MiniReview Article

Biomaterials – Novel Advances in Nasal Medical Implants, 3D Printing Applications

ABSTRACT

The scope and applications of biomaterials have spread out throughout a broad spectrum. In pharmacy particularly, biomaterials are an attractive choice because they can be modified to decrease toxicity, increase the targeting ability among many other aspects of drug delivery. Extensive studies have led to the development of many metal-based, ceramic, biocompatible and biodegradable biomaterials for medical purposes among many others. Ear, nose and throat complications, like many other disciplines, are exploring the potential applications of biomaterials. The utilization of 3D printing in this discipline is a very novel research subject with infinite potential. Personalized and customized nasal implants are a great option to increase patient compliance and 3D Printed accurate anatomical structures are rendered to be effective tools of learning. One of the biggest disadvantages of biomaterial-based implants is the formation of a thick fibrous capsule formation around the implant, others being breakage, soft tissue loss and so on. Regulatory aspects are less explored for nasal implants. 3D printing is a unique technique that allows for a high degree of customisation in pharmacy, dentistry and in designing of medical devices. Current research in 3D printing indicates towards reproducing an organ in the form of a chip; paving the way for more studies and opportunities to perfecting the existing technique. In addition, we will also attempt to shed light on the impact of 3D printing in the COVID-19 pandemic.

Key words: Biomaterials, 3D Printed biomaterials, 3D printing in otorhinolaryngology, 3D Printed nasal implants, 3D Printing biomaterial Regulatory aspects

INTRODUCTION

The concept of biomaterials can be found in the middle of various subjects like chemistry, materials science, surface science, biology, medicine and many more[1]. The field, since its discovery and introduction has been on a constant climb in terms of field of research interest, creating many branches, novel ideas and applications along the way.

If a biomaterial is to be define
d, "a non-viable material used in a medical device, intended to interact with biological systems" would be the most commonly used definition.[1][2]
Biomaterials are a result of constant collaborative work between engineers, biologists, clinicians and physicists for more than sixty years [3][4].

1.1 Rationale for the requirement of biomaterials in medicine:

The need and applications of biomaterials in the field of pharmaceutical sciences are described in Figure 1.[3][5–9][10–15]

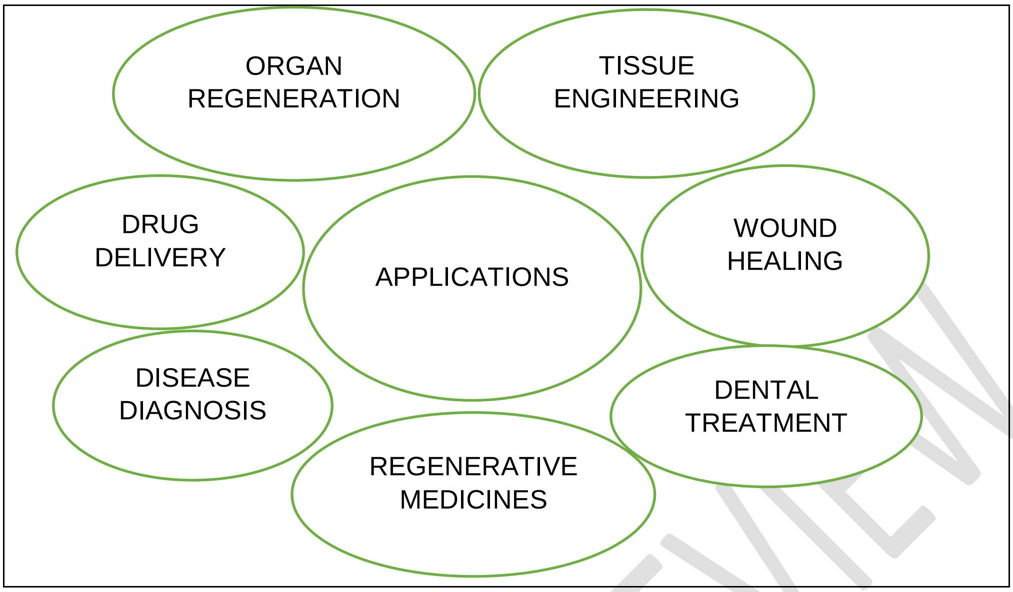

Figure 1: Applications of Biomaterials in Pharmaceutical sciences

1.2 Biomaterials in implants

1.2.1 Brief historical background

Implants for medical use have evidence to have been in use for at least two thousand years. The modern era of implants started when a British ophthalmologist named Harold Ridley made an observation on spitfire fighter pilots in the 40s, when he observed that the accidental implantation of a plastic shard healed without complications[1]. This led to the invention of a lens for the eyes.

