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Visuo-Ocular Prosthesis and the Road Ahead

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Abstract

Ocular prosthesis has been a popular rehabilitation modality ever since their introduction in 1960s for patients with congenital or acquired ocular defect and patients with conditions like phthisis bulbi or sunken non-functional eye. Various advancements in materials, techniques and technology to fabricate a customized prosthesis including use of implants, Magnetic dilating pupil and others aims to satisfy patient's expectations and improve quality of life. Function however, still remains a challenge when using conventional or modified ocular prosthesis. Concepts of treatment used for ophthalmic patients with poor or complete absence of vision includes retinal prosthesis such as bionic eye, durette implants are promising alternatives for restoring partial vision in cases with interrupted visual pathway. Concepts of biomedical engineering such as optogenetics, photovoltaic stimulation, gene based therapies holds potential for revolutionizing the treatment modalities to restore form, esthetics and function for such patients.

Keywords: Ocular Prosthesis; Congenital; Phthisis Bulbi; Prosthodontics

Abbreviations

BRIP: Boston Retinal Implant Project; BVA: Bionic Vision Australia; ChR2: Channelorhodopsin-2; PRIMA: Photovoltaic Retinal Implant; CRISPR: Clustered Regularly Interspaced Short Palindromic Repeat Technique; STS: Suprachoroidal-Transretinal Stimulation; HR: Halorhodopsin.

Introduction

Opthalmological Defects may vary over a wide spectrum from total loss of entire contents of the eye causing complete blindness to damage to some part of visual pathway causing partial blindness. Based on etiology, treatment options and prognosis, the options for rehabilitation vary from ocular prosthesis to visual prosthesis (Table 1). Rehabilitation of ocular defects to restore form and esthetics thereby contributing to social acceptability of an individual is what a maxillofacial prosthodontist strives for. Anophthalmia is a clinical condition characterized by loss of eye and/or its contents. It may be congenital or acquired as a consequence of surgical ablation of cancers or trauma. Surgical procedures for removal of defective eye are classified as evisceration which involves removal of intraocular contents of globe leaving optic nerve intact, enucleation where removal of entire globe is done with preservation of other orbital contents and exenteration which involves removal of entire orbital contents [1]. Other clinical conditions such as phthisis bulbi or discolored blind eye also require rehabilitation. Loss of vision, visible maxillofacial defect, and increased frequency of eye infections greatly affects patient's ability to interact socially and leads to depression or altered psychology due to loss of part of body [2]. Ocular prosthesis has been a revolutionary development for such patients. Materials like irreversible hydrocolloid elastomeric impression materials are used for impression making with a stock or more often a custom tray. Nowadays, recent various advanced digital modalities like digital impressions and 3D printing are also used. The wax pattern is fabricated either conventionally or using 3D printing. This is then tried in the patient and adjusted, gaze is set, selection of iris using various modalities. The conditions leading to loss of vision are caused by interruption in visual perception at various levels. Based on etiology of loss of vision, anatomically targeted approaches have been tried and approved for management of conditions like Retinitis pigmentosa, macular degeneration, dystrophy, blindness. Ocular prosthesis has seen various modifications in designs, customized as per patients' needs and desires and is now progressing towards visual prosthesis where attempts are being made either to utilize or stimulate remaining structures or implant a bioelectronic system to restore function along with form and esthetics.

Ocular Prosthesis	Visual Prosthesis
Congenital or acquired anophthalmia	Congenital or acquired damage to any link in visual pathway
Enucleation, Evisceration, Exenteration	Retinitis Pigmentosa, Macular degeneration, Choroideremia

Table 1: Ocular vs. Visual Prosthesis.

The aim of this article is to highlight the options for ocular prosthesis, visual prosthesis and a futuristic insight into visuo-ocular prosthesis.

