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Review Article

Utilizing Adipose Tissue-Derived Stem Cell Strategies for Obtaining Regeneration of Respiratory Tract Fistulas-A Systematic Review

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Abstract

Fistula of the respiratory tract represent an aberrant communication or passage among the respiratory system as well as the digestive tract or the nearby organs. They might originate congenitally or more commonly, iatrogenic with a heterogeneous presenting features. These fistulas of the respiratory tract might cause decreased health-associated Quality of Life (QOL) as well as short lifespan. Treatment is basically dependent on an endoscopic surgical procedure but mostly patients need continued hospitalization as well as might develop complications. Thus with the advent of stem cells, the more conservative strategies utilizing regenerative medicine strategies basically dependent on lipotransfer, have been evaluated. After having reviewed the role of Adipose Tissue-Obtained Stem/Stromal Cells (ASC'S) in various kinds of regenerative medicine, here we tried to conduct a systematic review on ASC. Adipose Tissue (AT) might be administered in the form of unprocessed tissue or subsequent to enzymatic treatment to be able to obtain the cellular Stromal Vascular Fraction (SVF).Thus here we conducted a systematic review on the same. With role of stem cells be it Mesenchymal Stem/Stromal Cells (MSCs) or Adipose tissue-derived stem/ stromal cells (ASC'S) in the repair of respiratory tract fistulas. Utilizing the Pubmed search Engine, along with Google Scholar ,Web of Science Scopus, Clinicaltrials.gov for clinical trials utilizing MeSH terms like

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Bronchopleural Fistula (BPF); to Tracheooesophageal Fistula (TEF); Mesenchymal Stem Cells (MSCs); Mesenchymal stromal cells; Adipose tissue-derived Stem/ Stromal Cells (ASC'S); respiratory tract fistulas; post cancer head and neck fistulas; lipoaspirate from 1960-2020 till date . We found a total of 175 articles out of which we selected 110 articles for this review. No meta-analysis was done. With minimal clinical experience maximum of which comes from case reports as well as case studies, a total concluding proof is still not there. But definitely it is a gradually evolving field with more experience gained, grafting of adipose tissue obtained stem/stromal cells might turn out to me the least invasive as well as more conservative therapy alternative towards the more mutilating damaging extensive surgeries. The safety as well as tolerance observed in earlier studies might aid in strategizing as well as designing larger designs in future which might utilize novel methods with regards to tissue processing along with utilization of scaffolds as well as 3D printing in the longer plans for enhancing the clinical results.

Keywords

Respiratory Tract Fistulas; Adipose Tissue; Mesenchymal Stem/Stromal Cells; Adipose Tissue-Derived Stem/Stromal Cells; Lipotransfer; Head and Neck Cancer Surgeries; Tracheooesophageal Fistula (TeF); Bronchopleural Fistula

Introduction

Earlier we have reviewed the role of various kinds of stem cells from embryonal stem cells to mesenchymal stem cells and subsequently role of Mesenchymal Stromal Cells (MSC's) as well as Adipose tissue-derived Stem/ Stromal Cells (ASC's) in regenerative medicine including in Diabetes Mellitus (DM), burns along with Very Small Embryonic Like Stem Cells (VSEL) in gynaecologic oncology [1-7]. Fat grafting, also known as lipotransfer, consists of Adipose Tissue (AT), harvesting, processing of this fat that has been removed to remove oil, liposuction fluids as well as blood constituents as well as then reinjection of this modulated tissues into the area requiring treatment [8]. The original surgical fat grafting process was in 1893 by Neuber, et al., who detailed the AT transfer obtained from the forearm into periorbital area for rectification of depressed scar [9]. Coleman in 1987 formed a novel method of liposuction that aided in obtaining AT under Local Anaesthesia (LA) with less injury relatively [10].This method of fat grafting has been extensively evaluated for healing soft tissue volume loss (reconstructive surgery) as well as to improve cosmetic looks (cosmetic surgery) [10]. Furthermore currently fat grafting has been utilized to facilitate tissue or organ healing (regenerative medicine) [8,11,12].Various parameters like fat preparation, implantation procedures, as well as recipient areas might influence graft retainment [13]. Due to this, in the lack of a general agreement on a standardized technique, the clinical results of lipotransfer cannot always be anticipated [14]. Zul et al., in 2001, showed that within AT multipotent cells

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are located with the ability to differentiate *in-vitro* into adipogenic, chondrogenic, myogenic as well as osteogenic cells [15]. This facilitated more support for utilization of AT obtained material with regards for regenerative aspects [16]. The identification as well as removal of multipotent cells implicates these steps:

1. Fat digestion by a solution possessing collagenase
2. Removal of tissue debris by filtration
3. Centrifugation for harvesting the cellular part of the Stromal Vascular Fraction (SVF)
4. Expansion of these cells identified in culture to get tissue-obtained mesenchymal cells as well as
5. Flow cytometry evaluation for phenotypic properties of these isolated cells.