1.2.2 Mechanism of wound healing:

In order to understand the process that occurs *In vivo* following implantation, it is important to understand the wound healing process. Wound healing is a complex process that involves many mechanisms. The main four phases of wound healing are represented in Figure 2, and the other mechanisms occurring in between these phases are discussed.[16]

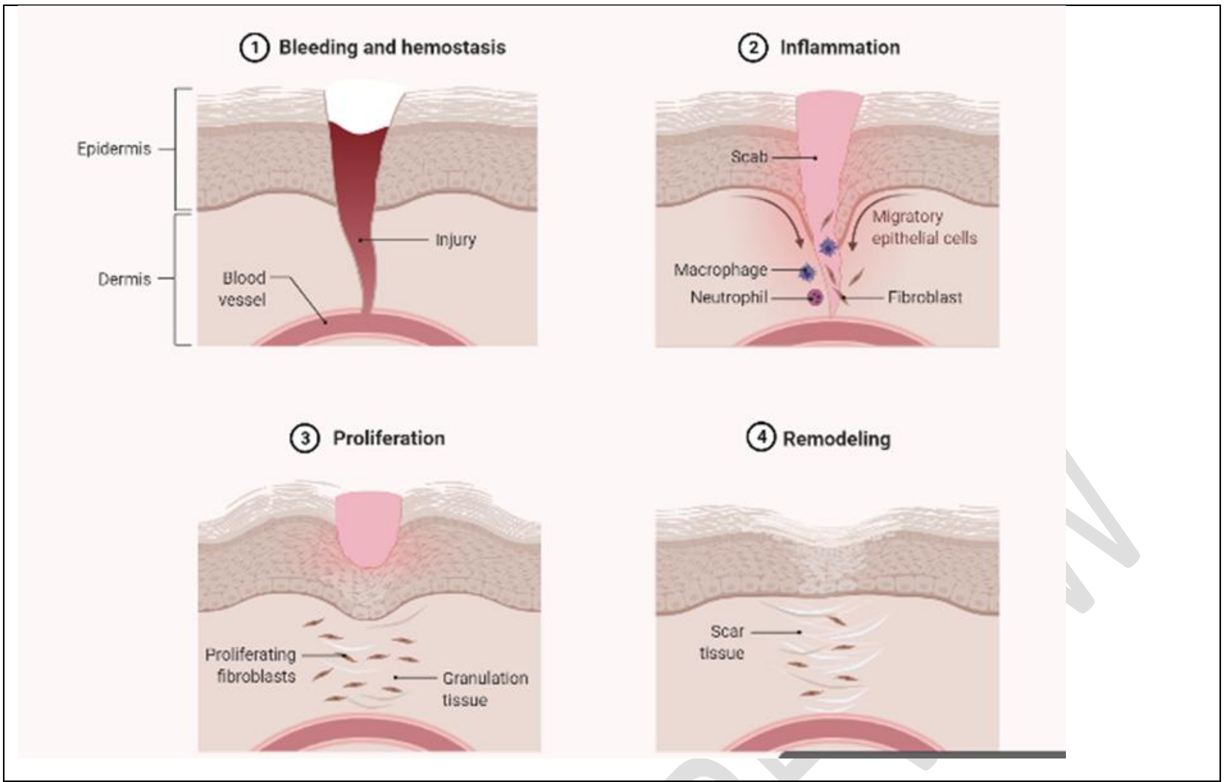

Figure 2: Mechanism of wound healing

1: An immediate surge in blood flow to the injured area. Blood clot formation due to the entrapment of platelets by activation of fibrinogen to mesh like fibrin network.
2: Cytokines and growth factors attract WBC's and Neutrophils, monocytes differentiate into macrophages and accumulate at the site to clean out any bacteria, dead cells and other foreign materials and then the conversion of the blood clot into a highly vascularized granulation tissue occurs.
3: Extracellular matrix (ECM) replaces granulation tissue.
4: Either complete tissue architecture restoration; or replacement of granulation tissue with scar tissue occurs.

