Chapter

Future Prospects of Organ Transplantation

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Abstract

The gap between organ demand and supply is an universal problem in organ and tissue transplantation therapy. The gap is growing in spite of efforts spent in medical, educational, social areas and mass media support. This reality has created the need for completely new therapeutic alternatives for the management of end-stage organ disease. The present research should continue in future aiming to discover systems and devices capable of totally replacing the traditional transplantation. On the other hand, a different progress in underway in transplantation. The indication for solid organ transplantation is to save life and promote quality of life. The new developing transplantations of composite tissue, uterus and face are performed with completely different indications. Facial defects caused by various insults cause serious functional and esthetic disorders, psychological and social problems. Facial transplant surgery is accomplished to overcome such problems. Uterus transplantation is emerging as an alternative to female infertility. Transplantation of composite tissue includes different organs. The main purpose of composite tissue transplantation is to restore reduced or completely lost functions and to increase the quality of life. Nerve regeneration must occur as a consequence of transplant to regain sensory and motor functions. It appears that the future of transplantation involves developments in two main streams; invention of completely new tools for solid organ transplantation and advances in the transplantation of different organs including uterus, face and composite tissue.

Keywords: composite tissue, facial, solid organ, transplantation, uterus

1. Introduction

The idea of replacing a malfunctioning diseased organ by the same organ dates back to antiquity, but major inventions and successful practice of transplanting solid organs have occurred in the second half of the 20th century. Pioneering work in human-to-human organ transplantation started in the 1950's and in following decade. Since then, improvements in surgical techniques, better postoperative management in the intensive care units, the introduction of brain death concept and its beneficial effect of enlarging the donor pool, a better understanding of the natural course of the various diseases leading to organ failure, new immunosuppressive agents have all contributed to transplantation activities. Today organ transplantation is a definitive treatment for an end-stage disease with low morbidity and mortality rates. Efforts directed to the education of medical staff and the general public, controlled system of financial payment for the living donor, similarly gifting to deceased donor's family, extending the donor criteria,

acceptance of paired organ donation, organ donation campaigns and media support are among the other measures to promote transplantation.

2. Discussion

Organ transplantation is a definitive and curative treatment for end-stage organ disease. The preferred source of organs is from the deceased. Particularly in developing countries, organ harvesting is more from living donors. Although the morbidity and mortality rates for living donors are extremely low, completely healthy individuals are exposed to medical, surgical, psychological and sometimes to economic risks.

While organ transplantation will continue to be the definitive treatment for the present and foreseen future, the statistical evidence revealing the gap between demand and supply and the experience of the global medical community has clearly shown that even the centers with best figures of organ supply are far from meeting the growing need. Therefore the scientific world has arrived at a point to think and search for alternative solutions and different therapeutic modalities for end-stage organ diseases. An overview of the present state of organ transplantation suggests that future interest and work will be focused on three major points:

a. increasing the frequency, safety and outcome of traditional transplantation activities. This would cover research to discover ways of expanding donor pool, especially cadaveric, and innovative work for longer and safer preservation of harvested organs and methods that would help to obtain better graft and survival rates. Weissenbacher and associates have reported the beneficial effects of ex-vivo/ex-situ hypothermic and normothermic machine perfusion in the transplantation of liver, kidney, intestine and pancreas. The beneficial effects include viability, organ utilization and improved initial graft function. The authors have considered the potential role of normothermic regional perfusion to re-condition donors after circulatory death organs before retrieval. Machine perfusion presents superiority over the traditional cold preservation method. Since organ preservation is an essential aspect of the transplantation process, these developments provide hope for better organ quality and longer viability [1].

