	↑ (equal)	↑ PRP > fat at 1 mo.	PRP: early advantage; MPT sustained at 12 months
Pagano	↑	↑	↑	↑ jitter; – shimmer	↑	Stable at 12–58 months; no revisions
Umeno	NR	NR	↑ HV > LV	↑ HV > LV	↑	Volume-dependent effect; CT/histology: long-term graft viability
van den Broek	↑	–	–	NR	NR	VHI and dynamic range only significant outcomes

4.4. GRAFT LONGEVITY AND RESORPTION

In the context of vocal fold medialization, graft survival depends on timely revascularization. Injected adipose tissue initially relies on plasmatic diffusion for oxygenation, without adequate capillary ingrowth, adipocytes undergo necrosis, resulting in volume loss, fibrosis, and oil cyst formation (44). The long-term stability of the injected fat graft was assessed using direct radiological and histological evidence, longitudinal functional data, and indirectly the effects of adjunctive strategies targeting resorption.

Jin (78) provided the only direct volumetric data, with serial CT confirming persistent fat tissue in all patients at 24 months. Residual volume was higher in the collagen scaffold group, although not statistically significant. Umeno (81) reported persistent graft presence on CT at 6 years and 7 months in one patient, with maintained medialization. Histological analysis from a second patient at 2 years demonstrated intact adipocyte morphology without inflammatory infiltration, supporting long-term graft viability.

However, such evidence remains limited to small cohorts and isolated cases, with only one study providing objective volumetric assessment (81).

Pagano (80) found no change in MPT, MFR, jitter, VHI, or GRBAS between early and late follow-up, and no correlation with time. Salmerón-González (83) reported stable outcomes at a mean follow-up of 20.7 months, while Umeno (81) demonstrated sustained improvement across parameters for up to 5 years.

Importantly, stable functional outcomes do not necessarily reflect true graft persistence, as compensatory mechanisms may conceal partial resorption. Although none of the four RCTs reported functional decline, follow-up in three studies did not exceed 12 months, thereby limiting conclusions regarding long-term resorption.

Tsou (62) reported smaller glottic gaps in the PRP group at 6 months, suggesting reduced medium-term resorption. Fawaz (79) found no difference at 12 months, indicating convergence over time. Jin (78) provided the clearest functional evidence of improved graft retention, with deterioration in the fat-alone group correlating with greater volumetric loss on CT (Figure 4-1).

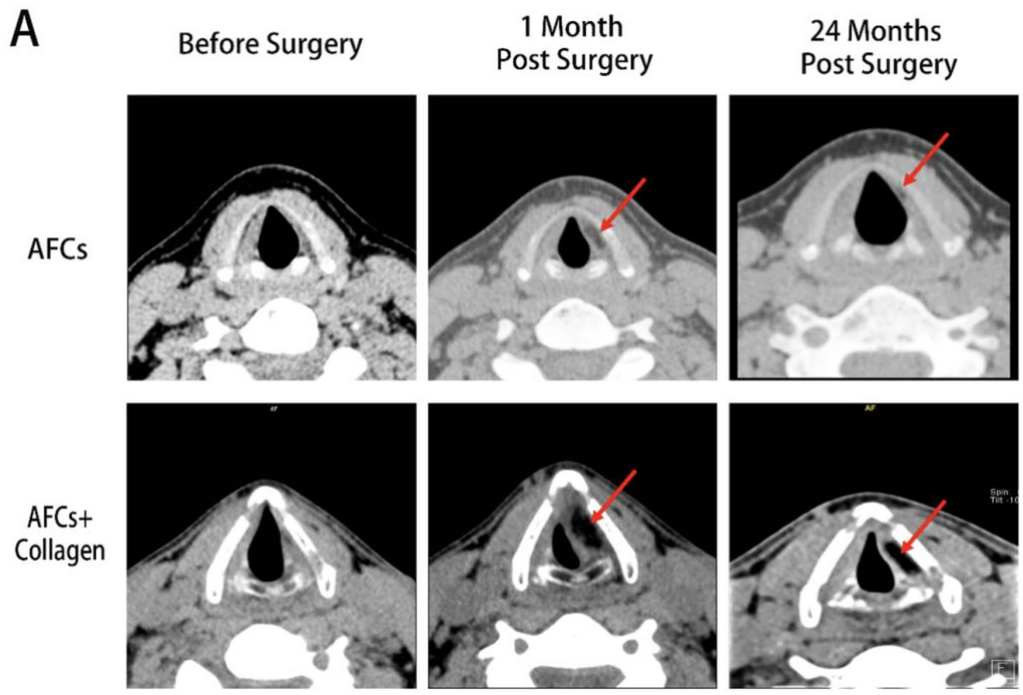

Figure 4-1. Representative axial CT images of the vocal folds
Representative axial CT images of the vocal folds in the AFCs and AFCs + collagen groups at the laryngeal level, obtained preoperatively and at 1 and 24 months postoperatively. The dark area (red arrow) represents injected fat cells or collagen scaffold. Adapted from (78)

Evidence regarding the effect of injected volume is inconsistent, with Umeno (81) demonstrating greater and more sustained improvement at higher volumes, while Pagano (80) found no association with functional outcomes. Overcorrection at the time of injection was applied as standard practice across all included studies to compensate for anticipated early resorption, yet its independent contribution to graft longevity was not isolated as a study variable in any of the included series.

Adjunctive strategies, like PRP and collagen scaffold, showed an association with reduced resorption in two studies. Lasso (64), Fawaz (79), and van den Broek (82) did not formally assess graft longevity. Other potential determinants, including tissue characteristics, processing techniques, and patient factors, were inconsistently reported and not systematically analyzed.

4.5. COMPLICATIONS AND REVISION RATES

No life-threatening complications, permanent airway compromise, granuloma formation, rejection reactions, or procedure-related deaths were reported across any of the 243 patients enrolled in the eight included studies. Overall, the safety profile of autologous fat injection laryngoplasty appears highly favorable, with no evidence of severe adverse events in the available literature.

