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Review Article

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Review about Tissue 3D Printing Directed to Organ Transplant and Birth Defects

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Abstract

End-stage disease, trauma, or malformation require an organ transplant to treat patients. Low organ supply creates a long waiting list. 3D-printed functional artificial organs may be used in future transplant surgeries. 3D-printed artificial cells can emulate in vivo tissue. Also, 3D printing has other applications in medicine as a learning tool and surgical guide. Birth defects case reports indicate how 3D printing helped with patient treatment. Further development of this technology is required.

Keywords: Bioprinting, Birth Defects, Organ Transplant

1. Introduction

The human body depends on various systems to survive. All these carry specific functions and depend on body organs to do so. The heart, lungs, and kidneys, among other organs, represent their respective system, performing their function to keep us alive. Due to illness, trauma, and old age, these organs can malfunction, leading to disease and ultimately death. While some people are fortunate enough to get a transplant, the majority will try to carry on until they get favored or succumb to their pathology. But what if these malfunctions due to accidents, aging, or disease can be solved by replacing the body parts for most people? Human body function starts to diminish as its ages. Cumulative damage over time slows the physiological repair capacity due to DNA damage, protein incorrect folding, and the accumulation of cellular waste products. These are some of the mechanisms that deteriorate the body and cause aging [1]. On a macroscopical level, we can evidence that neuronal atrophy, smooth muscle weakening, decreased liver metabolism, sclerotic changes in the glomeruli, myocardial fibrosis, cardiac muscle thickening, and decreased lung elasticity are some of the major organs affected by aging [2].

Even though these are physiological changes that will happen to every person that reaches a certain age, there are also pathological changes due to trauma, chronic and acute disease, and genetics that can damage and deteriorate key organs. As a solution, we can think of replacing these defective body parts with new ones. Organ transplant has dated from ancient times with teeth, bones, and limbs. Due to medical and scientific progress and innovation, now a day's kidney, liver, pancreas, intestine, skin, heart, and lung transplants are a reality, but the main problem is the high amount of people in need of a transplant and the low number of organ availability and donors [3]. Data from 2013 reports that approximately 118,000 individuals are waiting for an organ transplant [4]. UNOS data reveals transplant waiting list mortality dating from 1988 to 1996. 23,214 ill patients needing a transplant died while on the waiting list and other patients, whose pathology progresses, were removed from the list due to the advanced disease [5]. This means the organ demand is far superior to the supply and the breach grows wider due to an increasing incidence and diagnosis of illnesses such as Type II Diabetes, Hypertension, and alcoholic induced liver disease, among others [6].

2. Materials and Methods

A literature search was carried out using databases such as PubMed, NCBI, and Google Scholar. The search window was between January 2021 and June 2021. The native language for the research papers was mainly English and Spanish. No time windows were utilized to filter the articles and no type of studies were used to exclude information search. The keywords typed for the search were the following: "3D Printing", "Birth Defects", "Congenital Abnormalities", "Organ Transplantation", "Medicine", "Biomedical Research" and "Epidemiology". The authors revised the articles found to confirm their relevance in the review topic. Finally, the information was organized to fit the format of a review article.

3. Results and Discussion

3.1. Congenital Abnormalities

Most of the cases stated before are patients that suffer from these illnesses later in life but there is also a group to be considered. Congenital Abnormalities have a birth prevalence of around 3% [7]. Congenital abnormalities can be divided into mayor and minor abnormalities. Mayor abnormalities require medical treatment due to structural or functional reshaping of organs.

Minor abnormalities are mostly cosmetic, and individuals can function properly if left untreated. However, the presence of three or more minor malformations widens the probability of a mayor abnormality. The most common malformations by organ systems in Colombia are cardiovascular (cardiac chambers, cardiac septum, and great arteries), musculoskeletal (polydactylies, limb malformation), renal (pelvis and ureter), and microtia. Around 50% of congenital defects can be treated via surgery which will significatively improve or cure the medical condition [8]. The prior defects can be solved with organ transplantation and tissue regeneration. Other abnormalities including kidney, liver, and bone pathologies can be treated with transplantation [9,10]. The solution to this can be the implementation of new technologies such as xenotransplants and organogenesis via 3D-Printing [11].