In solid-organ transplant, cell therapy is used as an immunomodulation therapy or as a functioning graft. The beneficial effects of cell therapy in solid-organ transplantation are long-term kidney allograft survival and avoiding the well-known adverse effects of immunosuppressive drugs. Cell-based therapy in solid organ transplant is indicated for the treatment of ischemic reperfusion injury, for the prevention of chronic allograft nephropathy and induction of long-term allograft tolerance. Immunoregulatory cells act when it is necessary for immune suppression and there are several mechanisms by many pharmacologic targets [2].

b. developments in relatively new, emerging transplantations including the uterus, face and composite tissue. Such transplantations are expected to be performed with increasing frequency.

c. the ultimate goal of producing completely new devices or bioartificial organs which eventually would replace organ transplantation and maintain immunosuppressive free life. Nowadays may be considered as the transition period where devices can at least partially take over the functions of the failing organ and bridge patients to transplantation.

3. Xenotransplantation

Xenotransplantation, not a new concept in this field, is a controversial issue. Xenotransplantation which means transplantation of an organ, tissue, or cells between two different species, has regained attention because of advantages such as rich source, the chance of planned, and multiple transplantations. The main disadvantages are the possibility of animal disease transmission, immunologic, and physiologic differences.

In the sixteenth- century animal blood has been transferred to humans. Skin, corneal and blood vessel xenotransplantations were the early attempts. The kidney was the first solid organ of xenotransplantation. Dr. Keith Reemtsma, working at Tulane University, performed 13 xenotransplants in the 1960's using both chimpanzee kidneys on each surgery. Only one patient survived for nine months while the rest died within 4 to 8 weeks due to either infection or rejection. Dr. Thomas Starzl performed the first liver xenotransplant using baboons as donors [3].

In October 1984, orthotopic cardiac xenotransplantation on " Baby Fae" was performed by Dr. Leonard Bailey and his co-workers. The recipient was a 12-day neonate harboring hypoplastic left heart syndrome. The donor was an immunologically-selected baboon. The baby died on the 20th postoperative day. Neither humoral nor cellular rejection of the xenograft was noted [4].

Galactosyl-α-1-3, galactose [GAL] is the most important antigen in xenotransplantation. GAL is expressed in most cells of all mammals except humans, including porcine. GAL is found in intestinal bacteria, and there are antibodies against GAL in humans. Antibodies to nonGAL antigens are still a problem. The primary methods to prevent hyperacute rejection are the elimination of antibodies by plasmapheresis and immunoadsorption and depletion or inhibition of complements [5].

In the last 30 years, researchers have determined that the pig is the most suitable animal for xenotransplantation. The reasons for this are short maturation time, the human similarity in size and physiological aspects, and low risk of animal disease transmission. Genetically modified pigs have been developed to overcome the molecular incompatibility between species. Another important step is the development of "knockout" pigs lacking the 1,3 galactosyl transferase gene encoding enzymes responsible for immunologic expression. Genetic engineering techniques can be easily applied to create rejection-resistant pig organs [6].

Knockout pigs have contributed to prolonged survival particularly in heart and kidney transplantation. Survival of pig-to-nonhuman primate heterotopic heart, kidney, and islet xenotransplantation over 900 days, over 400 days, and over 600 days respectively has been reported [7]. Bioartificial organs that contain pig cells or tissues have gained considerable clinical experience and the risks have been reduced [8]. For the time being, the indications of xenografting seem unclear but should be kept aside for exceptional cases.

4. Rare organ transplants

4.1 Composite tissue transplantation

When body structures composed of multiple tissues derived from ectoderm and endoderm is transplanted then the procedure is named composite tissue allotransplantation. Such transplants are also known as " vascular composite allografts". The concept of composite tissue transplantation includes hand, face, larynx, joint, abdominal wall transplantations. This type of transplant has a life-changing nature, as the main goal is to restore reduced or completely lost functions and to increase

the quality of life. Unlike solid organ transplants, nerve regeneration must occur in the transplant to restore sensory and motor functions.

The first hand transplant was tried in Ecuador in 1964 with failure. The failure was believed to be associated with inadequate immunosuppression [9]. Dubernard and his coworkers transplanted the right distal forearm and hand from a deceased donor to a 48- year- old male patient who had had a traumatic amputation of the distal third of his right forearm. Motor and sensory recovery were evaluated as excellent six months postoperatively and no serious signs of rejection were observed [10].