Transient airway symptoms were the most frequently described complication. Umeno (81) reported such symptoms in 10 of 73 patients (13.7%), with durations ranging from 20 minutes to eight hours. All cases resolved with conservative management, and none required airway intervention. Salmerón-González (83) reported one case of mild dyspnea lasting two months following a second injection, which resolved spontaneously. The remaining studies did not report airway-related complications.

These findings suggest that when airway symptoms occur, potentially related to higher injected volumes, they are typically mild and self-limiting.

Harvest-site complications were uniformly minor. Salmerón-González (83) noted diffuse mild abdominal ecchymosis in most patients, resolving without intervention. Pagano (80) reported conservative hematomas at the liposuction site in several patients, one case of tongue base oedema from laryngoscope compression resolving with oral corticosteroids, two cases of inflammatory postoperative dysphonia treated with corticosteroids, and one fat extrusion into the ventricular space managed conservatively without functional consequence.

One patient in Pagano (80) had an intraoperative superficial injection corrected immediately by re-injection at the correct depth. Jin (78) reported one case of transient pharyngalgia in the collagen scaffold group. No complications related to the intervention were documented in Tsou (62), Fawaz (79), van den Broek (82).

In Lasso (64) two adverse events, septic shock and glottic oedema, occurred in one patient but were attributed to the intubation procedure rather than the injection itself; this patient was subsequently withdrawn from the study. No study reported long-term structural complications such as fibrosis, granuloma formation, or implant-related stiffness.

Revision rates varied across studies and indications. The highest rate was reported by Salmerón-González (83), with 5 of 21 patients (23.8%) undergoing repeat injection. Of these, three patients showed objective improvement, while two demonstrated limited objective gains with persistent subjective impairment. Van den Broek (82) reported revision in 4 of 24 procedures (16.7%) within twelve months, comprising two repeat injections and two escalations to medialization thyroplasty.

Umeno (81) reported re-injection in 5 of 73 patients (6.8%), with four of the five cases occurring in the low-volume group. Pagano (80) reported no revisions over a follow-up period of 12 to 58 months. No re-interventions were reported in the four randomized controlled trials within their respective follow-up periods.

However, interpretation of revision rates is limited by heterogeneity in indications, injection techniques, and follow-up duration, as well as the absence of standardized criteria for re-intervention. Overall, revision appears to be driven primarily by insufficient or declining medialization rather than procedure-related adverse events, and interpretation of revision rates is limited by heterogeneity in indications, injection techniques, and follow-up duration.

A detailed summary of complication and revision rates is provided in Annex 11.

4.6. EVIDENCE QUALITY AND STUDY HETEROGENEITY

The methodological quality of the included studies was low to moderate, with several consistent structural limitations diminishing the strength of conclusions that can be drawn from the available literature. Overall, the evidence base is characterized by limited internal validity and restricted external generalizability. Accordingly, the overall level of evidence can be considered low.

Regarding study design and risk of bias, the four randomized controlled trials were limited by incomplete blinding, as surgeon blinding is inherently impractical in surgical interventions. Reporting of allocation concealment was insufficient in most trials. Patient blinding was described in only one study (62). Assessor blinding was only partially implemented, Salmerón-González (83) blinded GRBAS raters to recording time point, and Fawaz (79) blinded phoniatricians to group allocation, but no study described complete outcome assessor blinding across all domains.

This incomplete blinding introduces a potential risk of detection bias, particularly for perceptual and patient-reported outcomes.

The retrospective designs introduced risks of selection and information bias. In Umeno (81), volume stratification was based on intraoperative decision-making rather than random allocation, introducing potential confounding despite subsequent statistical adjustment. Important confounding variables, such as baseline glottic gap size and degree of vocal fold atrophy, were not consistently controlled across studies.

All studies were limited by relatively small sample sizes, ranging from 10 to 73 patients, and none reported an a priori power calculation. Consequently, the studies are likely underpowered to detect clinically relevant differences between techniques. Non-significant between-group findings, for example the acoustic parameter differences in Jin (78) and the ADRC outcomes in Lasso (64), cannot therefore be interpreted as evidence of equivalence.

Multiple secondary outcome comparisons in Tsou (62) and Fawaz (79) were conducted without correction for multiplicity, inflating the risk of type I error (false positive). Conversely, small sample sizes also increase the risk of type II error (false negative), further complicating interpretation of negative findings.

Substantial clinical heterogeneity was observed across patient populations, including variation in underlying pathology, aetiology, and disease duration prior to intervention. Follow-up duration ranged from 6 months to 5 years across studies, limiting the comparability of outcome data across time points.

The technical heterogeneity described in Section 4.2 prevents attribution of outcome differences to individual procedural variables, directly limiting the ability to answer the central research question of which technical factors optimize voice outcomes, graft longevity, and complication rates. The

absence of imaging-based graft survival assessment in seven of eight studies restricts mechanistic interpretation of functional outcomes. Outcome assessment was heterogeneous in VHI instrument version, acoustic analysis methods, recording conditions, and postoperative assessment timing, preventing systematic synthesis.

Taken together, these limitations restrict the level of evidence and preclude robust conclusions regarding the superiority of specific techniques. The available evidence is insufficient to support definitive conclusions, and future studies should prioritize adequately powered, methodologically rigorous trial designs with standardized outcome measures and objective assessment of graft survival.

5. DISCUSSION

5.1. INTERPRETATION AND SYNTHESIS OF FINDINGS

Across the included studies, autologous fat injection laryngoplasty appears to be a safe and effective intervention for glottic insufficiency. The consistent improvement across heterogeneous study designs suggests that the fundamental mechanism, medialization through volume augmentation of the thyroarytenoid muscle, is robust across a range of technical variations, provided that key procedural principles are respected.

The magnitude of clinical improvement appears to depend primarily on the underlying pathology. Patients with paralytic or atrophic glottic insufficiency tend to achieve greater functional gains, whereas outcomes are more limited in structurally altered vocal folds, such as in scarring or sulcus vocalis. This pattern indicates that the effectiveness of fat injection is constrained by the degree of irreversible tissue alteration rather than by technical factors alone.

Among the technical variables, injection volume emerges as the most relevant modifiable factor. Higher injection volumes may provide a functional reserve against early resorption and are associated with improved functional outcomes and lower revision rates in some studies. This suggests a potential threshold effect, in which a minimum effective volume is required to achieve stable medialization, rather than a simple linear dose–response relationship. In contrast, insufficient volume may result in suboptimal augmentation and increased likelihood of revision.