Ocular Prosthesis

Conventional Ocular Prosthesis

Fabrication of conventional ocular prosthesis involves various steps starting from examination of defect site for the negative volume, presence of favorable soft tissue undercuts, extent of defect and remaining structures [3]. This is followed by recording of defect by making an impression using irreversible hydrocolloid or elastomeric impression materials, using a stock or a custom tray or the use of digital technology using 3D printing, the wax pattern fabricated is tried in the patient and adjusted, setting of gaze can be done by various techniques, selection of iris is done either by using stock eye of appropriate size, color and appearance, iris painting method or by digital technology using iris button technique, once satisfactory outcome is achieved in wax pattern, it is flasked, customized by stains and pigments, finished and delivered to the patient (Figure 1). A review article highlights the history of ocular prosthesis and the futuristic outlook but integrating vision in the prosthesis is still a field which requires development [4].

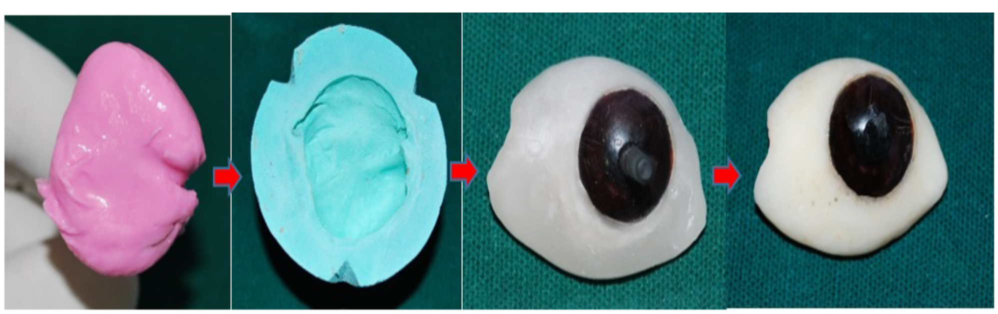


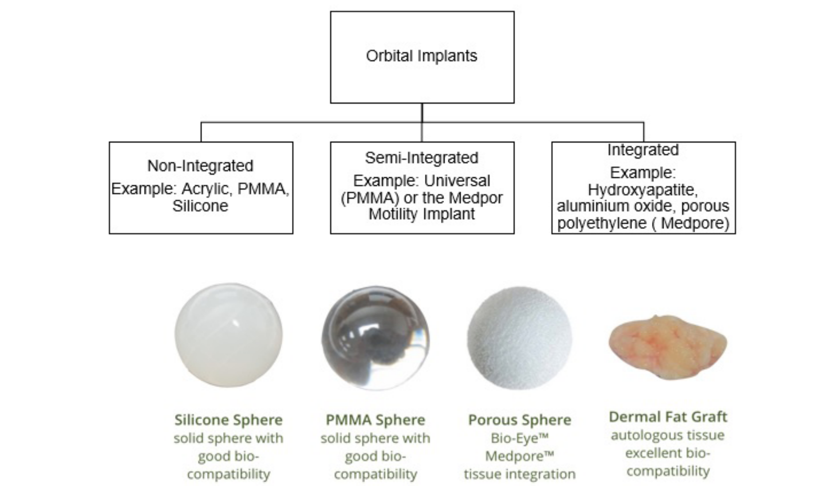
Figure 1: Processing of Conventional Ocular Prosthesis.

Silicone Ocular Prosthesis

Maxillofacial silicone has been widely used in rehabilitation of maxillofacial defects. Its use, however in form of ocular prosthesis is limited. The material has been patented by Singer and Singer Matthew, Memphis, TM, USA (US 2008/0046078 A1) in which the prosthesis included a white-tinted silicone for the posterior sclera portion formed using molding process. Authors have also attempted fabrication of ocular prosthesis using maxillofacial silicone and have achieved satisfactory results [5].

Orbital Implants

Orbital Implant is placed to restore the lost orbital volume following enucleation and evisceration. Various kind of orbital implant materials have been tried including autologous materials like dermal fat grafts, cortical and cancellous bone grafts with temporalis muscle flap, thigh flaps, post-auricular skin grafts and others. Polymeric implants like silicone non porous spherical implants, PMMA, polyethylene, expanded polytetrafluoroethylene (Gore-tex) spherical implants, ceramic implants including glass, hydroxyapatite, alumina, bioactive glass, teflon based composite implants, surface coated implants. (Figure 2). In conditions requiring evisceration, the extraocular muscles remain attached to scleral implants and do not require reattachment. However, in enucleation, reattachment of muscles is required. According to Baino F, et al. [6] uses of compliant materials such as composites or moldable hydrogels are more viable option for orbital implants. Two most common issues with Orbital implants include migration of implant and retention of ocular shell to implant.