The same group performed surgical intervention involving bone fixation, arterial and venous anastomosis, nerve suturing, tendon, and muscle joining in a 33-year old, bilateral forearm amputated patient. They applied physical therapy, electrostimulation, and occupational therapy in the postoperative period. In the postoperative 15th month, they observed satisfactory sensory and motor improvement as well as improvement in the quality of life. This procedure was the first human double-hand transplantation with satisfactory results [11]. It is generally believed that bilateral below-elbow amputation is the most accepted indication for hand transplantation.

In a study comparing the functional and psychosocial outcomes of hand transplantation and prosthesis options, upper extremity functions were globally evaluated with ARAT [Action Research Arm Test] and SHAP [Southampton Hand Assessment Procedure]. The study revealed that functional results are not significantly different. The advantages of transplantation are that it provides sensory and self-perception in addition to providing motor activity. Complications due to immunosuppression pose a disadvantage in transplantation. However, if immunosuppression is well tolerated, regeneration of an organ with its like is naturally an advantage. In bilateral below-elbow amputees, it is understood that the benefit is greater when the acquisition of motor and sensory functions is compared with the risks of immunosuppression. Unilateral amputees can compensate for many functional deficits by using healthy limbs and prostheses. Also, In addition, there is no need for a long-term rehabilitation program after prosthesis implantation, as in transplantation. For these reasons, the prosthesis option is a priority in patients with unilateral below-elbow amputees [12].

4.2 Facial transplant

Facial defects caused by congenital malformations, gunshot injuries, animal bites, burns, traumas, or tumors such as neurofibromatosis cause serious functional and esthetic disorders, psychological and social problems. Basic requirements for a successful face transplant are craniofacial and microsurgical techniques, triple immunosuppression therapy, intensive physical therapy, and psychological support initiated in the early postoperative period for functions such as smelling, eating, drinking, laughing and speaking. In surgery, maxillary and facial branches of the external carotid artery are used for arterial anastomoses. Facial, external jugular and thyrolingofacial veins are preferred for venous anastomoses. Vascular anastomoses are followed by nerve anastomoses. The most problematic aspects of surgery are prolonged anesthesia, excessive blood loss, and transfusions to replace this loss, complex vascular anatomy due to trauma and changes related to previous reconstructive surgeries [13].

Since the surgical experience with facial transplantation is limited, there are no algorithms on long-term results, late complications and their management. In a study conducted to clarify these issues and to get the opinions of physicians experienced in face transplantation, the training of the recipient, how to define the

failure in facial transplant, approach to complications and their management were investigated. Approximately 30% of those who received a survey responded. While 93.8% of the participants stated that facial transplant failure, 91.1% mortality, and 78.8% chronic organ rejection are the points that should be discussed, the answers revealed that there is no consensus about the definition of mortality rates and facial transplantation. Also, it has been observed that even in centers with experience in facial transplantation, there are no protocols for the treatment of rejection in the chronic period [14].

The first partial facial transplant was performed in Amiens France with success. The patient was a victim of dog bite thus losing lips, nose and, central cheeks. The patient had recovered sensory and motor for a long period of time [15]. Immunosuppressive therapy complications and graft rejection, which are common problems in all organ transplants, are valid in face transplantation, and also a case diagnosed with beta-cell lymphoma and eventually developing chronic graft rejection has been reported [16]. Squamous cell carcinoma developed in the fourth case of face transplant performed by Dr. Özkan and his associates. After treatment, severe infection, respiratory failure and allograft rejection developed. Despite the removal of the graft, the patient was lost [17].