In comparison, fat processing techniques appear to have a less pronounced impact on clinical outcomes. No clear superiority of any specific method was identified, and satisfactory results were achieved across a range of approaches. Processing refinements, such as emulsification or cell enrichment, may improve graft efficiency under specific conditions, particularly when smaller volumes are used or in less favorable tissue environments. However, the available evidence suggests that adequate volume and correct placement are more critical determinants of outcome than the specific processing technique applied.

Adjunctive biological strategies, including platelet-rich plasma, collagen scaffolds, and cell-based enrichment, demonstrate variable and generally preliminary effects. Platelet-rich plasma appears to

provide consistent short-term benefits, likely related to enhanced angiogenesis and early graft integration, although its long-term impact remains uncertain. Scaffold-based approaches show the most promising signal for improved graft retention, but current evidence is limited. Cell-based therapies have demonstrated improvements in patient-reported outcomes in small studies but lack consistent objective confirmation. Overall, these strategies should be considered experimental and applied selectively.

Complication rates were uniformly low across all included studies, and no technical factor was associated with a clinically relevant increase in adverse events. This suggests that procedural variations primarily influence effectiveness rather than safety. Revision procedures were predominantly driven by insufficient or declining medialization rather than complications, further supporting the central role of volume adequacy and graft persistence.

Long-term functional outcomes were generally stable, indicating that a clinically meaningful proportion of the injected fat persists in many patients. However, direct evidence of structural graft survival remains limited, and functional stability cannot be assumed to reflect complete graft retention.

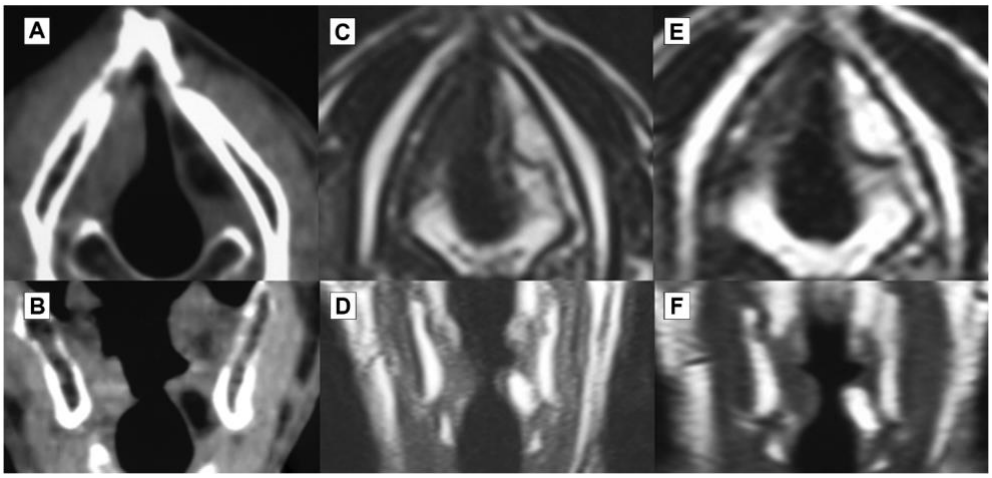

Figure 5-1. Long-term CT and MRI images following fat injection
Computed tomography (A, B) and magnetic resonance imaging (C, D) in axial and coronal planes show long-term persistence of grafted fat in the left paralyzed vocal fold at 25 months. Serial MRI (E, F) confirms graft stability at 42 months.
Adapted from (84)

Supporting evidence from outside the included literature reinforces the radiological persistence of fat grafts via CT and serial MRI, with no change in graft volume detected between assessments performed 12–18 months apart, confirming structural stability up to 42 months postoperatively (84). However, direct evidence of this kind remains scarce within the included studies, and functional stability cannot be assumed to reflect complete graft retention. This represents a key limitation in the current evidence base and restricts mechanistic interpretation of long-term outcomes.

A central limitation across the included studies is the substantial technical and methodological heterogeneity. Variations in harvesting, processing, injection technique, volume, and outcome assessment prevent isolation of individual variables and preclude definitive conclusions regarding

optimal technique. Consequently, the available evidence does not support the identification of a single superior fat grafting protocol.

Taken together, the findings suggest that autologous fat injection laryngoplasty should be understood as a technically flexible intervention in which outcomes are primarily determined by achieving sufficient and stable medialization. Injection volume and accurate placement within the thyroarytenoid muscle represent the most critical factors, while processing techniques and adjunctive strategies appear to play a secondary and less clearly defined role.

5.2. CLINICAL IMPLICATIONS AND PRACTICAL CONSIDERATIONS

The available evidence supports autologous fat injection laryngoplasty as a clinically effective and safe option for the management of glottic insufficiency, particularly in patients without significant vertical level asymmetry (20,85). Patient selection remains critical, as the procedure primarily corrects horizontal glottic gaps and may be insufficient in cases with complex structural abnormalities requiring additional surgical intervention.

Injection volume represents the most relevant modifiable technical factor in clinical practice. Adequate volume selection is essential to achieve sufficient medialization and reduce the likelihood of revision (81). Underinjection should be avoided, while moderate overcorrection remains a pragmatic strategy to compensate for early resorption (50,81). Volume should be individualized based on anatomical characteristics, underlying pathology, and patient-specific factors.

Accurate placement of the graft within the thyroarytenoid muscle is a fundamental technical requirement. Superficial injection should be avoided, as it may impair mucosal wave propagation and negatively affect voice quality (80). Technical precision in depth and distribution of the injected material seems therefore more important than the specific harvesting or processing technique.

While centrifugation is commonly used and represents current standard practice, simpler techniques can achieve comparable outcomes. The primary objective should be a consistent and standardized processing approach that preserves adipocyte viability rather than adherence to a specific method.

Adjunctive strategies may be considered selectively. Platelet-rich plasma may provide short-term benefits, particularly in less favorable tissue environments, although its long-term effect remains uncertain (62,79). Other approaches, including scaffold-based techniques and cell enrichment, are not yet supported by sufficient evidence for routine clinical use.