As per the definition of International Federation of Adipose Therapeutics (IFATS), International Society for Cellular Therapy (ISCT), uncultured SVF cells consists of a heterogenous population which are stromal cells, endothelial cells, erythrocytes, fibroblasts, lymphocytes, monocytes, macrophages as well as pericytes [17,18]. Mesenchymal Stromal Cells (MSC's) also called Adipose Tissue-Derived Stromal Cells (ASC's), have the properties of fast plastic adherence in culture; further more they express the phenotype markers CD90, CD73, CD105, as well as CD44,whereas they do not display CD45 as well as CD31 expression ; Additionally, MSC's have the capacity of differentiation into osteocytes, adipo cytes as well as chondrocytes *in-vitro* in proper stimulating media [15].Over years adipose tissue-derived multipotent cells were given the name of stem cells, as mesenchymal stromal cells as well as more recently as medicinal signalling cells that sustains the MSC acronym [17-20]. This evolution of the nomenclature suggests a major shift on how MSC's are thought to act or bring about their therapeutic actions with regards to regenerative medicine techniques. Actually this term ''Multipotent Stem Cells'' was initially given to reflect that MSC' may differentiate into cells that take part in tissue healing (like building block action). Lots of experimental as well as clinical proof later pointed that, inspite of various processes trying to enhance cell engraftment [21], the amount of cells that do survive as well as remain following a transplant, for differentiation *in-vivo* as well as participate in tissue regeneration are much less likely to give justification for the clinical advantages seen in cell therapy methods [22]. Hence concentration was given to suggest the capacity of MSC's as medicinally signalling cells to generate trophic, immunomodulatory factors , either directly or through Extracellular Vesicles (ECV), that might facilitate tissue regeneration as well as /or tissue stem cells homing pointing to a homing action [23]. The precise molecular modes beneath the regenerative potential correlated with AT as well as cell-based therapies still need to be totally tested [24]. MSC's are thought to evoke their proreparing action basically via liberation of paracrine factors as well as ECV that might induce the migration as well as activation of local tissue particular stem cells might aid in tissue - regeneration, facilitation of neoangiogenesis, manipulation of inflammatory as well as immunomodulatory responses as well as, escalation of anti-oxidative as well as antiapoptotic actions [25]. Various regenerative medicine clinical trials utilizing MSC's cell transplant methods have been conducted [26]. Specifically therapy of perianal fistulising Crohn's disease, that represents a chronic inflammatory problem of the Gastrointestinal (GIT), utilizing cell-based therapies has been markedly evaluated for the

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immunomodulatory properties of MSC's [27,28]. A phase III study confirmed the safety as well as effectiveness in longterm closure of perianal fistulas by local injection of adipose tissue-derived MSC's [29].

Currently placing an esophageal stent or bioprosthetic tissues are utilized regarding the treatment of various esophageo-respiratory fistulas [30,31]. Problem is this type of surgical technique mostly needs long hospital admission as well as might be correlated with a marked chances of side effects. Hence here we decided to conduct a a systematic review on the same, with role of stem cells be it MSCs or ASC'S in the repair of respiratory tract fistulas.

Materials and Methods

Utilizing the PubMed search Engine, along with Google Scholar, Web of Science Scopus, Clinicaltrials.gov for clinical trials utilizing MeSH terms like Bronchopleuralfistula; Mesenchymal Stem Cells (MSCs); Mesenchymal stromal cells; Adipose Tissue-Derived Stem/ Stromal Cells (ASC'S); respiratory tract fistulas; post cancer head and neck fistulas; lipoaspirate from 1960-2020 till date.

Results

We found a total of 175 articles out of which we selected 110 articles for this review. No meta-analysis was done.

Role of Adipose Tissue-Derived Substances for the Therapy of Respiratory Tract Fistulas-Clinical Utilization

A respiratory tract fistulas is defined as the aberrant passage that communicates among any portion of the respiratory tract or with any part of the respiratory tract or surrounding organs. On leaving untreated, respiratory tract fistulas get correlated with a high chance of mortality [32,33]. The commonest therapy is stent based. Additionally, greater conservative methods are dependent on regenerative medicine strategies have also been taken into account. Here, a brief summary of tissue or cell based clinical studies that have been detailed for the therapy of various kinds' respiratory tract fistulas is given.

Oroantral Fistulas

This comprises of a pathologic communication among oral as well as the antral cavities .The resection of the maxillary posterior teeth is believed to be the main etiological factor for Oroantral Fistulas (OAF) generation. The OAF that are small have a small size possess a chance of healing on their own spontaneously, whereas surgical intervention is needed for those over 3 mm. Considering the size of OAF as well as the condition of the surrounding tissues ,various Treatment strategies are assessed [34]. Larger deficitis, like the ones secondary to tumor removal, may need the utilization of autogenous bone as well as soft tissue grafts, placing of

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allogenous substances or xenografts. Flap utilization of local tissue, like buccal as well as palatal flaps can get utilized for closure of moderated sized defects. Specifically, buccal fat application, a lobulated part of AT has been markedly utilized since it was shown in 1977 [35,36]. This AT utilized for repairing OAF is usually coated utilizing the surrounding mucosa in 4-6 weeks, hence facilitating epithelialisation of the area that receives treatment [37].

Pharyngocutaneous Fistula

It is a pathological communication. Implicating the digestive tract as well as the skin of the neck represents the Pharyngocutaneous Fistula (PCF). It is a frequent complication following head as well as neck surgery [38]. Once there is PCF presence it might prolong as well as delay the adjuvant oncologic therapies. Most of such patients get managed utilizing conservative treatment to facilitate spontaneous healing. Nevertheless, about 30% of the cases need greater extensive surgical management. In two separate case reports successful PCF repair via fat grafting in patients who had had taken a partial pharyngectomy [39,40]. Specifically, in the case report that was documented by Hespe et al., two rounds of autologous fat grafting that was administered in the region that was just surrounding the PCF utilizing both blunt cannulas as well as 18 gauge needles were conducted for attaining total fistula repair [40]. On the other hand, Sapundzheiv et al., documented a case report of a patient who had delivery of autologous fat around the internal opening of the PCF utilizing a Pretti angular injection cannula utilizing an endoscopic access towards the neopharynx [39].

Tracheoesophageal Fistula

Communication among airway as well as upper GIT is referred to Tracheoesophageal Fistula (TEF), which require immediate recognition as well as treatment for avoiding recurrent as well as intractable infections secondary to tracheobronchial contamination. Broadly TEF get classified into congenital as well as acquired fistulas with the latter group further sub classified into malignant as well as non-malignant. Congenital TEF take place in 1in 3000-5000 LB [41], as well as get diagnosed mostly in 1st year of life, whereas presentation in adults occurs occasionally [42]. Acquired non-malignant TEF are mostly correlated with traumatic damage, foreign body or caustic intake [43]. Most of the Acquired non-malignant TEF are secondary to compression from an inflated endotracheal or tracheostomy tube cuff that may take place rarely in about 0.5% of patients undergoing tracheostomy or intermittent positive pressure ventilation (Fig. 1) [44,45]. Rarely, acquired non-malignant TEF might original from local inflammation as well as infection, like TB as well as granulomatous infection [46].

