International Journal of 3D Printing Technologies and Dijital Industry
Uluslararası 3B Yazıcı Teknolojileri ve Dijital Endüstri Dergisi

THREE DIMENSIONAL PRINTER APPLICATIONS IN THE HEALTH SECTOR: CURRENT SITUATION AND FUTURE

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ABSTRACT

Three-dimensional printers are a rapidly developing technology that is used in many places today. In this research, we have examined the developments in the field of health of the three dimensional printers which are frequently used today. Three-dimensional (3D) bioprint has become a powerful tool for the design and full placement of biological materials, including living cells, nucleic acids, drug particles, proteins and growth factors, to revitalize tissue anatomy, biology and physiology. As a material in these researches; synthetic polymers, natural polymers, and ecm are selected. Generally as the method; inkjet, micro-extrusion and laser assisted preferable.

Bioprinting has evolved significantly over the last decade and will be used extensively in future live tissue production. Most patients think that by means of developing technology, tissue damage and organ transplantation problems will be solved with three-dimensional bioprinteres with customized models. In this study, three-dimensional bio-printer technology was introduced, tissue engineering, regenerative medicine and so on. Applications and uses in the field of health were examined.

Keywords: Bioprinter, Tissue engineering,

1. INTRODUCTION

Three-dimensional printing is the process of printing any object in solid form using a computer aided design (CAD) program. Devices that perform this process are called three-dimensional printers [1]. Although the three-dimensional printing technology in our lives since the 1980s, it has become widespread in a short time on the market. The first working three-dimensional printer was created by Chuck Hull in 1984 [2]. In 1986, Charles "Chuck" Hull patented the stereolithography machine, one of the oldest 3 dimensional printers. A few years later in 1988, another 3dimensional printing technology called Scott Crump, Fusion Deposition Modeling (FDM) was created [3]. Figure 1 shows a printer invented by Hull [4].

Figure 1. The first 3 dimensional printer invented by Charles (Chuck) Hull [4].

However, the RepRap project started in 2005, and open source printers became able to produce their own parts [5]. Consumers have MakerBot established in 2009 and have obtained one of the first three-dimensional printers offered to consumers [6].

Rapid prototyping (Additive Manufacturing) technology uses different methods and different raw materials. The most common working principle for design is to divide a three-dimensional object created in computer environment into layers in the computer environment (conversion to STL format) and then to construct a real object by building layer layer [7]. Three dimensional (3D) printer has multiple manufacturing technology. These technologies are Stereolithography (SL), Fused Deposition Modeling (FDM), Shape Deposition Manufacturing (SDM), Selective Laser Sintering (SLS), Objet Polyjet, Multijet and ColorJet [8]. Today, the most commonly used FDM method in production process is to obtain a three-dimensional product by stacking two-dimensional layers of cismin with a three-dimensional model in the computer. These technologies use different materials such as ABS (acrylonitrile butadiene styrene), PLA (polylactic acid), metal, plastic, iron powder [9].

In today's technology, bioprinter technology, which is a type of three-dimensional printer technology, is seen spreading to health sector applications such as artificial organ printing, complementing missing bone parts and making private prosthesis. Especially in the past 10 years, bioprinter technology has made significant progress in the creation of tissue skeletons or living tissues and organs by precisely positioning living cells, natural or synthetic biomaterials in laboratory environments. Most patients have problems such as tissue damage and organ transplantation, it is seen that this technology has been solved with models custom made for the person. In this work, three-dimensional bio-printer technology is introduced, tissue engineering, regenerative medicine and so on applications and uses in the field of health have been examined.

2. THREE-DIMENSIONAL TISSUES AND BIO-PRINT PROCESS

In the bio-print process, primarily the damaged tissue and its surrounding are imaged with CT (computer tomography), MRI (magnetic resonance imaging) and X-ray devices. Biomimetic tissue is designed for self-assembly and mini-tissue building stones, alone or in combination. The choice of materials and cell source is tissue-specific, specifically also made up, and common materials include synthetic and natural polymers, extracellular medium (ECM). These components are selected by a method compatible with inkjet, micro-extrusion and laser-assisted bioprint systems. Some tissues require a maturation period in the bioreactor prior to transplantation [10]. Alternatively, 3 dimensional tissue is used for in vitro applications. When this process is completed, the process of obtaining the desired tissue is shown in Figure 2 [10].