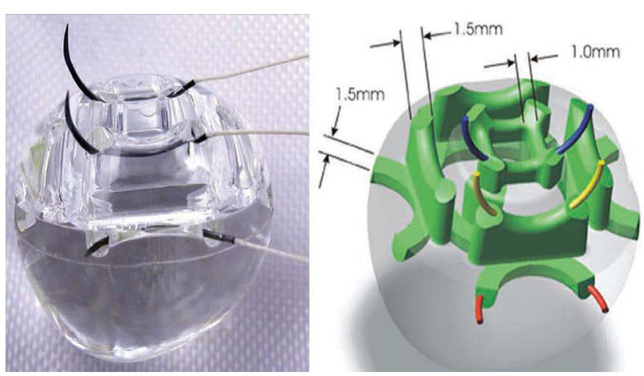


Source: Adapted from: https://nweyedesign.com/eyes/eye-conditions/

Figure 2: Types of Orbital Implants.

Durette Implants

To overcome the problem of migration and enhance stability of orbital implants, the residual muscles can be utilized by use of Durette Implants. These are smooth surfaced PMMA implants with a network of 20 interconnected tunnels which permit direct soldering of eye muscles and allow new tissue to be formed thereby helping implant integration. Used for enucleation, evisceration and secondary implantation (Figure 3) [7].



Source: Adapted from Durette JF (2005)[8]

Figure 3: Durette Implants.

Surface Coated Implants

Surface coatings have the potential to induce fibro vascularization allowing integration of implant within the socket. You, et al. attempted use of alumina and hydroxyapatite to stimulate fibro vascularization. Jin, et al. used a biomimetic coating over porous Hydroxyapatite. They used a layer by layer technique using collagen and heparin to modify the surface of implant and produce successful results [9].

Magnetic Implants

These implants allow the retention of prosthetic shell over the surface of implant using magnets. Two magnets are used, one on the prosthesis on lateral side and the other within the frontal area of the implant. However, due to excessive magnetism it may induce complications like ectropion and superior sulcus deformity. Also, the increased chances of corrosion of magnets due to presence of continuous moist environment and ability of PMMA to absorb fluid overtime act as a major hinderence for using them as a common modality [9].

3D Printing

Authors have used semi-automated techniques in which impression of defect site is made, light intensity 3D scanners are used to obtain a 3D model data. Digital light processing 3D printer are used for additive manufacturing of prosthesis using polymer resin [10].

Miscellaneous

Many practitioners have proposed various techniques for incorporating dilating pupil using polarizing films and spectacles, blinking eye using orbicularis oculi, dynamic ocular prosthesis using a solar cell, photochromatic pupil, magnetic interchangeable pupil, and use of 0.3mm nanoretina to improve the fabrication of ocular prosthesis [11-13].