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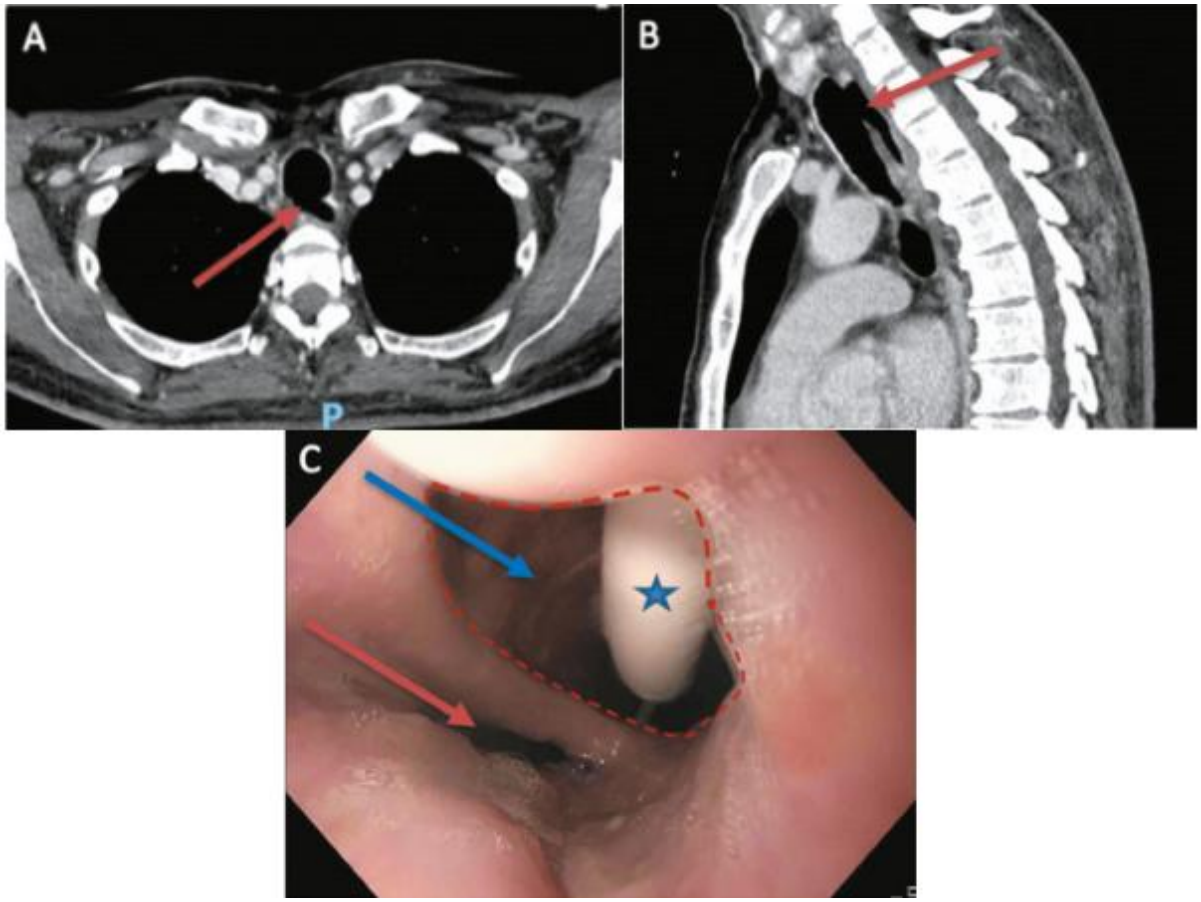

Figure 1: Courtesy ref no-45-Iatrogenic tracheoesophageal fistula after emergency orotracheal intubation. Computed Tomography (CT) images showing a large tracheoesophageal fistula (red arrow) in axial (a) and sagittal plane (b). Endoscopic image (c) of the fistula (red dashed line) between esophageal lumen (blue arrow), with a nasogastric tube inside (blue star), and tracheal lumen (red arrow).

Malignant acquired TEF have got correlated with various kinds of malignancies. Specifically incidence of TEF has been documented to be 4.5% after primary esophageal tumors as well as 0.3% in case of primary malignant lung tumors [47]. Invasion of tumors as well as cancer - associated tissue necrosis might aid in the pathogenesis of malignant TEF. Additionally, chemoradiotherapy as well as antiangiogenic therapy, influencing, local architectural as well as vascular tissue alterations can, escalate the risk of TEF generation (Fig. 2) [33]. Concerning this, cell based-therapies might ameliorate chemotherapy- stimulated tissue injuries [48].

Small size- TEF might close on their own, whereas fistulas >20 mm in size correlated with poor survival [49]. Hence, immediate therapy is required for prevention of contamination, of the airway as well as aiding in normal feeding. Various strategies have been formed to take care of both acquired non-malignant as well as malignant TEF [32,33,47,49]. Surgical managements are esophageal stent placement, bypass, resection as well as surgical repair. Conservative therapies, as next to surgical methods, majorly are supportive care for avoiding contamination of the respiratory tract. Furthermore, the utilization of autologous tissue-aided

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regenerative method may be a useful therapeutic method. Concerning this, a case report of a 55 years old man having congenital TEF got treated with success utilizing local injection of autologous fat with a pressurized injection device [50]. Total healing in long term was correlated with 2 sessions of delivery of autologous fat with the patient continuing to be asymptomatic over 10 years.

Tracheomediastinal Fistula

A communication among trachea as well as mediastinum is referred to as Tracheomediastinal Fistula (TMF). TMF generation is rare as well as mostly correlated with tumors of the airway. A case report of TMF got, documented by Diaz-Agero-Alvarez after an endoscopic laser therapy of Tracheal cancer, who received therapy with bronchoscopic delivery of autologous ASC in fibrin glue suspension [51]. Specifically, autologous ASC got removed via collagenase digestion from 150 ml of aspirate .Then roughly, 5×106 cells got mixed in fibrin glue as well as injected via a bronchoscope into the cavity of a 2 cm^2 TMF. One year follow up displayed total closure of the fistula with re-epithelialization as well as neo-vascularization of the area (Fig. 2 and 3) [51].