Future progress in face transplantation can be achieved with the contribution of different fields of science and technology. Naturally this holds true for the progress of other organ transplantations. These include tissue engineering, creation of functional autogenous-mucosal-cutaneous junctions, neural regeneration, 3-D printed bioresorbable scaffolds, and elimination of antigenic transplanted tissue [18]. The drawbacks of facial transplantation are the cost, relatively small number of potential recipients and only cadaveric donation.

4.3 Uterus transplant

Uterus transplantation has emerged as an alternative solution for female infertility. The first success in uterine transplantation was to ensure pregnancy by replantation of the uterus and ovaries in dogs [19].

The first example of human application was a live uterine transplant in Saudi Arabia on April 2000, to a 26-year old woman who lost her uterus six years ago due to postpartum hemorrhage. The donor was 46-year old lady. The patient had acute vascular thrombosis 99 days after transplant and had a hysterectomy. Although acute thrombosis and infarction were detected in the vessels in macroscopic and microscopic examination of the excised uterus, no findings suggesting rejection were found [20]. An important milestone in uterine transplantation is the allograft uterine transplant performed to a 23-year-old woman diagnosed with Mayer-Rokitansky-Kuster-Hauser syndrome in 2011 at Akdeniz University, Turkey. Embryo transfer was provided 18 months after transplantation and live birth was not possible although clinical pregnancy was detected by transvaginal ultrasound [21].

The first clinical applications in Sweeden were made with nine living donors. In 2013, uterus transplantation was performed on a 23-year-old woman with congenital absence of uterus [Rokitansky syndrome] at Sahlgrenska University Hospital in Gothenburg, Sweeden. The donor was a living 61-year old lady. The patient, who had a menstruation on the 43rd day after the transplant, continued to have regular menstruation. One year after the transplant, a single embryo transfer resulted in pregnancy. Therefore, the triple immunosuppression was started. The patient, pregnant for 31 weeks and five days, was admitted to the hospital with complaints of preeclampsia and was taken to cesarean section due to abnormal cardiotocography findings. A healthy male baby, with APGAR scores of 9,9,10 and with a weight

compatible [1775 gr] with gestational age, was born. Thus, the first live birth was achieved with the uterine transplantation method in the medical literature [22].

Uterine transplantation does not carry a vital indication. Medical, surgical, legal, ethical, psychological, and social aspects of the process are discussed in medical and related communities. Common requirements for recipient and donor are good general health, no history of infection and cancer in the last five years. The upper age limit for the recipient is 35–40 and 55–65 for the donor. In elderly women, it is believed that the vessels be affected by arteriosclerosis, probably due to the atrophic nature of the uterus. The effect of age on graft success is unknown. Among the peroperative problems is the long duration of surgical intervention, especially in the donor.

A characteristic of uterine transplantation is the removal of the transplanted uterus after one or two births to prevent the patient from immunosuppressive therapy for a longer period. This period is foreseen as an average of five years. Therefore, it is not particularly superior to prefer live donors. Besides, psychological problems that the recipient may feel against the donor are eliminated by the use of cadaver uterus. Ethical foundations of uterine transplantation are gathered under the name of Montreal criteria. Accordingly, six conditions should be fulfilled for the recipient, four conditions for the donor, and four conditions for the healthcare team performing the treatment [23].

5. Future prospects

5.1 Organ bioengineering and regenerative medicine

The field of tissue engineering is evolving rapidly and is opening new horizons for novel treatment opportunities. Tissue engineering and regenerative medicine includes artificial and biological materials.

Whole organ decellularization and recellularization have gained importance in recent years. Decellularization, as the name implies, means the removal of all cellular components from the organ and at the same time, the micro and macro anatomy of the extracellular matrix is preserved. These scaffolds are repopulated with patient- derived cells or stem cells to construct an individual specific organ. Consequently immunosuppression is no more needed. Bioreactors are used for decellularization and recellularization [24].