3.2. 3D Printing in Medicine

The idea of having an object in a computer and turning it into reality passed from science fiction to reality in the 80's. Due to various optimizations and user-friendliness now a day's people can obtain a 3D printer at a reasonable price and design clothing, prototypes, accessories, etc. If this technology advances, will it be possible to print livers, hearts, or lungs at demand? First, an overview of how 3D printing works. It is based on constructing a 3D model from a 2D drawing whether it is a computer-aided design (CAD) or software that converts medical images to 3D models. Between programming and designing in these CAD programs, one can get the desired design to print [12]. This technology can be useful in the medical field by helping with educational purposes, training for surgical procedures, biomedical investigation, and tissue generation, among others. For example, cadaveric materials to train medical students are used to better understand human anatomy. However, there are ethical issues involved and the process to store and conserve these materials has an economic cost. 3D printing can accurately reproduce anatomical structures and anatomical variants with models that possess different morphology without having to face ethical concerns and save the costs of formaldehyde and refrigeration [13].

Another use for this technology is surgical training. Patient-specific 3D models based on their scans are used to analyze the best surgical approach and train for each patient's individual case. For instance, to apply regional lung chemotherapy, some patients got their pulmonary arteries printed to further study their individual anatomy and surgical planning. Another patient got a guided surgery due to a Pancoast tumor which got resected with the help of his cancer's 3D model used to study his procedure [14,15]. Training experienced surgeons before advanced and complex procedures and training novice surgeons without having to fear their mistakes are going to harm people and, in the worst-case scenario, take a life are other accomplishments 3D printing can bring to the medical field.

Scaffolds and prosthetics such ad hydrogels and polymers can also be 3D printed to study new materials and designs to further advance biomedical research. Ingenious drug delivery systems and designs can be done due to this technology. For example, multi-layered pharmaceuticals can further control the active ingredient's bioavailability by modifying patient dosage. Also, different designs for fast dilution after oral consumption and skin patches for pain-free self-administration are other ways bioprinting can help in biomedical engineering and research [16]. Ultimately this technology can also be used for tissue generation by bioprinting cells, tissues, and finally organs [17]. As an example, now a day's 3D bioprinting is being tested to modify organs for xenotransplantation. Modified pig hearts and kidneys were transplanted into primates and kept them alive for six months [18]

3.3. 3D Printing Mechanisms

To understand the applications of 3D printing in tissue engineering and transplantation there are some basic printing techniques to discuss. These are Laser Sintering, Thermal Inkjet, and Fused Deposition. Laser Sintering consists of beaming a laser to a powder, heating and fusing it together in specific places to get the desired shape. Thermal Inkjet uses a predetermined ink material to heat it and expel the ink on a tiny nozzle. Finally, Fused Deposition has a similar principle to Thermal Inkjet. Plastic or polymer is used as an ink, heated, and condensed layer by layer. All these have previous instructions from a program that guides the printer to make the model or prototype as accurate as it can be [19]. To bio-print cells into 3D scaffolds a common technique is via Inkjet. To nurture the cells, they are encapsulated in a hydrated polymer. This polymer-cell ink is heated in specific regions to create bubbles. The bubbles generate pressure which ejects the ink via the nozzle, positioning the cells where desired [20].

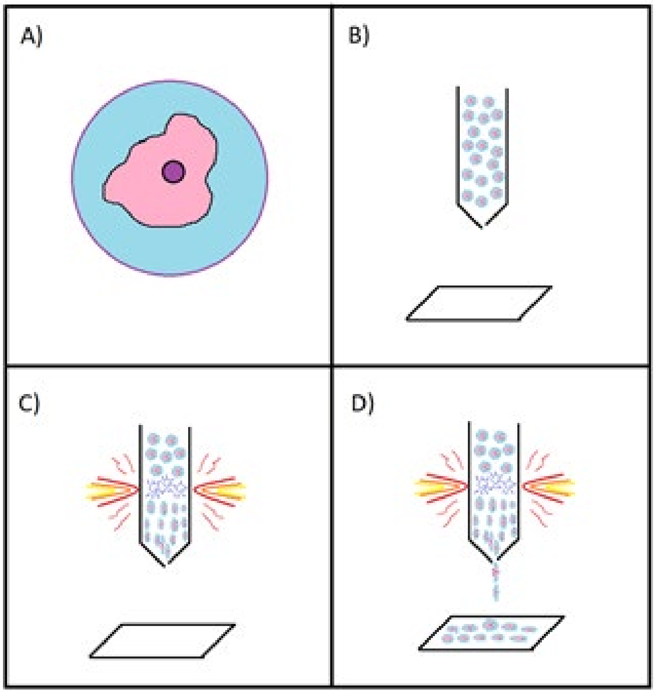

Figure 1: Schematic of cell Bioprinting using Inkjet.
A) The cells are encapsulated in a polymer. B) These cells are stored as the bio-ink. C) Heating causes bubbles that propel the ink downwards. D) The printer moves to place the cells where the program commands.