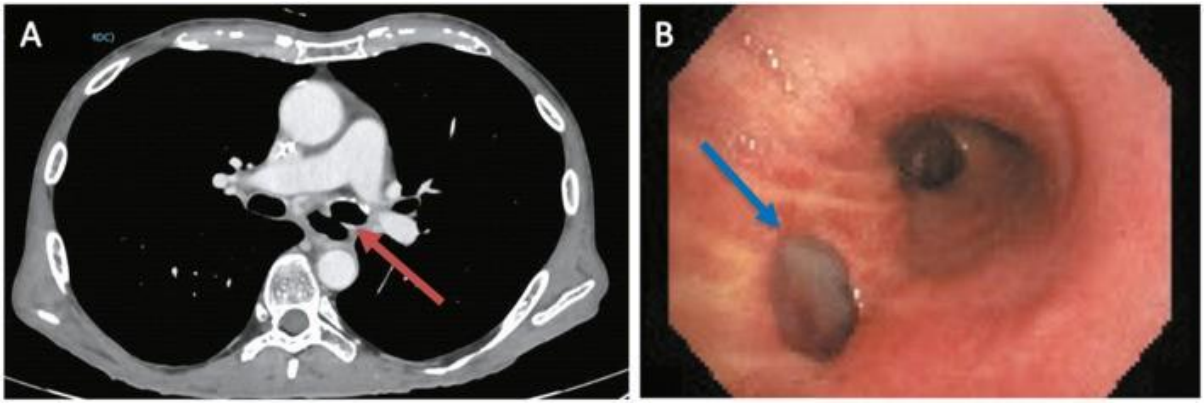

Figure 2: Neoplastic bronchoesophageal fistula after inductive radiotherapy. A: CT image of the fistula between esophageal lumen and left main bronchus (red arrow). B: Bronchoscopic view of the same fistula (blue arrow) on the membranous side of left main bronchus.

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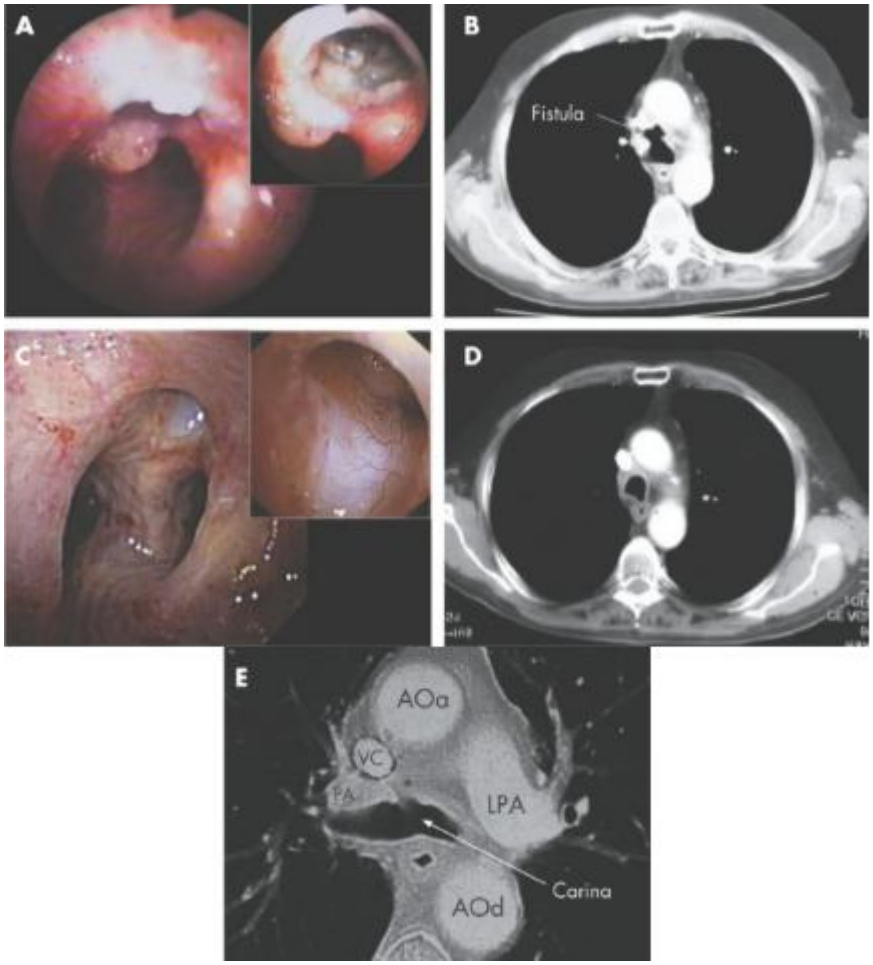

Figure 3: Bronchoscopic and CT images from the region of the fistula. A: Bronchoscopic image recorded before cell therapy. The fistula can be seen on the anterior tracheal wall which had been totally destroyed after the laser treatment of the tumor. The entrance was about 10 mm in diameter and the bronchoscope could pass through it. Inset: Anthracotic mediastinal lymph nodes as seen through the wall of the fistula. B: CT image recorded before cell therapy. The fistula was situated between the trachea and a pretracheal mediastinal cavity with an area of 2 cm^2, next to the superior vena cava and pulmonary artery, near the ascending aorta. C: Bronchoscopic image recorded 1 year after cell therapy. The entrance to the fistula was much smaller (diameter 3-4 mm). Inset: The walls of the fistula were covered with "new" epithelium and vessels as a result of neovascularisation and epithelialisation. D: CT image from the same region of the fistula 1 year after cell therapy. One year after treatment the cavity had disappeared. E: CT image from the region of the fistula recorded 1 year after cell therapy. This image is the only one to show remnants of the previous fistulous tract. It is clear that the fistula had closed. *Small depression; VC, superior vena cava; AOa: ascending aorta; AOd, descending aorta; PA, right pulmonary artery; LPA, left pulmonary artery.

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Bronchopleural Fistula

A pathological communication among the bronchial tree as well as the pleural space is a Bronchopleural Fistula (BPF) [52]. BPF represents a severe post-operative complication of pneumonectomy or other pulmonary removal with great morbidity as well as mortality (Fig. 4). Hence, surgery or bronchoscopy is required for facilitating the closure of BPF.