1.2.3 Foreign body reaction

Foreign body reaction, although a boon to protect the body from potential harmful foreign bodies, is rendered more harmful when it comes to implants. A fibrous capsule form around the implant made of biomaterial which hinders the healing process. This points out the enormous amount of development that is needed in the designing of biomaterial implants. Foreign body reaction is slightly different than wound healing mechanism. The same is represented in the figure 3.[16]

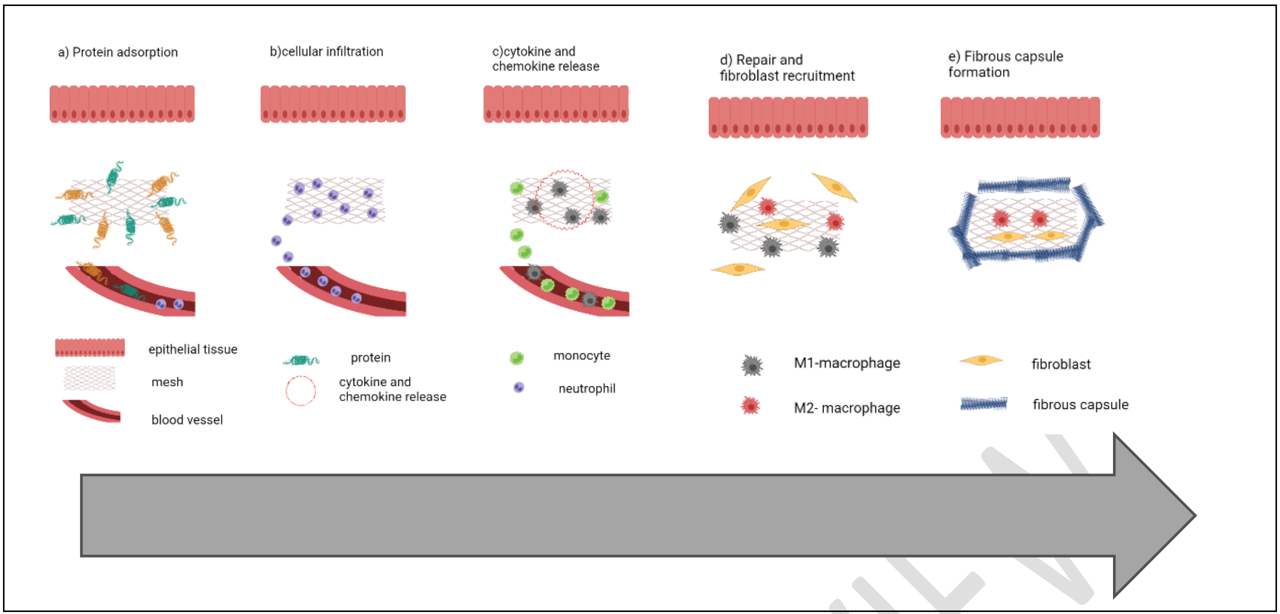

Figure 3: Foreign body reaction to a biomaterial-based implant

From Figure 3,
A) Protein absorption.
B) Cellular infiltration.
C) Interrogation and attack by neutrophils, then macrophages.

D) Giant cell formation, Cytokine release.

E) Thick, Avascular capsule made of collagen- Around three weeks after implantation.

2. Biomaterials in implants- Current advances

Many people from around the globe require prosthesis, implants and drug eluting devices due to trauma, external injury and to prevent oral intake of drug every day. Implants can also be designed to hold the drug and release at a constant rate for longer periods of time. The main reason for the failure of implants is the rejection due to foreign body response. Hence, extensive research is being carried out to make the biomaterials more biocompatible. Many studies are being undertaken to make the polymers biodegradable in order to avoid secondary procedure to take the implant out, in case if it is a drug eluting type, which requires to be in the body for only a short period of time. The table 1 summarises usage of biomaterials in various disciplines in medical field.