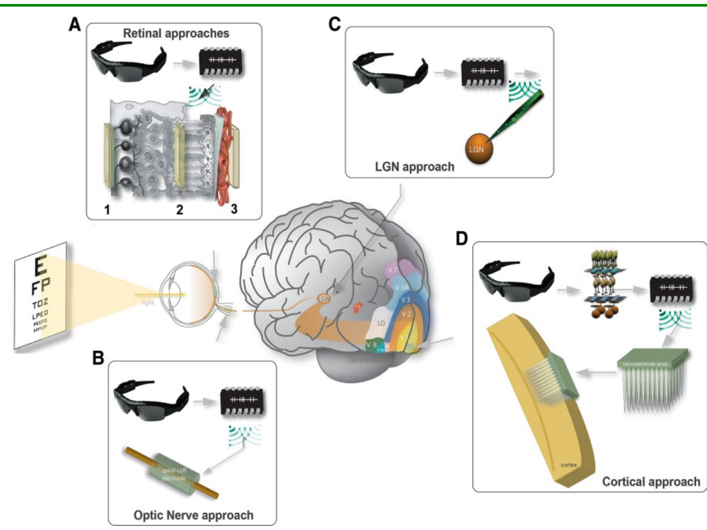
Visual Prosthesis

Bionic Eye Prosthesis

Bionics is the use of microelectronics and semiconductor devices into biological applications [14]. Bionic eye or retinal prosthesis system consists of an external camera that is integrated to a pair of eyewear. When the image is captured, signals are sent to externally worn processing unit. The processed data is received by the receiver device implanted in the patient and to the retinal implant placed at back of retina. This causes stimulation of photoreceptors present in retina and via optic nerve impulses are transmitted to visual center of brain and image is formed and interpreted (Table 2). Main approaches towards visual prosthesis based on the site and their action to maintain restore integrity of visual pathway are highlighted in Figure 4.

Camera attached to eyeglasses	Processing unit	Receiver device	Retinal implant at back of eye	Electric impulses via visual pathway	Vision processing centre of brain

Table 2: Functioning of Bionic Eye.

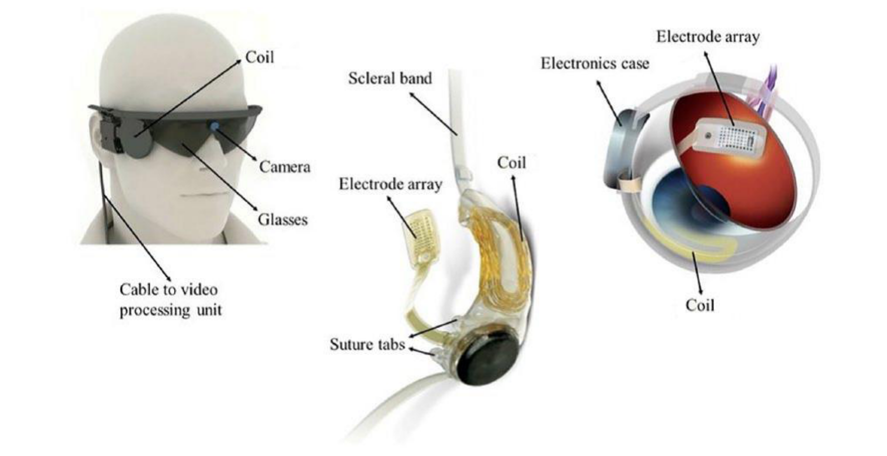


Source: Adapted from Fernandez E (2018) [15].

Figure 4:

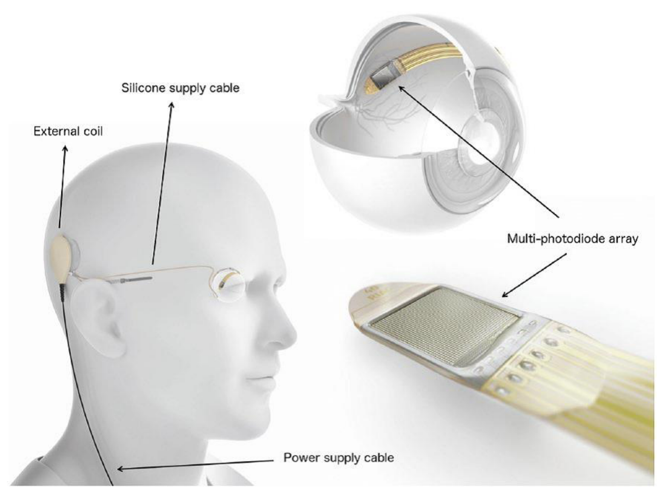
A. Cross section of retina and method of stimulation: 1, Epiretinal; 2, Subretinal 3, Suprachoroidal.
B. Optic nerve based prosthesis.
C. Lateral geniculate nucleus of the thalamus (LGN) based visual prosthesis.
D. Cortical approach.