Perioperative management should focus on optimizing graft stability and functional recovery. Short-term voice rest and structured voice therapy may support outcomes, although evidence remains limited. Early postoperative voice quality should not be interpreted as definitive because of the overcorrection, and outcome assessment should be delayed. Revision should generally be deferred until sufficient time has elapsed for graft stabilization. When required, repeat fat injection represents a safe and appropriate first-line strategy (83).

Autologous fat injection laryngoplasty offers several clinically relevant advantages compared to alternative injectable materials such as hyaluronic acid filler and calcium hydroxylapatite (CaHA). As an autologous material, fat is fully biocompatible and avoids the risk of foreign body reaction (11). Compared to hyaluronic acid, which is typically resorbed within 6 to 12 months, fat grafts may provide longer-lasting medialization when sufficient vascularization is achieved, potentially reducing the need for repeated interventions (86).

In contrast to CaHA, which offers intermediate durability but may increase tissue stiffness and impair mucosal wave propagation, fat more closely resembles the viscoelastic properties of the native vocal fold and is therefore less likely to negatively affect vibratory function (77). In addition, fat injection can be safely repeated and allows for intraindividual adjustment over time. These characteristics support the use of autologous fat particularly in patients where long-term augmentation and preservation of vocal fold pliability are primary treatment goals.

Patients with structurally altered vocal folds should be counseled regarding potentially reduced treatment response and higher likelihood of revision. Overall, clinical outcomes appear to depend more on appropriate patient selection, sufficient injection volume, and accurate graft placement than on specific technical refinements. Standardization of procedural protocols and outcome assessment would be necessary to further improve consistency and comparability in clinical practice.

5.3. LIMITATIONS OF THE AVAILABLE EVIDENCE AND RESEARCH GAPS

Beyond the methodological constraints outlined in Section 2.6, the primary literature is subject to several important limitations. The available evidence shows substantial clinical and technical heterogeneity. Differences in patient populations, underlying pathologies, fat harvesting and processing techniques, injection approaches, and injected volumes make it difficult to isolate individual variables and limit causal conclusions about optimal fat grafting strategies.

Most included studies were small and likely underpowered, and none reported a priori sample size calculations. As a result, both positive and negative findings must be interpreted with caution. Non-significant results cannot be considered evidence of equivalence, while statistically significant findings may be affected by type I error.

Follow-up duration was inconsistent and often too short to assess long-term graft stability. Since fat resorption occurs mainly in the early postoperative phase, the lack of standardized and sufficiently long follow-up further limits the interpretation of long-term outcomes.

A major limitation is the lack of objective assessment of graft survival. Only one study used imaging-based volumetric analysis, while most relied on indirect functional outcomes. This limits mechanistic interpretation because functional improvement does not necessarily reflect actual graft persistence.

Another important limitation is the absence of studies designed to identify predictors of treatment success. Relevant factors such as baseline glottic gap, tissue characteristics, vascularity, and patient-specific variables were reported inconsistently and were not systematically analyzed.

Reporting of technical details was often incomplete, especially regarding harvesting parameters, processing techniques, and injection methodology. In addition, complications related to fat harvesting and grafting were reported inconsistently. Donor site morbidity, including pain, hematoma, infection, or contour irregularities, was rarely assessed in a systematic way, and injection-related complications were not uniformly reported. This lack of detailed safety data limits a comprehensive evaluation of the risk profile and makes comparison with alternative injectable materials more difficult.

Overall, these limitations reduce reproducibility and prevent meaningful comparison between studies. Outcome assessment was heterogeneous, with variation in measurement tools, timing, and reporting standards. The absence of a standardized outcome framework further limits comparability and synthesis of results.

Future research should focus on adequately powered, prospective, and ideally multicenter studies with standardized protocols. Key priorities include defining the optimal injection volume, clarifying the role of adjunctive strategies, and incorporating objective methods to assess graft survival. Standardized outcome measures and better reporting of technical variables are essential to improve comparability and strengthen the evidence base.

6. CONCLUSION

6.1. SUMMARY OF KEY FINDINGS

This review evaluated the current evidence on autologous fat injection laryngoplasty for glottic insufficiency, with particular focus on how technical factors influence voice outcomes, graft longevity, and complication rates. Given the heterogeneity of the available evidence, the use of a narrative synthesis was appropriate, although it limits the ability to draw causal conclusions.

Across eight studies comprising 243 patients, the available evidence consistently supports the safety and clinical effectiveness of the procedure, while also highlighting substantial methodological limitations that restrict the strength of causal conclusions.

Autologous fat injection laryngoplasty produced clinically meaningful improvements in voice function across a range of indications, including unilateral vocal fold paralysis, vocal fold atrophy, sulcus vocalis, and post-resection scarring. Improvements were observed consistently across patient-reported, perceptual, acoustic, and aerodynamic outcome measures. The magnitude of improvement varied by indication, with greater gains in paralytic and atrophic conditions and more limited improvement in scarred vocal folds, reflecting underlying structural constraints.

With respect to graft longevity, functional outcomes were generally stable over time, suggesting that a clinically meaningful proportion of injected fat persists in many patients. However, direct evidence

of long-term graft survival remains limited. Only one study provided objective volumetric imaging, and histological confirmation is restricted to isolated cases. Functional stability does not necessarily reflect structural persistence, and the relationship between residual graft volume and voice outcome remains insufficiently defined.

Among technical factors, injected volume emerged as the most clearly relevant modifiable variable. In the only study directly examining this relationship, higher injection volumes were associated with greater functional improvement and lower revision rates, whereas no association was observed in a separate study using substantially lower volumes, suggesting a possible threshold effect rather than a linear relationship.

Fat processing techniques showed no clear superiority. While refinements such as emulsification may improve graft efficiency, particularly at lower injection volumes or in fibrotic tissue, satisfactory outcomes were also achieved with centrifugation and simpler methods such as filtration.