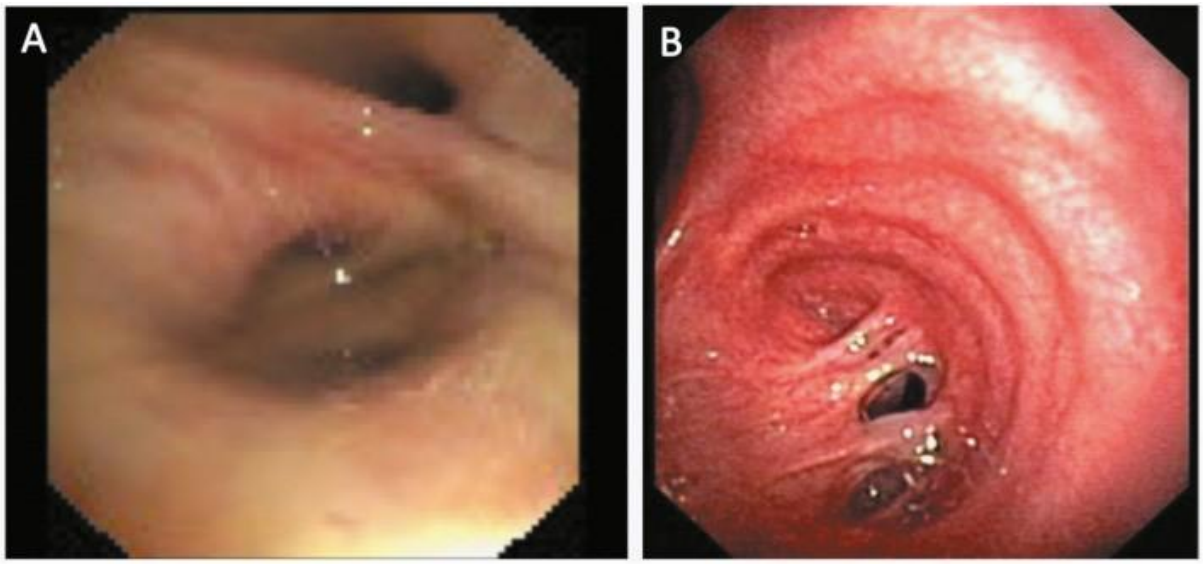

Figure 4: Bronchopleural fistulas after pulmonary lobectomy and pneumonectomy for lung cancer. A: Bronchoscopic view of the fistula (and muco-purulent secretions) in the inferior right bronchial stump. B: Endoscopic view of the bronchial stump fistula after right pneumonectomy.

In view of conservative other methods for greater damaging extensive surgeries, delivery of mesenchymal cells has been carried out for facilitating healing of the tissues that surround the fistula [53,54]. Specifically, Petrella et al., detailed a way of autologous bronchoscopic perilesional transplantation of 10 million Bone Marrow (BM)-obtained mesenchymal stem cells for the therapy of a small sized measuring 3 mm BPF formed in a 42 years old man following right extra pleural pneumonectomy regarding malignant mesothelioma [55]. Another case report of a patient 66 years old presenting with a big (1.5 cm) BPF that was given treatment by Aho et al., utilizing matrix graft seeded autologous mesenchymal stem cells .Cells that were received following collagenase digestion from autologous AT as well as underwent 3 passages of amplification *in-vitro*, as well as ultimately, 2.5×10^7 MSC's got seeded on a matrix of synthetic bioabsorbable polyglycolide trimethylene carbonate copolymer under Good Manufacturing Practices (GMP). Five days following cell seeding, the matrix graft got surgically positioned over the BPF for facilitating repair [56]. This patient continued to be asymptomatic at the clinical follow up of 1.5 years. Influenced further another two patients were detailed by Diaz Agero-Alvarez et al., presenting with BPF by bronchoscopic delivery of

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AT-obtained Stromal Cells (ASC's) obtained by collagenase digestion as well as not expanded in culture [57]. One patient, afflicted with a 6 mm diameter BPF, had a delivery of 4.0×106 ASC's that resulted in the 80% closure of the fistula. Subsequently following 6 months they again repeated it delivering of extra 5.0×10^6 ASC's for getting total healing. They kept following up the patients for a 3 years follow up as well as no treatment -associated side effects were seen. More recently Zeng et al., documented a case report of a patient where successfully BPF measuring 5 mm × 2 mm was closed that occurred secondary to a lobectomy, that received delivery via a flexible bronchoscope of 2 × 107 umbilical-cord MSC's around the fistula [53]. A Computerized Tomography (CT) Scan done 6 months following the treatment displayed fistula repair as well as the BPF did not relapse during the 2 years follow up. A separate way utilized by Huramoto et al., in case of lung cancer patients going through lobectomy .They pointed that the utilization of isolated pericardial fat tissue to close the bronchial stump might avoid the BPF formation [58,59]. Recently endoscopic delivery of autologous fat was conducted for the therapy of BPF in 8 cases as well as resolution was seen in all patients [60].

Adipose Tissue-Obtained Substance for Facilitation of Tissue Regeneration in the Oropharyngeal Tract-Clinical Uses

Here a small overview of the local delivery of the studies on reconstructive/regenerative surgery evaluating local delivery of fat or adipose tissue-obtained mesenchymal stromal cells for restoration of tissue lost injured in the oropharynx.

Tracheoesophageal Puncture

Tracheoesophageal Puncture (TEP) with voice prosthesis positioning is a commonly utilized process for restoration of vocal action in cases going through total laryngectomy as well as pharyngo laryngectomy. One of the commonest side effects of this method, that needs to change the voice prosthesis, is enhancement of the puncture, with saliva or food leaking [61]. Delivery of autologous fat surrounding the puncture has been detailed as an efficacious as well as safe method that helps in preserving the voice prosthesis, by facilitating the, escalatation of the thickness of the tracheoesophageal wall [61]. Specifically, 4/10 patients receiving treatment sustained long-term (up till 65 months). Tracheoesophageal speech with no leakage.