The technology used for organ bioengineering includes seeding cells on supporting scaffolding materials. The cell-scaffold technology uses adult cells, various progenitor cells, and progenitor cells that may differentiate into specific adult cells. Bioreactors are used for uniform scaffold distribution, nutrient supply, and waste removal. The regeneration process takes place in the bioreactors and consequently, bioengineered tissues and organs can be harvested for analysis and implantation. Bioreactors facilitate, monitor, and control biochemical and biophysical processes [25].

Mostly used scaffolds are decellularized allogeneic extracellular matrix which in turn is recellularized by autologous or stem cells. A wide variety of human tissues and organs have been decellularized for tissue engineering. These include cartilage, bone, skeletal muscle, tendon, adipose tissue, heart, arteries and veins, gingiva, cornea, vocal folds, peripheral nerves, intestine, liver, pancreas, kidney, bladder, male and female reproductive systems, products of child birth and complex composite structures. Decellularization requires efficient removal of immunogenic cellular materials and maintenance of nonimmunogenic extracellular matrix. Human tissues are harvested from cadavers and surgery. An advantageous point is the fact that

extracellular matrix derived from decellularization of a certain tissue may be used for tissue engineering of another tissue type [26].

Organ bioengineering aims to develop extracorporeal systems to compensate or completely replace the functions of a diseased organ. As an example, an extracorporeal method designed to substitute liver function should have the capacity to detoxify, synthesize, and regulate. The artificial liver support system has beneficial effects on the prognosis of patients with acute-on-chronic failure. These beneficial effects are generated by improving jaundice, ameliorating hemodynamic instability, reducing portal hypertension, and improving hepatic encephalopathy.

The de-and recellularization technique has been used to produce heart, lung, liver, kidney, and intestine. Despite of some laboratory success, the technique seems to be improved before clinical application [27].

5.2 Bioartificial organs

Dialysis treatment initiated the development of artificial organs. Bioartificial organs are aimed to fully compensate for the functions of a failing organ and they closely mimic human organs. Bioengineering is the mainstay of producing bioartificial organs, but an interdisciplinary approach including the contribution of material science, cell biology, mechanics, chemistry, informatics, surgery, computer science, physics, and medicine is required. Organ manufacturing, in its simplest definition, is producing bioartificial organs using living cells, other material, and advanced processing technologies. Organ manufacturing technologies are basically classified into three groups: fully automated, semi-automated, and hand- manipulated [28].

5.3 3D bioprinting

3D Bioprinting is a rapid prototyping and additive manufacturing technique used to produce artificial implants. Tissue and organ regeneration is one of the fields where 3D bioprinting is used. Bioprinting is layer-by-layer depositing of biological material with living cells using computer-aided transfer processes. Although whole vascularized organs for transplantation have not been produced by bioprinting yet, generation of the scaffold-free tubular trachea [29] and generation of scaffold-free nerve constructs using human gingiva-derived mesenchymal stem cell spheroids were reported [30]. 3-D bioprinting has been used in the production and transplantation of several organs including tracheal splints, vascular grafts, cartilaginous structures, heart tissue, multi-layered skin, and bone. The final goal is industrial bioproduction of individualized functional 3D organs for clinical application.

Nanotechnology has been useful for localized, sustained, and controlled delivery of drugs including immunosuppressive agents and clinically relevant biomarkers. Nano particles can also be used to deliver contrast agents to assist in delineating anatomy and therefore nanotechnology contributes to imaging of clinically relevant biomarkers and functional parameters for diagnosis and treatment [31].

Gene therapy has the potential to eliminate problems associated with immunosuppression by allowing the production of immunomodulatory proteins in the donor grafts resulting in local immunosuppression. Gene therapy may also prevent chronic rejection [32].