Adjunctive biological strategies showed variable and generally preliminary effects. Platelet-rich plasma provided consistent early improvements with uncertain long-term persistence. Collagen scaffold delivery demonstrated the most promising signal for improved graft retention, supported by both functional and imaging findings, although based on limited data. Adipose-derived regenerative cell enrichment resulted in significantly improved patient-reported outcomes in one small trial, but without consistent corresponding improvements in objective voice parameters.

Complication rates were uniformly low across all studies, with no serious adverse events reported. Minor complications were transient and self-limiting. Revision procedures were primarily performed for insufficient or declining medialization and appeared to be influenced by injected volume and underlying tissue condition.

A key finding of this review is the substantial technical heterogeneity across studies, which limits comparability and precludes definitive identification of optimal techniques.

In direct relation to the research question, the available evidence suggests that technical factors do influence outcomes in autologous fat injection laryngoplasty, but to different degrees. Injection volume represents the most clearly supported modifiable factor, while correct placement within the thyroarytenoid muscle is a fundamental technical requirement. In contrast, the impact of processing techniques and adjunctive biological strategies remains less well defined and is supported only by limited and heterogeneous evidence. As a result, no single optimal technique can currently be identified.

6.2. RECOMMENDATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

The findings of this review support several practical recommendations, which should be interpreted as guidance rather than definitive standards due to the limitations of the current evidence.

In clinical practice, a stepwise treatment approach should be considered. Early injection with hyaluronic acid can be used as a temporary and less invasive option, particularly in the early phase of glottic insufficiency or when spontaneous recovery remains possible. If insufficient improvement is observed or a persistent deficit is present, autologous fat injection laryngoplasty may be considered as a longer-lasting intervention.

Autologous fat injection laryngoplasty represents an appropriate surgical option for glottic insufficiency in patients without a vertical glottic level difference, particularly in unilateral vocal fold paralysis, vocal fold atrophy, sulcus vocalis, and selected scarred vocal folds. In cases of vertical height mismatch, additional procedures such as arytenoid adduction should be considered (67).

Injection volume appears to be the most relevant modifiable technical factor. It should be individualized according to anatomy and disease severity, and underinjection should be avoided. In the only study directly addressing this relationship, higher volumes (≥3 mL) were associated with improved outcomes in male patients with unilateral vocal fold paralysis (67).

Correct placement within the deep thyroarytenoid muscle is essential, while superficial injection should be avoided due to its negative effect on vibratory function (66,67).

Fat processing technique appears to be of secondary importance. Centrifugation can be regarded as current standard practice, while more complex methods such as emulsification may be useful in specific settings, particularly in fibrotic or scarred tissue (69).

Adjunctive strategies should be applied selectively. Platelet-rich plasma may provide short-term benefit, particularly in poorly vascularized or fibrotic tissue (53,65), while collagen scaffold-supported fat delivery shows promise for improving graft retention but remains experimental (64). Current evidence does not support routine use of adipose-derived regenerative cell enrichment.

Perioperative management should focus on protecting graft stability and optimizing functional outcomes. Short-term voice rest, postoperative voice therapy, and selective use of corticosteroids may be considered. Final outcomes should not be assessed before several months, and revision should generally be deferred for at least 12 months. Repeat fat injection appears to be a safe first-line revision strategy.

Future research should prioritize adequately powered, multicenter trials with standardized protocols and longer follow-up. Key priorities include defining optimal injection volume, clarifying the role of adjunctive therapies, and incorporating imaging-based assessment of graft survival. Standardized outcome measures and improved reporting of technical variables are essential to enable meaningful comparison between studies.

Overall, while autologous fat injection laryngoplasty is a safe and effective intervention, its optimal technical application remains incompletely defined and requires further high-quality evidence.

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8. APPENDICES

Annex 1. PICO Framework used to define the review question

Table 8-1. PICO Framework applied

Population	Intervention	Comparison	Outcome
Patients undergoing vocal fold medialization	Autologous fat grafting using a defined processing, preparation or injection technique	No comparison or autologous fat grafting using a different technique, or with adjunctive biologic therapies	Voice outcomes, graft longevity, complication rates

Table 1. The comparison column reflects variations within autologous fat grafting only; studies without a comparator group were also eligible, studies comparing fat to non-biological materials or surgical procedures were excluded.

Annex 2. Search Terms Overview

Table 8-2. Search terms included across the databases

Concept	MeSH-Terms	Free-Text Terms (Title/Abstract)
Population	“Vocal Cords” [MeSH] “Vocal Cord Paralysis” [MeSH]	vocal fold*, vocal cord*, vocal fold medialization, glottic insufficiency
Procedure	“Laryngoplasty” [MeSH] “Injections, Intralesional” [MeSH]	injection laryngoplasty, vocal fold injection, medialization injection
Intervention	“Adipose Tissue” [MeSH]	fat graft*, fat injection, autologous fat, fat augmentation, fat transfer

Table 2. Overview of search terms used across all databases (PubMed, Cochrane Library/CENTRAL, and Scopus), organized by conceptual block. MeSH terms were applied in PubMed and Cochrane; free-text terms were used across all three databases.

Annex 3. Inclusion and Exclusion Criteria for Study Selection

Table 8-3. Inclusion and Exclusion criteria

Category	Inclusion Criteria	Exclusion Criteria
Population	Patients with glottic insufficiency of any etiology undergoing vocal fold injection with autologous fat with the goal of medialization	Animal studies, cadaver studies, in vitro or ex vivo studies Only involving healthy volunteers or experimental phonation models Unclear indication for injection medialization
Intervention	Injection medialization using different autologous fat grafting techniques. Studies were required to report at least one technical aspect of fat procedure, processing, fat preparation (including biological adjuncts), or injection technique (volume). Single-arm studies reporting technical and clinical outcomes were also considered eligible.	Surgical medialization techniques (e.g., thyroplasty) Using non-fat materials for injection medialization Using autologous fat without reporting technical details of processing, or preparation or injection technique. Studies where fat grafting is not the primary intervention
Comparators	No comparator or studies comparing different autologous fat grafting techniques	Studies comparing only non-biologic materials or unrelated interventions
Outcomes	Reporting at least one of the following: • Objective voice outcomes • Validated subjective voice outcomes (e.g., Voice Handicap Index) • Graft longevity or resorption over time • Procedure-related complications	Studies lacking clinical outcomes, lacking follow-up data, or with insufficient reporting of relevant endpoints
Study Type	Randomized controlled trials, non-randomized comparative studies, prospective or retrospective cohort studies, case series and single-arm interventional studies	Narrative reviews, editorials, letters to the editor, and conference abstracts without full-text articles
Follow-up Period	Follow-up of at least 6 months	Follow-up <6 months or unclear follow-up duration
Sample Size	Studies with ≥10 participants	Studies with < 10 patients
Language	English	Non-English publications without translation

Table 3. Predefined inclusion and exclusion criteria applied during title/abstract and full-text screening. All criteria were established prior to study selection to minimize selection bias.