In 2013, Argus II retinal prosthesis (Second sight medical products, Inc.) first bionic eye received FDA approval for human use. It is an epiretinal device that contains 60 electrodes and bypasses degenerated photoreceptors to restore vision (Figure 5) [16]. Other epiretinal systems include Intelligent Medical Implant system. IRIS II and EPI-RET3 Retinal Implant System.



Source: Adapted from Second Sight Medical Products, Inc., Sylmar, CA, USA
Figure 5: The Argus II Retinal Prosthesis System.

Subretinal implant systems include Alpha IMS (Retinal Implant AG, Reutlingen, Germany) using 1500 microphotodiodes to elicit visual perception (Figure 6). Others include Boston Retinal Implant Project (BRIP), artificial silicon retina with wireless retinal stimulation using ambient light and PRISMA.



Source: Adapted from Retina Implant AG, Reutlingen, Germany
Figure 6: The Retina Implant Alpha AMS System.

Subchoroidal Prosthesis includes Bionic Vision Australia (BVA), suprachoroidal-transretinal stimulation (STS) system and others [17].

Future Perspective

Optogenetic Strategy

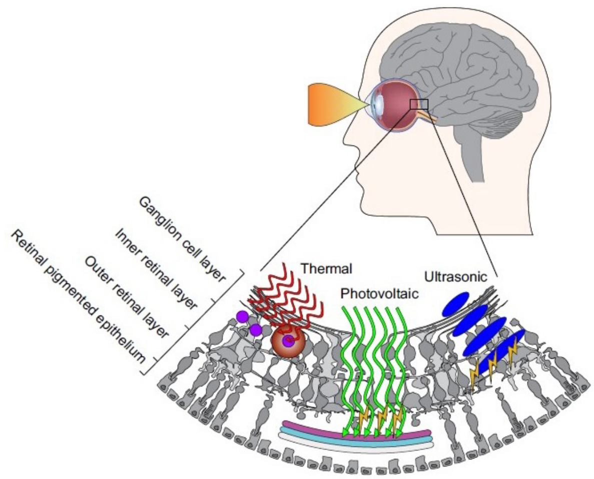
This technique involves genetic photosensitization of neural tissue. This may be achieved by:

- Light sensitive ion channels
- Light sensitive charged pumps
- Light sensitive signal transduction pathway
- Genetically modified receptors with optically activated ligand is chemically attached

Serotypes of lentivirus or adeno associated viral vectors with specific target cells are incorporated with variants of ChR2 (channelorhodopsin-2) and HR (halorhodopsin). The advantage of this therapy over visual prosthesis includes no invasive surgery for placement of implant as for bionic eye prosthesis, more biocompatibility. The specifically modified viral vector is injected and appropriate stimulating pulses are applied for activation. As it targets the biological system by genetic photosensitization of neural tissue, the vision is expected to be better than other systems. However ethical clearance and toxicity of viral vectors are some limitations [18].

Photovoltaic Stimulation

This technique uses implantation of photovoltaic sub-retinal implants to restore light response in degenerated eye (Figure 7).



Source: Adapted from Ghezzi D (2015)[19]
Figure 7: Photothermal, Photovoltaic and Ultrasonic stimulation.

It includes-

- Photothermal stimulation uses infrared laser pulses or black u particles which act as photoabsorbers, absorbing light and converting it to heat which is used for stimulation of cells.
- Photovoltaic stimulation utilizes silicone or conjugated polymer photoresponsive surfaces which generate a charge upon absorption of light and stimulates the cells in vicinity.
- Ultrasonic stimulation ultrasonic waves are used for excitation of retinal neurons [19].

Example includes Photovoltaic Retinal Implant (PRIMA) bionic vision system (Pixium Vision S.A.) is a subretinal system which contains a 1-mm-wide hexagonal chip, with 142-pixel cells having thickness of 30-μm-thick. Visual information is perceived using a pair of customised glasses. This photic energy stimulates photodiodes which in turn generate an electrical current, polarizing the adjacent neuronal tissue.