Tracheostomy Scar-Hypertrophic

Development of a hypertrophic scar- at the tracheostomy site occurs very commonly. This scar might get adherent to the trachea resulting in problems at the time of swallowing .Various surgical methods have been detailed for ameliorating the hypertrophic scar [62]. Fat, adipose tissue-obtained mesenchymal stromal cells, as well as stromal cells-obtained factors contain antifibrotic action that influence a positive effect in tough scar therapy [63]. A minimally invasive technique for the therapy of post tracheostomy hypertrophic scar via intralesional delivery of AT has been utilized by Mazzola, et al., leading to very efficient cosmetic outcomes as well as enhanced skin quality as well as texture [64]. All the 10 patients included in this study attained satisfactory aesthetic as well as functional enhancements.

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Reconstructive Surgery of Head As Well As Neck Following Radiotherapy

Regarding functional as well as cosmetic soft tissue restoring in patients with head as well as neck cancers reconstructive surgery might be needed. Basically head as well as neck cancers. Therapy might need the surgical resection of a large quantity of tissue that surrounds the tumor, furthermore adjuvant treating irradiation might cause massive tissue injury as well as stimulation of radiation-stimulated skin fibrosis. Delivery of autologous fat has been analyzed as a proper technique for the end result of both esthetic as well as functional reconstruction regards to head as well as neck oncology patients that partly restores the volume that has been removed, decreasing escalated scare development along with radiation-stimulated skin fibrosis. In the regions getting therapy [65-68]. Over 60 cases have received therapy utilizing autologous fat delivery in 3 separate studies [65-68]. Certain worries have been enquired regarding the probability of delivered fat to facilitate remaining tumor cell invasion as well as metastasis [69]. Initial data received utilizing Head as well as Neck cancer cell lines *in-vitro* as well as *in-vivo* point that this process might be safe, but more evaluation is needed on patient-obtained tumor samples.

Velopharyngeal Incompleteness (VPI)

This occurs if there is incomplete Velopharyngeal closing. Nigh et al., reviewed how delivery of autologous fat has been collected for the therapy of VPI in over 250 patients [70]. Recently, the technique was for extra 11 adult patients [71]. On the basis of these earlier studies, the technique of pharyngoplasty utilizing autologous fat could be thought in the form of a safe as well as efficacious treatment method for mild VPI.

Scars of the Vocal Fold

Scars of the Vocal fold represent scarring awa fibrotic generations in the thin layer of the vocal fold. Preclinical studies corroborate the basis for utilizing cell therapy for treating the Scars of the vocal fold that might take place secondary to surgical or any iatrogenic damage [72]. At the Hopitaux De Marseilles, France, a clinical team facilitated a clinical trial with the title innovative, treatment for scarred vocal cords by local injection of autologous stromal vascular fraction''(NCT 02622464), detailed the 1st clinical case report, as well as have recently documented the outcomes of another 8 patients [73,74]. Initially autologous AT was retrieved, followed by enzymatic digestion, isolating ASC's under GMP situations, as well as same day local delivery at the laryngeal level of 2.2-13.60 × 10^6 viable uncultured cells. On follow up evaluation done at 12 months pointed an enhancement in the voice handicap index score without any serious side effects that could be causally ascribed to the treatment. Additionally, Cantarella, et al. detailed the outcomes of the injection of about 0.2-0.3 ml of autologous fat in 24 patients presenting with Scars of the Vocal fold [75]. Recently they again detailed the treatment of 7 patients presenting with Scars of the vocal fold by nanofat as well as microfat grafting [76]. Specifically, in this type of patients, microfat was delivered deeply in the vocal folds as well as nanofat emulsion got injected in the most superficial layer of the vocal fold in the scarred tissue. On follow up evaluation done at 3 months showed enhancement in the voice handicap index score.

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Recurrent Laryngeal Nerve Paralysis-Unilateral

This might occur due to damage to recurrent laryngeal nerve due to cancers, trauma as well as surgery. Mikaelian, et al., documented an initial report detailing the method of autologous fat injection into a paralyzed vocal cord in 3 patients presenting with unilateral vocal cord paralysis in 1991 [77]. Subsequently the process has been done on lot of more patients detailing vocal parameters getting improved for over a year following a single fat injection [75,78-81]. Specifically, in a clinical trial (NCT02904824), a group of patients received treatment by delivery of AT as well as a 2nd group with the same quantity of AT in the presence of a not-properly measured quantity of ASC (cell-assisted lipotransfer) [79]. Nevertheless, from the study no conclusions could be drawn regards to clinical results among the 2 groups [79].

Future Work

Maximum evidence-based results have been retrieved from single case reports or series of case studies. Actually, the design of bigger, clinical trials at multiple sites gets interfered by the small amount of persons that are afflicted who can get included in the trial as well as absence of clinical institutions having enough insight as well as resources regards to utilizing novel treatment in this area. Thus the total amount of clinical trials that have been conducted or are going on at present is still minimal. BM, AT, UCB are the most commonly uses sources for MSCs with regards to clinical trials, that are the ones detailed for fistula repair as well as tissue regeneration in the oropharynx [82]. BM, as well as it represent resources that can get replenished for MSCs that are adequate for autologous transplantation [83]. Collecting BM represents an invasive method, whereas subcutaneous, AT gets easily collected [84]. AT possesses around 500 > MSCs as compared to an equal quantity of BM, furthermore AT-obtained MSCs get simply expanded *in-vitro*, having >proliferation rate as compared to BM - obtained MSCs [85]. Additionally, MSCs obtained from AT facilitate more robust immunosuppressive actions as compared to MSCs that were collected from different sources [86]. MSCs in UCB are rare Nevertheless, can get *in-vitro* amplified, knowing that they can undergo higher amount of cell divisions as compared to MSCs obtained from adult tissue prior to attaining senescence. Ideal storage of cryopreserved UCB tissue or MSCs is needed for autologous utilization. Usually ease of collecting as well as processing make AT the most optimum material that is optimum for clinical studies with the aim of facilitating tissue healing in the respiratory tract. Overall, till now the results collected till now point the clinical efficacy of administration of AT-obtained material for the therapy of respiratory-digestive tract fistulas [87]. Nevertheless, a great requirement for optimization as well as standardization of the protocols for processing of AT for enhancing the reproducibility of the method. Furthermore, the follow up conditions need to be defined properly for better analyzation of the advantageous actions of the treatment.