Annex 4. Cochrane Library (CENTRAL) Search Strategy

```
Search Name:    Masterthesis
Date Run:       11/01/2026 15:48:00
Comment:

ID      Search  Hits
#1      MeSH descriptor: [Vocal Cords] explode all trees        221
#2      MeSH descriptor: [Vocal Cord Paralysis] explode all trees
        111
#3      MeSH descriptor: [Injections, Intralesional] explode all
trees   849
#4      MeSH descriptor: [Adipose Tissue] explode all trees     3585
#5      MeSH descriptor: [Laryngoplasty] explode all trees      16
#6      #3 OR #5        865
#7      #1 OR #2        312
#8      #7 AND #6 AND #4        0
#9      (vocal fold* OR vocal cord* OR glottic insufficiency OR
vocal fold medialization):ti,ab,kw      2009
#10     (injection laryngoplasty OR vocal fold injection OR
medialization injection):ti,ab,kw       53
#11     (fat graft* OR fat injection OR autologous fat OR fat
augmentation OR fat transfer):ti,ab,kw  2287
#12     #7 OR #9        2009
#13     #6 OR #10       909
#14     #4 OR #11       5646
#15     #12 AND #13 AND #14     12
```

Final Cochrane Library (CENTRAL) search strategy used for study identification (search conducted on 11 January 2026).

Annex 5. PubMed Search Strategy

Search: (("Vocal Cords"[MeSH] OR "Vocal Cord Paralysis"[MeSH] OR vocal fold*[tiab] OR vocal cord*[tiab] OR glottic insufficiency[tiab] OR vocal fold medialization[tiab])
AND ("Laryngoplasty"[MeSH] OR "Injections, Intralesional"[MeSH] OR injection laryngoplasty[tiab] OR vocal fold injection[tiab] OR medialization injection[tiab])
AND ("Adipose Tissue"[MeSH] OR fat graft*[tiab] OR fat injection[tiab] OR autologous fat[tiab] OR fat augmentation[tiab] OR fat transfer[tiab]))
Filters: in the last 10 years, English, Humans

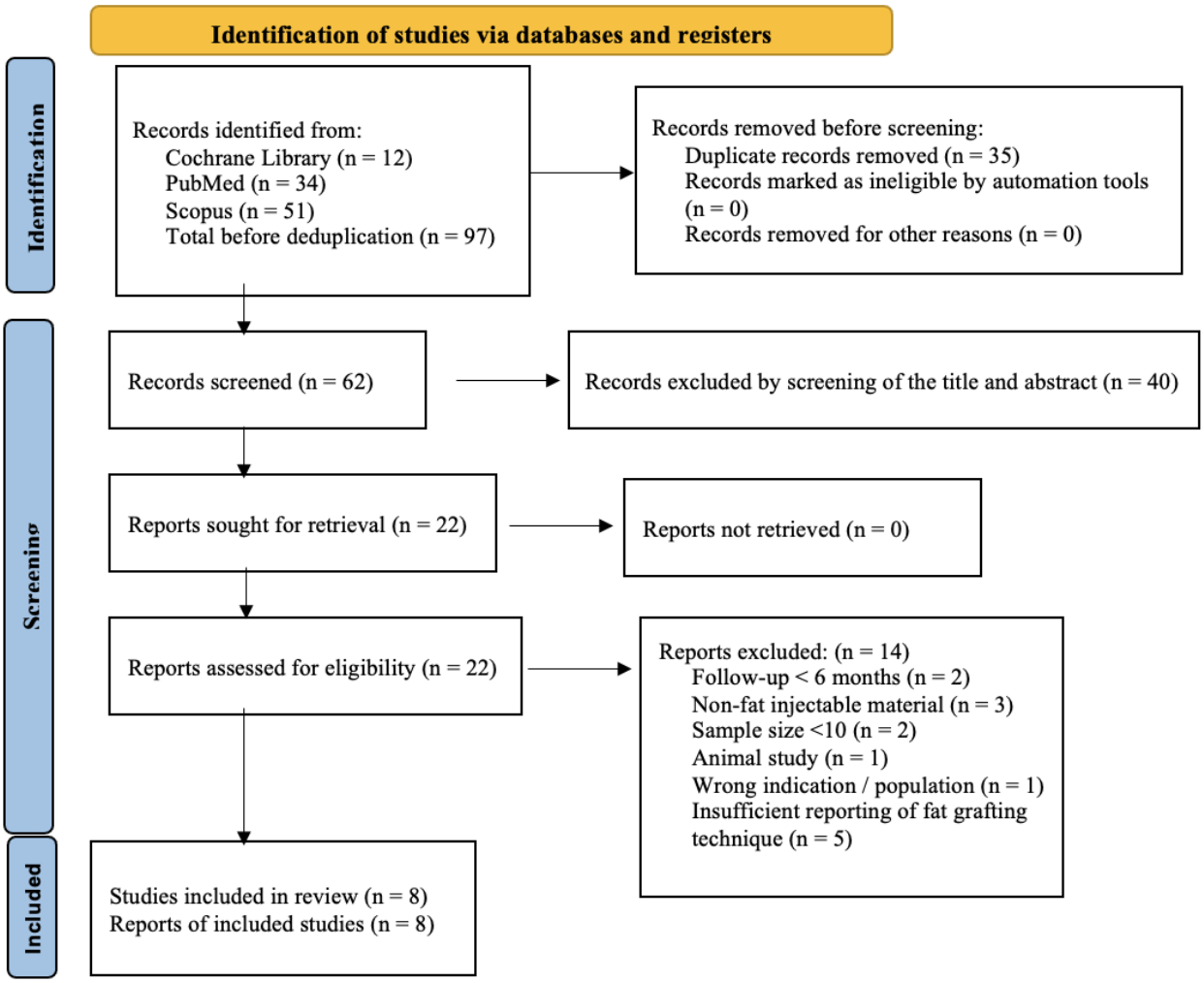
Final PubMed search strategy used for study identification (search conducted on 11 January 2026).