Table 1: Biomaterials and their intended use in various disciplines in medical field

Sl no	Area of research	Biomaterials used	Uses/intended applications	Reference
1	Cardiovascular	Polypropylene, Polyamide, among others.	Pacemakers, an assisting device for left ventricle	[17] [18]
2	Orthopaedic	a. poly(aryl-ether-ether-ketone) (PEEK) Biomaterials. b. Metallic- cobalt alloys, titanium alloys, Magnesium alloys among others.	a. Extending the longevity as compared to existing traditional biomaterial implants b. cobalt alloys show better strength and better resistance towards corrosion. Titanium alloys offer better biocompatibility and corrosion resistance whereas, magnesium alloys are third generation biomaterials designed to improve healing rate of	[19][20][21][22][23][24–26] [27] [28]

			fractured bone and are bioresorbable.	
		c. Biodegradable polymers: polylactic acid (PLA), poly3-caprolactone (PCL) and others.	PLA has wide array of scopes. From sutures to biodegradable implants. It is compliant with 3D printing. PCL can be stretched and pressed, it is biocompatible and biodegradable and is used as a drug delivery system.	[29][30]
		d. Ceramics-alumina, zirconia, bioactive calcium hydroxyapatite, bio glass and others.	d. Alumina's inertness is attractive in the fabrication of orthopaedics, Zirconia is used in total hip prosthesis, Calcium hydroxyapatite shows better Osseo integration and from bio glasses, microspheres and porous implants can be produced.	[31–33][34]
		d. Biodegradable/ bioresorbable ceramics- tri calcium phosphate	Bone vacuum fillers (patented) In a study by Cutright and others showed a very good bone growth and re-formation of bone marrow in rats, 48 days after surgically implanting a bone replacement.	[35][36]
3	Plastic surgery	Silicone, polypropylene, polydimethylsiloxane, Polyethylene terephthalate and many others	Breast implants, lip implants, cheek, jaw and chin implants	[1]
4	Trauma, spinal	i) Nylon 6-10, polysulphone (PS), polybutylene terephthalate (PBT), poly(aryl-ether-ether-ketone) (PEEK) among others. ii) Polyaryletherketones (PAEK)	i) Owing to their high biocompatibility and high-performance, they show good potential as fracture fixation devices and composite hip stem development. ii) For the treatment of back pain due to spinal instability or degenerative disc disease.	[19][37]
5	Dental implants	Polymethylmethacrylate, Titanium alloys	Dental implants, dentures.	[17][38]
6	Ear, nose, throat	Parylene, liquid crystal polymer, silicone, polylactic glycolic acid (PLGA) and others.	Nasal implants, cochlear implants, stapes implants and others.	
7	Orbital implants	a. Autologous- autologous tissues b. Polymeric-Silicone, polyacrylamide hydrogel,	a. As a wrapping material to increase the implant biocompatibility. b. Highly biocompatible, inexpensive orbital	[39]

		Polyethylene, PMMA among many others. c. Ceramic- Glass, Bioactive glass, Alumina and others. d. Composite- Teflon/ Carbon fibres, Silicone/Alumina and others. e. Magnetic.	implants. c. decreased complication, more mobile prosthesis. d. To increase the success rate of the implant. e. Integration of implant and prosthesis by sandwiching the conjunctiva between the two elements to impart better movement.	
8	Hard tissue replacement	Hydroxyapatite (HAp) composites and ceramics.	Potential application in hard tissue replacement implants.	[40]

2.1 Biomaterials in Otorhinolaryngology

After discovering the enormous amount of personalisation potential offered by three-dimensional printing, the said technique has successfully made its way to Otorhinolaryngology. From teaching anatomy and training for surgery using 3D Printed prosthesis based on high resolution CT images which gives highly accurate anatomical structures, to overcoming the otology related defects arising from defective ossicular chains and to 3D Printed scaffolds for correcting the septal perforation, 3D printing finds an enormous amount of application in otorhinolaryngology[41][42–46]. 3D replicas of patient in full scale facilitates the surgeons to fully understand the problem, even conduct a practice surgery to improve skills, decrease the error margin to get better results. An effort has been made to 3D print a splint for a lethal condition of bronchomalacia with promising outcome[47][48]. 3D tissue printing has been a boon in the reconstruction of damaged ear pinna due to a trauma or defects seen post-operation[49] and many other conditions such as anotia where the external ear pinna is completely absent. The studies on various biomaterials used in ear, nose and throat for various purposes are enlisted in the table 2.