5.4 Machine perfusion

Machine perfusion is a novel technique aimed to increased use of suboptimal grafts and consequently to enlarge donor pool. Large animal experiments have

revealed the superiority of machine preservation. The possibility of perfusing high-risk livers consistently for 24 hours has been shown. During that period little evidence of deterioration of the functional and histologic characteristics of the livers were noted. It has been claimed that perfusion may overcome the time limitations related with utilization of high risk livers. Another advantage of normothermic machine perfusion is measuring the functional parameters which give an idea about the viability of the organ [33] and this feature of machine perfusion is also valid for heart. The clinician may predict the risk of primary graft dysfunction. Repair and conditioning of thoracic organs are at experimental level for the time being. It has been reported that machine perfusion may also act as an immunoregulatory agent for lung [34]. Hypothermic and normothermic machine perfusion and controlled oxygenated rewarming keep kidney grafts functionally and metabolically active during preservation. Ex-vivo kidney perfusion has found clinical practice and on the other hand, preclinical results reveal that prolonged warm perfusion appears superior than a brief end-ischemic reconditioning as far as renal function and injury is concerned [35].

6. Specific organs

6.1 Liver

The liver has vital functions including plasma protein synthesis, hormone production, detoxification, decomposition of red blood cells, and regulation of glycogen storage. Due to these important functions, liver failure poses a threat to life. Historically, liver transplantation is second to kidney transplantation. Liver transplantation is a definitive treatment modality for acute liver failure and end-stage chronic liver disease. The shortage of organ supply has initiated the usage of new therapeutic systems to reduce mortality and bridge patients to transplantation.

Albumin dialysis, plasmapheresis, column perfusion, and hybrid devices are among the instruments that have been used to compensate for liver function.

Artificial liver support systems may replace the failing functions of the organ and therefore time is gained for liver regeneration or transplantation. Artificial liver support systems are expected to detoxify, replenish plasma proteins, and reverse the inflammatory process. Among the artificial liver support systems, molecular adsorbent recirculating system [MARS], therapeutic plasma exchange [TPE], single- pass albumin dialysis [SPAD], and Prometheus can be named. MARS uses albumin dialysis to replace the detoxification function of the liver while TPE improves survival in patients with acute liver failure. MARS and TPE improve systemic hemodynamics and the grade of hepatic encephalopathy [36, 37].

Extracorporeal liver support systems are either cell- based [biological] or non-cell-based. Non- cell-based systems include high volume plasma exchange and albumin dialysis. Bioartificial liver systems improve neurologic function, reduce intracranial pressure and increase cerebral perfusion pressure Biological extracorporeal liver support systems aim to support the failing liver through detoxification [38].

Shen Yi and colleagues have performed a time-series-based meta-analysis of randomized clinical trials and observational studies that examined differences in mortality in acute-on-chronic liver failure patients treated with artificial liver support systems. The results revealed that an artificial liver support system had reduced the risk of short-term [1–3 months] mortality for patients with acute-on-chronic liver failure by nearly 30%. As the results of the meta-analysis suggested, an artificial liver support system might reduce medium-term [6 month-1 year]

mortality risk by 30% and long-term [3 years] mortality risk by 50% in acute-on-chronic liver failure patients [39].

The parenchymal cells of the liver are hepatocytes that constitute nearly 70–85% of the liver volume. Treatment of congenital metabolic disorders affecting the liver and acute liver failure using allogenic hepatocyte transplantation has been proposed. The transplanted cells provide the impaired or missing hepatic function once engrafted into the recipient's liver. Mature hepatocytes have been considered the most obvious cell type for liver cell transplantation. Some advantages of these cells have been noted. They are less invasive and less expensive not involving complex surgery, may be repeated in case of need, cryopreserved cells isolated from donor livers are immediately possible when required and native liver stays in place [40].

Demetriou AA et al. have shown favorable results on survival in patients with acute liver failure using an extracorporeal liver assist system. The system was composed of 7 billion porcine hepatocytes within a hollow-fiber bioreactor. This phase II/III, prospective, randomized, multicenter, controlled trial included patients with fulminant-subfulminant hepatic failure or primary nonfunction [41].

6.2 Kidney

Long-term hemodialysis and peritoneal dialysis have been widely used in the treatment of end-stage renal failure patients**.** These treatment modalities have bridged thousands of patients to transplantation. The kidney is the first solid organ whose function could be replaced by an external device. Portable and wearable dialysis devices for the treatment of patients with end-stage kidney failure are being developed.