Most of the acquired clinical knowledge is dependent on the studies that exploit the delivery of unprocessed autologous AT accumulated by liposuction (Fig. 5 and 6) [88]. AT is basically made up of adipocytes , that make upto 90% volume, extra part of the SVF are MSCs, pre

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adipocytes, fibroblasts , endothelial cells, vascular smooth muscle cells, resident monocytes, macrophages, as well as lymphocytes. In view of MSCs possessing a perivascular origin, they contain > vascularised hypodermic AT [86]. Presence of cells having the capacity of differentiation as well as facilitation of regeneration as well as working in a paracrine manner fat has been recently again believed to be besides a simple physical filler for cosmetic surgery methods, a source of medicinal signalling cells as well [20,82,89]. Thus, either as an alternate to or along with lipotransfer, transplantation of AT-obtained cells have been clinically analyzed for treatment of a lot of regenerative reasons [26]. Specifically, Garcia-Olmo, in 2003 1st documented the efficacious treatment of rectovaginal fistula in Crohn's disease by delivery of autologous AT-obtained MSCs [90]. Later, extra phase I-III clinical trials, together including >300 Crohn's patients have been done pointing that cell transplantation is safe as well as efficacious [26,27,29,91]. Identification of MSC cells basically depends on collagenase digestion of fat accumulated by lipoaspiration from the control view point of enzyme dependent protocols cannot be thought of as minimal manipulation as well as hence manufacturing methods get subjected to control applied for Advanced Therapies Medicinal Products (ATMPs) [14,92]. Furthermore, amplification in culture of MSC needs GMP situations, consumes time, along with correlation with heavy cost away controlling burden. Thus ready to use - AT-obtained material have got formed away delivery of mechanically removed AT SVF has been done regards to treatment of various pathologies [93,94]. Specifically, delivery of homogenized AT has proven to be efficacious recently in the therapy of perianal fistulas in Crohn's disease patients giving a method that is proper alternative to MSCs delivery [95,96].

This is thought that same approach of AT transplantation, utilized for the facilitation of healing of perianal fistulas, might be efficiently utllized for managing the fistulas of upper esophageal tract (Fig. 5). Delivery of microfragmented obtained SVF(t-SVF) has lot of benefits as compared to lipotransfer or delivery of MSCs; t-SVF can be derived from lipoaspirate by nonenzymatic techniques with least manipulation with the method being fast as well as cost efficacious as well as can be conducted intraoperatively [93]. In case of t-SVF,the relative amount of MSC/tissue volume is greater as compared to AT, as adipocytes, RBC's, oil as well as aqueous fractions have been removed along with homogenized t-SVF can get delivered via a 25 -G needle , continues to contain as compared to enzymatically obtained SVF, micronized t-SVF) continues to maintain the native ECM, as well as perivascular structures, decreasing induction of anoikinis on transplant [97]. Further less possibility of oxidative stress result from microfat as compared to unprocessed fat, hence enhancing the harmful action on the survival of transplanted cell as well as AT [98,99].

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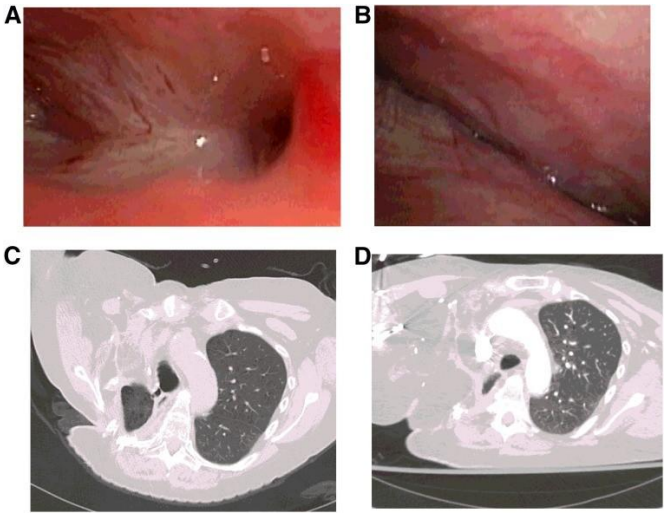

Figure 5: Preoperative imaging showing size and location of fistula, and postoperative imaging demonstrating disease resolution. (A): Preoperative bronchoscopy demonstrating large bronchopleural fistula (BPF) cavity and lateral extension of fistula tracts. (B): Postoperative bronchoscopy (3 months) demonstrating progressive healing of BPF site. (C): Preoperative computed tomography scan demonstrating large BPF with connection to atmosphere (additional axial slices inferiorly). (D): Postoperative computed tomography scan (16 months) demonstrating resolution of BPF.