Annex 6. Scopus Search Strategy

TITLE-ABS-KEY (("vocal fold*" OR "vocal cord*" OR "glottic insufficiency" OR "vocal fold medialization")
AND ("injection laryngoplasty" OR "vocal fold injection" OR "medialization injection")
AND ("fat graft*" OR "fat injection" OR "autologous fat" OR "fat augmentation" OR "fat transfer"))
AND PUBYEAR > 2015 AND PUBYEAR < 2026 AND (LIMIT-TO (LANGUAGE , "English"))

Final Scopus search strategy used for study identification (search conducted on 12 January 2026)

Annex 7. PRISMA Flowchart



PRISMA flow diagram illustrating the study selection process, including identification, screening, eligibility assessment, and inclusion of studies.

Annex 8. Main Characteristics of Included Studies

Table 8-4. Main characteristics of included studies

Author	Design	n	Indication/Aetiology	Main Outcome Measures	Follow-up	Adjunctive Strategy
Salmerón-González et al. (2020)	PC	21	Scarred VF, sulcus vocalis	VHI-10, GRBAS, MPT, Jitter, Shimmer, HNR	20.7 months (range 9–55)	Voice rest 7 days
Jin et al. (2022)	RCT	10	UVFP	VHI, MPT, Jitter, Shimmer, Videolaryngoscopy, CT volumetry	24 months	Fat + Bovine collagen scaffold, ratio: 1:1
Lasso et al. (2018)	RCT	14	UVFP	VHI-10, Laryngoscopy, Voice quality analysis (BioMet®Phon, 14 biomechanical parameters; LLIR)	Range 6–26 months	ADRCs group I; two-stage procedure (local + GA)
Tsou et al. (2022)	RCT	34	Type II sulcus vocalis	VHI-10, GRBAS, Stroboscopy, MDVP: Jitter, Shimmer, NHR, VTI, SPI, MPT	6 months	Fat + PRP group, ratio 4:1
Fawaz et al. (2025)	RCT	50	UVFI	Modified GRBAS, Laryngoscopy, Arabic VHI-30, MDVP: Jitter, Shimmer, NHR, MPT	12 months	Fat + PRP group, ratio 2:1
Pagano et al. (2017)	RS	18	UVFP	GRBAS, VHI, MPT, MFR, Jitter, Shimmer, Stroboscopy	Range 12–58 months	Tisseel fibrin glue; prednisone 3 d; antitussive 7 d; voice rest 48 h; preop. antibiotics
Umeno et al. (2025)	RS	73	UVFP	MPT, MFR, Bowing Ratio, Width Ratio, PPQ, APQ, NNEa, F0 range, SPL range	Range 3 months–5 years	NR
van den Broek et al. (2019)	RC	23	VF atrophy ± sulcus vocalis	VHI-30, GRBAS, MPT, Dynamic Range (dB)	12 months	Voice rest 24 h; postop. voice therapy from week 1

Abbreviations: PC = Prospective Cohort; RCT = Randomized Controlled Trial; RS = Retrospective Study; RC = Retrospective Cohort; UVFP = Unilateral Vocal Fold Paralysis; UVFI = Unilateral Vocal Fold Immobility; VF = Vocal Fold; NR = Not Reported; VHI = Voice Handicap Index; GRBAS = Grade, Roughness, Breathiness, Asthenia, Strain; MPT = Maximum Phonation Time; ADRC = Adipose-Derived Regenerative Cells; PRP = Platelet-Rich Plasma; GA = General Anesthesia

Overview of study design, patient population, primary indication, outcome measures, adjunctive strategies, and follow-up duration across the included studies.

Annex 9. Technical Parameters of Fat Harvesting, Processing, and Injection

Table 8-5. Technical parameters of fat harvesting, processing, and injection

Author (Year)	Fat Harvesting	Fat Processing	Injection Technique / Instrument	Injected Volume
Salmerón-González et al. (2020)	3 mm cannula; abdomen	Centrifugation (300 g, 3 min) + emulsification (10 passes between syringes)	TA muscle; 23-G needle; overcorrection 20–40%	0.1–0.6 mL
Jin et al. (2022)	Coleman technique; lower abdomen	5 min gravity sedimentation; middle layer retained. Bovine collagen scaffold (1:1 with fat)	Lateral to vocal process; TA muscle; Brüning's syringe; overcorrection	~3 mL
Lasso et al. (2018)	3 mm Mercedes-tip blunt cannula; infra-abdominal; minimum 180 cm^3 required (Celution system)	ADRC group: gravity sedimentation + Celution System (Celase enzymatic digestion), ADRCs mixed back into washed fat. CAF group: centrifugation (3000 rpm, 3 min)	Lateral to vocal process; TA muscle; 19-G needle; depth 2–3 mm; overcorrection 20–30%	Mean 1.79 ± 0.29 mL
Tsou et al. (2022)	18-G needle; lower abdominal	Centrifugation (3000 rpm, 5 min); middle layer washed with NaCl Fat : PRP = 4:1	Midcord and postcord, TA muscle; Brüning's syringe; overcorrection	1.5 mL
Fawaz et al. (2025)	Periumbilical; microlobular technique	Centrifugation (microlobular) Fat : PRP = 2:1	Paraglottic space; 12-G laryngoplasty syringe or Chiba needle; overcorrection	Up to 3 mL
Pagano et al. (2017)	2.1 mm cannula; periumbilical/flank/inner thigh	Centrifugation (1280 g, 3 min), 3-layer separation; buff-colored middle layer selected.	Lateral to vocal process; musculoligamentous area; 19-G butterfly needle, overcorrection; fibrin glue at withdrawal	Mean 0.75 mL
Umeno et al. (2025)	18-G needles; periumbilical	Filtration through saline-rinsed tea filter	TA muscle + fovea oblonga of arytenoid cartilage; 19-G endolaryngeal microsurgery needle; needle hole directed outward; overcorrection 20–30%	LV: mean 2.0 mL; HV: mean 4.3 mL; range 0.5–6.0 mL
van den Broek et al. (2019)	Abdominal liposuction or periumbilical incision	Centrifugation	TA muscle, anterior to vocal process; Brüning's syringe; overcorrection 1/3–1/4 VF width	NR