Gene Therapy

Human eye is considered as an ideal target for gene therapy due to compact size and easy accessibility. This therapy is mainly used for retinal disorders, inherited diseases and some non-inherited disorders. Patients suffering from phthisis bulbi and visual impairment leading to partial or total loss of vision and shrunken ocular contents often seek fabrication of a custom ocular prosthesis. Research has reported pathogenic variant in MARK 3 gene for progression of the condition. Blindness is also caused by a multigenetic mutation, repair of genome using clustered regularly interspaced short palindromic repeat technique (CRISPR) is under clinical development. Electroporation technique can be used to guide an RNA-guided Cas9 nuclease to cross cell membrane and edit targeted DNA. However ethical concerns and clinical trials are required to implement these techniques for treatment of degenerative diseases of retina. There use for traumatic defects is limited.

Stem Cell Therapy

Human eye consist of various cells, damage to any of these can cause defect in vision. Some of these cells are pluripotent with the ability to divide and regenerate the damaged cells. As per studies- Ciliary body, iris, sclera derived stem cells are in animal trials for replacement of degenerated photoreceptors, limbal, corneal and conjunctival stem cells are used for surface reconstruction in human trials. limbal stem cells have the ability to generate epithelium through centripetal migration. (Rama P, et al.) [20] in a 10 year clinical follow up, limbal cells showed promising results in corneal regeneration in 70% of cases. Adult mesenchymal cells derived from stroma (sMSCs) improve expansion and colonogenicity of limbal cells and help in self-renewal. Trabecular meshwork, orbital, scleral stem cells needs to be explored [21]. Though most of the gene therapy and stem cell therapy are for degenerative changes of eye, However development of these techniques can reduce the requirement of surgical enucleation or exenteration to preserve remaining healthy tissue to regenerate the eye.

Augmented Reality

Virtual Reality is an advanced computerized interface which permits user to navigate in a tridimensional environment in real time. Augmented Reality allows integration of virtual objects with real physical environment using multisensory equipment like high resolution camera or sensors. Use of augmented reality eyewear, auditory feedback, virtual reality, haptic clues and others have been tried for restoring partial loss of vision for cases like Retinitis pigmentosa and macular degeneration. However, clinical validation of these techniques is required to implement them as treatment alternatives [22-24].

Summary

Regenerative Prosthodontics has spread its wings to implant dentistry to regenerate lost bone to achieve sufficient bone structure for implant placement [25]. Regenerative maxillofacial prosthodontics is to utilize the regenerative therapies for benefit of restoration of function as much as possible. Ocular prosthesis with the limitations of being removable prosthesis, prone to infections, can only help in restoration of esthetics and maintenance of form. A summary of various options including contemporary, conventional and futuristic are summarized in Table 3. Use of a multidisciplinary approach in possible clinical scenario can provide a holistic therapy to patients at their best interest. Challenges in integration of various visuo-ocular prosthesis in patient care include integrating the concepts of engineering into the biological system and restore the lost function. These include technological limitations, ability to restore high resolution visual acuity, prosthetic biocompatibility and others [26]. The integration of these engineered prosthesis with the neural pathway so that it can restore function is the major challenge. Presently, advancements have led to use of artificial intelligence for improved Bionic systems. However, area of biomedical-engineering needs to be developed to explore clinically and ethically possible treatment modalities, combination of various visual implants, bio-prosthetic techniques, neuromodulation and regenerative medicine which would open newer horizons for patient care and successful rehabilitation with functional prosthesis.

Visuo-Ocular Prosthesis		
Conventional	**Contemporary**	**Futuristic**
Glass eye	Prothesis	Optogenetics
Stock shell	Epiretinal	Photovoltaic stimulation
Custom made acrylic eye	Subretinal	Gene therapy
Modifications-	Suprachorodial	Stem cell therapy
Hollow prosthesis	Chorodial	Augmented Reality
Blinking eye	Durette implants	Nanotechnology
Dilating/Magnetic interchanable pupil	Orbital implants	
UDMA based	3D Printing	

Table 3: Contemporary, Conventional and Future of Rehabilitation of Eye.

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