3D printing advances and foresight		
System	**Example**	**Foresight**
Respiratory System	Tracheal graft to correct tracheal defect on a rabbit	Tracheal trauma damage or malformation
Musculoskeletal and Locomotor System	Cartilage hyaluronic acid bio ink Calcium phosphate scaffolds to treat bone defects in sheep Bio ink based on calcium phosphate cement and alginate with chondrocytes Bio ink based on methacrylate gelatine and skeletal myoblast cells	Functional prosthetics for congenital limb loss and malformations Corrective scaffold that solve craniosynostoses 3D printed ears to correct microtia
Gastrointestinal System	Bio ink from decellularized layers of oesophageal tissue 3D hepatocyte/gelatine construct to test survivability 3D Hepatocellular carcinoma cells to study drug effectiveness Development of functional “mini-livers”	Oesophageal scaffolds for congenital malformations and other diseases GI track remodelling and regeneration
Nervous System	Nerve guides to improve injured nerve regeneration Bio ink based on a microgel suspension and cell culture medium neuron like cells PEG hydrogel encapsulating embryonic dorsal root ganglia 3D collagen construction with astrocytes and neurons 3D printing of ganglion, retinal and brain-like cells to test survivability	Nerve regeneration and function gain for patients with facial abnormalities such as osteochodroplasias, cleft palate, and dentofacial abnormalities
Cardiovascular System	3D printing heart valves Bioprinting of a 5-day-old chicken heart embryo 3D printing of patches with stem cells to promote cardiac muscle regeneration 3D printing of vascular smooth muscle cells	Cardiac remodelling due to congenital heart valves or septum defects
Others	Bio inks of human umbilical vein endothelial cells to promote differentiation and angiogenesis 3D printed rat vaginal tissue to study histological differences	Vaginal reconstructive surgery for congenital defects causing ambiguous genitalia

Table 1: Various medical research experiments which utilize 3D bioprinting and their foresight in congenital abnormalities [13,17,21-27].

3.4. 3D Printing in Congenital Birth Defects

Although many of these applications are based on research, this technology is already helping in cases of individualized pediatric surgery regarding congenital abnormalities. Congenital heart disease proves a challenge since children have smaller chest cavities and heart structures to modify while in surgery. 3D models were used to evaluate the preoperatory procedure for ventricular septum defects and aortic arc hypoplasia in paediatric patients. This surgical planning also helped paediatric patients with orthopedic deformities [27].

Another example of surgical planning involves an infant patient diagnosed with cleft lip and palate, a lymphovascular malformation, and epignathus. MRI imaging was used to model the 3D facial anatomy of the patient in utero for further examination and comprehension of the malformation and its complications. The 3D model was used to decide a plan of action, types of interventions, and treatment after delivery. After an exam of the 3D-printed anatomical model, it was decided to deliver the baby without an immediate surgical intervention due to a low probability of airway obstruction. The baby was born without complications and had reconstructive surgery scheduled 9 months after [28].

An additional case that used 3D printing as an anatomical guide consists of a patient diagnosed with gastrointestinal situs ambiguous. Normally, due to the abnormal anatomy regular exploratory exams like endoscopy and colonoscopy are not recommended as there is a high risk of organ perforation and thus exploratory surgery is normally the only viable option for a clear anatomical understanding. Using MRI, an anatomical 3D model was constructed showing the abnormal position of the abdominal organs. Having the model as an anatomical guide, a laparotomy was performed to correct the pylorus-duodenal malrotations of the patient [29]. Finally, 3D-printed ear lobes are being used in patients with microtia as an anatomical reference with promising transplant outcomes [25].

4. Conclusion

Cell survivability and 3D accommodation are key to resembling the function of the desired organ. Different types of scaffolds are required for cells to mature in the desired shape. Bio ink formulations must be specific for every type of cell to ensure nutrition, growth, and physiological function. Organ printing technology needs to be optimized to lower the prices of developing 3D bioprinters, materials for scaffolds, and bio-inks. Organ vascularization and blood flow need to be developed properly to increase the de size of printed organs, mimicking human conditions [21]. These are some of the challenges that medical scientists, biomedical engineers, computer scientists, and material engineers need to tackle to advance in this technology. Maybe someday any pathology regarding an organ failure will require only a 3D printer and a transplant surgeon to solve. Waiting on a transplant will be a thing of the past. With the advances of 3D bioprinting and other biomedical innovations, in the future, the organ shortage available for transplants may be solved and people can easily replace their failing organs to have a better aging and quality of life.

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