Table 2: Biomaterials for ear, nose and throat related complications

Sl No.	**Study**	**Intended target site**	**Biomaterial(s) utilised**	**3D Printing utilization**	**References**
1	Creation of biomimetic microstructure of auricular tissues by proliferating the chondrocytes and perichondrial cells in a continuous flow bioreactor, shadowed by cultivation in an appropriate medium.	External ear	Polypropylene bioreactor wells for creating bi-layered constructs.	Not utilized	[50]
2	Printing of external ear shaped structure.	External ear pinna	Norbornene-modified poly (glycerol sebacate) (Nor-PGS)	Utilised	[51]
3	Model scaffold design for complete ear reconstruction using a three-dimensional printing method.	Auricular reconstructio n	Polycaprolactone (PCL)	Utilised	[52]
4	Indirect utilisation of prototype for final prosthesis.	External ear	Powdered gypsum	Utilised	[53][54]
5	Custom 3D Printing of ear ossicular prosthesis	Middle ear	Not available	Utilised	[55]
6	Fabrication of biomimetic	Middle ear	Hydroxyapatite	Utilised	[56]

	ceramic ossicles.		and PCL		
7	Fabrication of human middle ear and potentially control the transmission behaviour.	Middle ear	White polyamide powder PA2200 (PA)	Utilised	[57]
8	Custom middle ear prosthesis.	Middle ear	Polycaprolactone	Utilised	[58]
9	Transparent temporal bone and vestibulocochlear organ fabrication.	Inner ear	White resin	Utilised	[59]
10	Fabrication of nose shaped 3D printed structures.	Nose	Norbornene-modified poly (glycerol sebacate) (Nor-PGS)	utilised	[51]
11	3D printing and validation of osteomeatal complex and frontal sinus.	Sinus	Not available	utilised	[60]
12	Bioresorbable Airway Splints for Severe Tracheobronchomalacia.	Throat	Polycaprolactone, Hydroxyapatite	Utilised	[61]
13	Stent for tracheobronchial related complications.	Trachea	PCL, TPU and others	Utilised	[62][63]

2.2 Nasal drug eluting implants- a barely explored research area with infinite potential

Over the years, to increase the effectiveness of the result of endoscopic sinus surgery (ESS), many biomaterials have been discovered to be utilised in rhinology. Some of them are absorbable and some others are not. The polymers are aimed to reduce post-operative inflammation as well as to increase the rate of healing process. Some biomaterials like Hyaluronic acid, Chitosan, Fibrin glue, Collagen and many others have been extensively studied for this purpose but due to contradictory results reported in different studies, there is no conclusive evidence of one polymer being superior over the others.[64]

Biomaterials find application in various areas and have different functions, which are represented in table 3

Table 3: Application and functions of biomaterials in rhinology[64]

	Mostly positive	**Mostly negative or neutral**
Mostly positive	Chitosan Fibrin glue PVA in latex glove finger	Hyaluronic acid Thermosensitive poloxamer
Mostly negative or neutral	PVA Gelatin foam with thrombin Flowable gelatin-thrombin admixture Oxidized cellulose powder MPH Polyurethane foam	Gelatin film Gelfoam CMC

Various studies are being undertaken in various fields of rhinology such as nasal reconstruction, Nasal Septum Perforation reconstruction, reconstruction of nasal cartilages and subchondral bone and many more. Some of these studies are represented in table 3.

Table 4: Biomaterials in some of Rhinology related studies

Sl no	**Study description**	**Biomaterial(s) Under study**	**3D printing**	**Authors**	**References**

1	Examining the biocompatibility and absorption profile of a nasal implant using Ovine model.	Poly (L-lactide-co-D, L-lactide) (PLA)	No	Rippy and co-workers.	[65]
2	An implant for nasal augmentation and for nasal surgeries such as septoplasty and rhinoplasty.	Polycaprolactone (PCL)	Yes	Park and others.	[66]
3	Developing a septal cartilage implant for the treatment of nasal septal perforations.	poly-L-lactic acid (PLLA)	Yes	Rajzer and others	[67]
4	Fabrication of electrospun scaffolds for nasal cartilages and subchondral bone reconstruction.	Layered gelatin/PLLA	Yes	Rajzer and others	[68]
5	Fabrication of customised nasal cartilage for augmentive rhinoplasty	Polycaprolactone (PCL)	Yes	Yi and co workers	[69]