Abbreviations: TA = Thyroarytenoid; G = Gauge; LR = Lactated Ringer's; epi = epinephrine; atm = atmospheres; neg. = negative; NR = Not Reported; PRF = Platelet-Rich Fibrin; PRP = Platelet-Rich Plasma; ADRC = Adipose-Derived Regenerative Cells; CAF = Centrifuged Autologous Fat; VF = Vocal Fold; fovea oblonga = anterolateral surface of arytenoid cartilage for TA muscle attachment

Summary of procedural variables relevant to the research question, including harvesting technique and instrument, fat processing method, injection site and instrument, injected volume, and degree of overcorrection.

Annex 10. Summary of Clinical Outcomes

Table 8-6. Summary of clinical outcomes across included studies

Author (Year)	VHI	GRBAS	MPT	Jitter	Shimmer	HNR / NHR	MFR	Glottic Closure	Key Finding
Salmerón-González et al. (2020)	↑	↑	↑	↑	↑	↑	NR	NR	All outcomes improved at 8 months; stable at 20.7 months
Jin et al. (2022)	↑ scaffold > fat	NR	↑	↑	↑	NR	NR	↑	Scaffold group: sustained VHI improvement over 24 months; fat-alone group deteriorated from 6 months. CT: scaffold > fat in residual volume
Lasso et al. (2018)	↑ ADRC > CAF	NR	NR	↑	↑	↑	NR	↑	ADRC group: better patient-reported outcomes; no biomechanical between-group difference.
Tsou et al. (2022)	↑ PRP > fat at 1 mo.; - at 6 mo.	↑	↑	↑ PRP > fat	↑ PRP > fat	↑ PRP > fat	NR	↑ PRP > fat at 6 mo.	PRP: consistent early advantage; acoustic and stroboscopic superiority at 6 months
Fawaz et al. (2025)	↑ -	↑ PRP > fat at 1 mo.; - at 12 mo.	↑ PRP > fat	↑ -	↑ -	↑ -	NR	↑ PRP > fat at 1 mo.; - at 12 mo.	PRP: early perceptual advantage; MPT sustained at 12 months; all other outcomes equivalent long-term
Pagano et al. (2017)	↑	↑	↑	↑	-	NR	↑	↑	All improved outcomes stable at 12–58 months; no revision required
Umeno et al. (2025)	NR	NR	↑ HV > LV	↑	↑	↑ HV > LV	↑	↑	High-volume (≥3 mL): greater MPT improvement; lower revision rate. CT and histology: long-term graft viability confirmed
van den Broek et al. (2019)	↑	-	-	NR	NR	NR	NR	NR	VHI and dynamic range (↑): only significant outcomes; comparable in atrophy-alone and atrophy+sulcus subgroups

Symbols: ↑ = significant improvement from baseline; - = no significant change; ↓ = significant worsening; NR = Not Reported. Between-group superiority is indicated with > (e.g. PRP > fat = PRP group showed superior outcomes compared with fat-alone group; HV > LV = high-volume group superior to low-volume group). Where > is shown without -, both groups improved but one was superior; where > replaces ↑, only the superior group reached significance.

Abbreviations: VHI = Voice Handicap Index; GRBAS = Grade, Roughness, Breathiness, Asthenia, Strain; MPT = Maximum Phonation Time; MFR = Mean Flow Rate; HNR/NHR = Harmonic-to-Noise / Noise-to-Harmonic Ratio; HV = High Volume (≥3 mL); LV = Low Volume (<3 mL); PRP = Platelet-Rich Plasma; ADRC = Adipose-Derived Regenerative Cells; CAF = Centrifuged Autologous Fat; CT = Computed Tomography; mo. = month(s).

Annex 11. Complications and Revision Rates

Table 8-7. Complications and revision rates across included studies

Author (Year)	n	Complications	Revision / Re-intervention	Revision Rate	Interpretation
Salmerón-González et al. (2020)	21	1 mild dyspnea after 2nd injection	5/21 repeat injections after ≥12 months	23.8%	Highest revision rate; driven by fibrotic indication; repeat injection feasible
Jin et al. (2022)	10	1 transient pharyngalgia (collagen group; spontaneous resolution)	NR	NR	No serious complications; collagen scaffold: no additional risk
Lasso et al. (2018)	14	1 patient (septic shock, glottic oedema); attributed to intubation; patient withdrawn	NR	NR	No intervention-related complications
Tsou et al. (2022)	34	0/34	NR within 6 months	NR	Clean safety profile; no complications in either arm
Fawaz et al. (2025)	50	0/50	0/50 within 12 months	0%	No complications or revisions; stability at 12 months in both groups
Pagano et al. (2017)	18	Harvest-site hematomas; 1 tongue-base oedema (corticosteroids); 2 postop. dysphonia (corticosteroids); 1 fat extrusion (conservative); 1 intraoperative superficial injection (corrected)	0/18 within 12–58 months	0%	Minor harvest-site events only; no procedure-related serious complications; long-term stability confirmed
Umeno et al. (2025)	73	10/73: transient airway sensation, 20 min–8 h; none required intervention	5/73 re-injection; 4/5 from LV group	6.8%	Volume-dependent airway risk; self-limiting; LV group higher revision risk
van den Broek et al. (2019)	23	NR	4/24 procedures: 2 repeat fat injection, 2× medialization thyroplasty	16.7%	Revision includes escalation thyroplasty; failure rate estimated 16.7–37.5%

Abbreviations: LV = Low Volume group (<3 mL); NR = Not Reported; postop. = postoperative; GA = General Anesthesia; min = minutes; h = hours

All reported adverse events, revision procedures, and re-intervention rates, stratified by study.