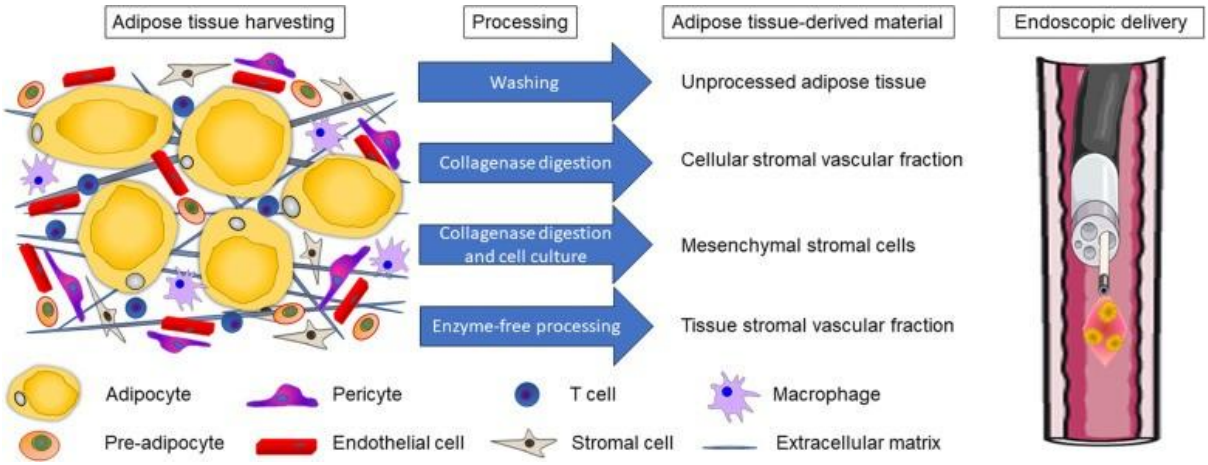

Figure 6: Schematic representation (not in scale) of the therapeutic intervention procedure proposed for the management of respiratory tract fistulas by endoscopic delivery of autologous adipose tissue-derived material.

Lot of preclinical studies evaluated the efficacy of Mesenchymal Stem Cells Therapy for laryngotracheal stenosis [100]. Therapeutic advantages correlated with MSC transplant has chances of liberating soluble factors as well as to liberate extracellular vesicles [82]. Actually delivery of conditioned medium obtained from MSC Cells cultured for treatment might work out by stimulation of resident Bronchioalveolar Stem Cells that supports the tissue regeneration

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in the respiratory system [101]. Furthermore delivery of Adipose Stem Cells derived extracellular vesicles generated by mixing in a MSC mixed Thermoresponsive gel has been demonstrated to facilitate esophageal fistula healing in a thermoattenuated delivery strategy in a porcine model [102]. On this basis the delivery of Mesenchymal Stem/stromal Cells- derived secretome and vesicles has been posited to be a therapeutic approach in a lung injury and acute as well as chronic disease [103]. Significantly micro fragmented human adipose tissue has been demonstrated to enhance the paracrine anti-inflammatory, anti-fibrotic as well as pro-angiogenic properties that aids in corroborating tissue regeneration as compared to cultured MSC Cells [104].

Combining autologous Mesenchymal stromal Cells as well as tissue engineering scaffold is a significant as well as fast evolving strategy in the regenerative medicine scenario, that is probably appropriate for the healing of large sized fistulas as well as partially or long segment defects of the esophagus [105]. The best scaffold needs to be biocompatible along with biodegradable, with a breakdown rate equivalent to the tissue regeneration time. Placing tissue engineered graft has been detailed maximum in preclinical studies, like the utilization of Adipose tissue attached to suture material or suture filament embedded with adipose tissue obtained MSC's has been utilized to promote entero cutaneous fistulas healing or closure in a rat model [106]. Facilitation of esophageal anastamotic leakage healing has got utilized in rabbits by delivery of fibrin scaffold that includes autografting stromal Cells in MSC's [107]. Similarly electrospun grafts seeded with autologous MSC's have been experimented on in remodelling of the pig esophagus after circumferential resection [108]. For overcoming, regeneration of esophagus using scaffold-free biometric embedded in MSC's adequate for regeneration of esophagus that has got formed by with bio-three-dimensional printing, as well as transplanted in rats [109]. Additionally, precise three-dimensional printed patient personalized stent dependent on 3D-reconstruction of the fistula stent designed for management of enterocutaneous fistula is an advanced strategy [110]. Clinical translation of these preclinical studies done on tissue engineering for airway defects has been till now limited but the fast pace of this technology progression in as well as tissue engineering as well as 3D-bioprinting can predict future therapeutic progress [111]. Further it has been known that Mesenchymal Stromal Cells (MSCs) are able to migrate and engraft at sites of inflammation, injuries and tumours, but little is known about their fate after local injection. Thus Rizzo, et al., aimed to to perform MSC tracking, combining *in-vivo* 7-T Magnetic Resonance Imaging (MRI) and histological assessment, following lung injection in a rat model. They injected five lungs with ferumoxide-labelled MSCs and five with perfluorocarbon-labelled MSCs and performed 7-T MRI. MRI acquisitions awa recorded immediately (T0), at 24 hr (T24) and/or 48 hr (T48) after injection. For eachrat, labelled cells were analyzed in the main organs by MRI. Target organs were harvested under sterile conditions from rats sacrificed 0, 24, or 48 hr after injection and fixed for histological analysis via confocal and structured illumination microscopy.

They observed that ferumoxide-labelled MSCs were not detectable in the lungs, whereas they were not visible in the distant sites. Perfluorocarbon-labelled MSCs were seen in 5/5 injected lungs at T0, in 1/2 at T24, and in 1/3 at T48. The fluorine signal in the liver was seen in 3/5 at T0, in 1/2 at T24 and in 2/3 at T48. Post-mortem histology confirmed the presence of MSCs

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inthe injected lung. Thus concluding that Ferumoxide-labelled cells were not seen at distant sites; a linear decay of injected perfluorocarbon-labelled MSCs was observed at T0, T24 and T48 in the lung. In more than half of the experiments, perfluorocarbon-labelled MSCs scattering to the liver was observed, with a similar decay over time as observed in the lung [112].

Conclusions

Thus one might come across fistula of the respiratory tract forming secondary to adverse events following surgical procedures, trauma along with foreign body accidentally getting ingested or caustic intake or occasionally might be congenital. The Fistulas that are small sized measuring under 2 mm usually heal on their own, whereas large ones might be correlated with strong even life impinging complications. After lot of case reports review it was gathered that endoscopic local administration of Adipose tissue-derived Stem/ Stromal Cells (ASC'S) or MSC's might depict a partially invasive as well as relatively safe method of treating these fistulas as an alternate option to extensive surgical procedure. Another probable approach that might be a future advancing is to administer micronized AT, that can get retrieved with least manipulation [93]. Nevertheless, lot of work still needs to be conducted before one can finally translate these clinically competitive as well as tissue based therapies to treat these Fistula of the respiratory tract .Specifically, standardization of these methods, as well as best clinical trial design formatting along with guiding in relation to follow up evaluation are required for analysis of the blockade of the fistulas in cancer cases.

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