The evolution of devices designed to treat renal impaired patients has followed the sequence of portable artificial kidney [PAK], second- generation PAK, a wearable artificial kidney [WAK], and implantable bioartificial kidney [BAK]. All of these devices are to be smaller, lighter and intended for use outside the clinic. BAK can partially replace tubular function and it provides an extension to conventional dialysis systems and artificial kidneys by incorporating elements of living cellular and tissue function. The key features for the development of a bioengineered kidney require three main components. These are, cellular components, material engineering, and emerging technologies. Hollow membranes, extracellular matrix proteins, porous structures, and novel chemistries are included in material engineering. Organoids, 3D printing, decellularized kidney and induced pluripotent stem cells compose the emerging technologies. Specialized kidney cells and stem cells constitute the cellular component. A bioartificial kidney is expected to be able to reproduce the metabolic, endocrine, immunomodulatory, and secretory functions of a normal kidney [42].

Bioengineering and regenerative medicine also play a role in the efforts to construct an artificial kidney as a final target. New branches of engineering like artificial intelligence and machine learning for the real-time analysis of equipment alarm, dialysis parameters and patient-related data contribute to developments in this field. The problems encountered in the transplantation of recellularized whole kidney scaffolds are needed to efficiently repopulate the endothelium of the vascular network of the engineered kidney before implantation and optimal source of cells to repopulate an acellular kidney scaffold [43].

Generation of human- induced pluripotent stem cells derived kidney organoids has been an important step in regenerative medicine and kidney organoids are expected to be used for disease modeling, drug discovery and ultimately be applicable for transplant [44].

6.3 Heart

Left ventricular assist device [LVAD] was developed as mechanical circulatory support [MCS] for heart failure patients. A long-term implantable continuous-flow LVAD named "the Heart II™ left Ventricular Assist system [Abbott Laboratories] has been approved by U.S. Food and Drug Administration for indications of destination therapy and bridging to transplantation. While the technology is advancing to achieve smaller size and eradication of drive lines, the expectation is to apply continuous-flow technology, which is in the experimental phase, to total heart replacement [45].

Implantation of a total artificial heart is indicated in end-stage heart failure patients. Acute hemodynamic restoration and clinical stabilization are achieved and the patient is then bridged to transplantation. It has been reported that a total artificial heart is associated with a post-transplantation survival rate very similar to national survival rates five years after transplantation [46] It has also been reported that total artificial heart patients have high rates of successful bridge-to-transplant and survival on par with biventricular assist device supported patients. The future objectives are decreased device size, continuous flow mechanisms, and use of bioprosthetic materials. Overcoming these hurdles will provide increased device longevity and decreased post-implant complications [47].

Taylor and associates have claimed that engineering a bioartificial heart has become a possibility. They have proposed a novel type of in vivo organ engineering utilizing pre-clinical models where decellularized hearts are heterotopically transplanted. The aim was to harness the capability of the body at least partly to repopulate the scaffold. The authors have added load and electric input and have posited that vascular and parenchymal cell maturation can occur. The authors have implanted porcine decellularized hearts acutely and chronically in living recipients in a heterotopic position and have demonstrated that short-term implantation promotes endothelial cell adhesion to the vessel lumens and that long-term implantation also promotes tissue formation with evidence of cardiomyocytes and endothelial cells present within the graft [48].

Pelletier et al. have reported that Rein-Heart-total artificial heart had shown safe and effective function in vivo and in vitro testing. The Rein-Heart has effectively replaced the native hearts' functions in animals for up to two days [49].

There are obstacles to overcome before obtaining a bioartificial heart. These obstacles are, achieving adequate durability, longer than five years, minimizing thromboemboli and hemolysis, better efficiency, maintaining pulmonary-systemic circulatory balance and reduced size to accommodate in women and small adolescents and children [50].