Chronic sinusitis is a very pertinent chronic disease and nasal drug loaded implants are a novel application of biomaterials in rhinology, especially for endoscopic sinus surgery (ESS). The idea of nasal implants is that on addition to the existing treatment regimen, a novel implant loaded with a corticosteroid drug is implanted on the site of surgery, allowing a constant rate of release of drug at the site to decrease the inflammation, as well as the design is such that it prevents the closing up of the sinus again due to post-operative inflammation, polyp formation and scar tissue formation, which requires a secondary treatment or surgery. The drug eluting implant should stay at the site of implantation and it should biodegrade within a short span of time to avoid another procedure to take the implant back out. PROPEL^{TM} is one such promising drug eluting nasal implant. The main advantage of nasal implants is that they help overcome the adverse effects caused by oral steroids, as well as help prevent the need for secondary surgical intervention in the long term. [70]

3. Risks and disadvantages of nasal implants [71]

As of now, no known implant has optimum characteristics. The effectiveness of the implant is decreased due to many factors. Some of the disadvantages and risks associated with nasal implants are represented in Figure 4.

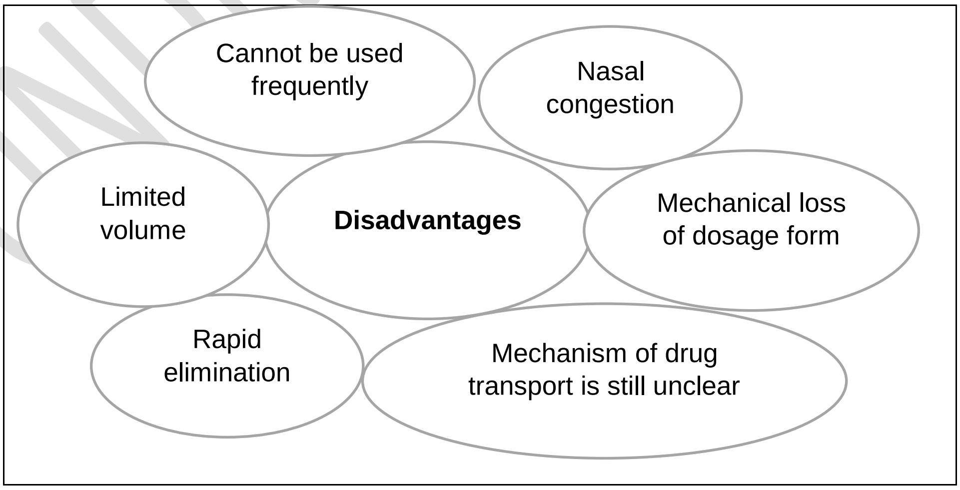

Figure 4: Disadvantages and risks related to nasal implants

4. Future prospect of 3D printing in Otorhinolaryngology:

4.1 Regulatory aspects

With a new application, comes a need for stringent regulatory requirements and Good Manufacturing Practices guidelines. There is a need for a control process for 3D printed medical devices. Some attempts have been made by various regulatory bodies of the world, such as the EU and USFDA in this aspect, which still needs a lot of refinement.[47]

4.2 Integration of electronics into 3D printed implants

In the form of bionics, a group from Princeton has attempted to create a coil antenna by the integration of chondrocytes of the cartilage as well as silver nanoparticles.

4.3 Tissue engineering

The idea behind tissue engineering is to impregnate 3D Printed scaffolds with living cells in order to build very complicated microarchitecture, which remains a very futuristic possibility.

The demonstration of cartilage growth by nasal and ear scaffolds using swine model has been done by Zopf and co-workers. Many studies have pointed towards the excellent cell viability of bio-ink extruded by inkjet or extrusion techniques.

5. CONCLUSION

Biomaterials find numerous applications in various fields of science. They are especially attractive in the field of medicine and pharmaceutical sciences due to their adaptability, biocompatibility and biodegradability. Combining 3D printing with biomaterials makes way for increased patient compliance, thus helping in the betterment of the said fields by increasing the degree of personalisation and customisation. One of the main issues to be tackled with biomaterial implants is the formation of a fibrous capsule around the implant which forms as a result of natural foreign body reaction. Although the usage of biomaterials in otorhinolaryngology is not a novel approach in the treatment regimen, using 3D printed biomaterials can be considered novel. As attractive the 3D Printing in otorhinolaryngology is, there is a need for more defined guidelines and stringent regulatory requirements for the success of this approach. Although some ideas appear to be only theoretically feasible, it is only a matter of time before the most futuristic-looking possibilities become a reality.

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