6.4 Lung

The structure of the lung is complex and lung decellularization is a complex process. The information is not sufficient. The most suitable cell types, media, and growth factors and how to provide the optimal conditions of ventilation, perfusion and oxygenation along the process of biofabrication are issues to be studied for further progress.

The key problem in producing a bioengineered lung is how to drive stem cell differentiation onto the different cell phenotypes. The role played by physical stimuli is also important in lung bioengineering because the cells within the organ are physiologically subjected to two main stimuli. These stimuli are ventilation and blood perfusion across the organ [51].

Extracorporeal membrane oxygenation and mechanical can be used temporarily as a bridge to transplantation. Experimental transplantation of bioartificial lung developed by perfusion decellularized synthetic scaffolds has been shown to provide gas exchange in vivo over a long period. The present level of achievements reveals that obtaining a transplantable artificial lung is not possible soon [52].

6.5 Pancreas

Artificial pancreas treatment is an alternative treatment that combines insulin pump and continuous glucose monitoring with a control algorithm to deliver insulin in a glucose- responsive manner. It is also named "closed-loop system" or "automated insulin delivery". The artificial pancreas can be either insulin-only or dual hormone [glucagon] type. A systemic review and meta-analysis conducted by Bekiari and associates have shown that artificial pancreas systems are beneficial and safe treatment options for patients with type 1 diabetes. The authors have noted that the current research evidence on artificial pancreas systems is limited by inconsistency in outcome reporting, small sample size, and short follow-up duration of individual trials. So the future efforts should focus on such issues along with exploring artificial pancreas use in relevant groups of people with type 2 diabetes such as those with inpatient hyperglycemia [53]. Other areas of interest for the future would be faster acting insulin in the artificial pancreas, increased accuracy, and reduced lag-time of continuous glucose monitoring. Self-learning adapting algorithms will improve the level of automation and effectiveness. Cost-effectiveness in the general public is another issue to be taken into consideration [54].

7. Conclusion

The basic indication for solid organ transplantation is the treatment of end-stage diseases posing threat to life. Solid- organ transplantation evolved to be gold standard therapy and became a routine procedure with minimal morbidity and mortality figures. Despite the achievements in different fields of transplantation activities, the gap between demand and supply is growing due to an increased percentage of the elderly population, and the increase in the number patients that require organ transplant from which considerable number are lost while awaiting a suitable organ. The unmatched shortage of organs and life-long dependency on immunosuppressive drugs and related complications of immunosuppression had warranted the development of alternative novel technologies for the repair or replacement of missing or malfunctioning organs.

Reproductive, functional, restorative, and psychologic indications have caused the emerging of transplanting different organs, namely face, extremity, and uterus. It is apparent that transplant procedures of these organs will be performed with increasing frequency in the future because successful results are closely associated with the accumulation of useful scientific data and experience.

The unmet demand for organs and the failure of immunosuppressive drugs to prolong long-term graft survival and a variety of complications associated with immunosuppression have caused the need for completely new therapeutic modalities in the treatment of diseased and malfunctioning organs.

For the time being, human grafts and artificial devices are not capable of performing all the functions of vital organs. Artificial devices are beneficial in bridging patients to transplantation, or organ regeneration or as independent implantable units. The ultimate goal is to obtain human grafts to be totally

restored in all their structural and functional aspects, and artificial devices that can completely replace native organs. The hurdles on the way can be overcome by close cooperation and integration of a wide variety of disciplines and technologies including tissue engineering, regenerative medicine, electronics, robotics, artificial intelligence, machine learning, 3D bioartificial printing, bioreactor technology, nano- technology, gene therapy, machine perfusion and cell biology. In light of the recent scientific developments, it can easily be assumed that reaching the goals mentioned is a matter of time. Tissue-engineered products and any kind of device expected to substitute totally human organs must certainly be safe, long durable, and non-immune. The cost-effectiveness and the ease of accessibility are issues to be managed in the future.

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