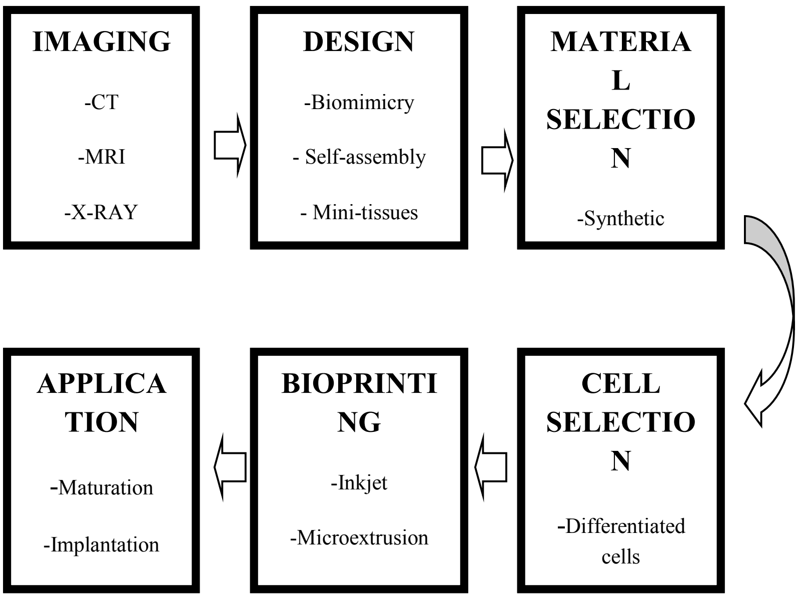

Figure 2. Bio-print process [10].

3. CURRENT APPLICATIONS IN HEALTH SECTOR

Applications of 3 dimensional printers in the healthcare sector are improvement everyday. The artificial organs and tissues produced, as well as the before surgery models at the same time, have started to be used frequently. In this study, we have been concentrating on kidney model, face implants, sacrum implant, maxilla formation, artificial trachea, embryonic heart and pelvis applications.

3.1. Kidney Model Applications with 3 Dimensional Bioprinter

In this section, three-dimensional prototype of a kidney and left kidney model shows the formation process. In recent years increasing number of patients awaiting transplantation and due to the insufficient number of transplants performed, the development of new tissue and organ prototypes was needed with 3-dimensional bioprint technology [11].

It differs from other printers in that it is a cellular biomaterial accumulation rather than a synthetic material. The printing process consists of three main sections. These; pre-processing (development of computer plan), processing (accumulation of biomaterial) and post-processing (tissue maturation and conditioning). In the pre-processing step of the printing process recommended in the kidney, firstly, the images of the subject organs are examined in computer environment. Subsequently, regenerative potential cells taken by the organ biopsy are isolated and replicated. Kept in nutrient-rich mixtures and transferred to the printer cartridge. Subsequently, the layer layer is processed, and a tissue structure identical to the natural human tissue is produced. There are specific methods for layer formation. These; ink jet, micro-extrusion and laser-assisted printing. In the ink jet technique, head portion is electrically heated, generates pressure pulses to provide a trickle. Bio printer using a piezoelectric and ultrasonic pressure removes the material from the nozzle. In the micro-extrusion, pneumatic or mechanical systems are used. In the mechanical system, extrusion is done by means of piston and shaft.

In the pneumatic system, this is done with the help of the gas press. In laser-assisted printing, this process is done with laser-welded printing. At the last stage in the, post-processing of some tissues prior to transplantation is performed in the bioreactor and the desired the new organ prototype of is obtained. Figure 3 shows a prototype of the kidney from a 3D bio printer [11].

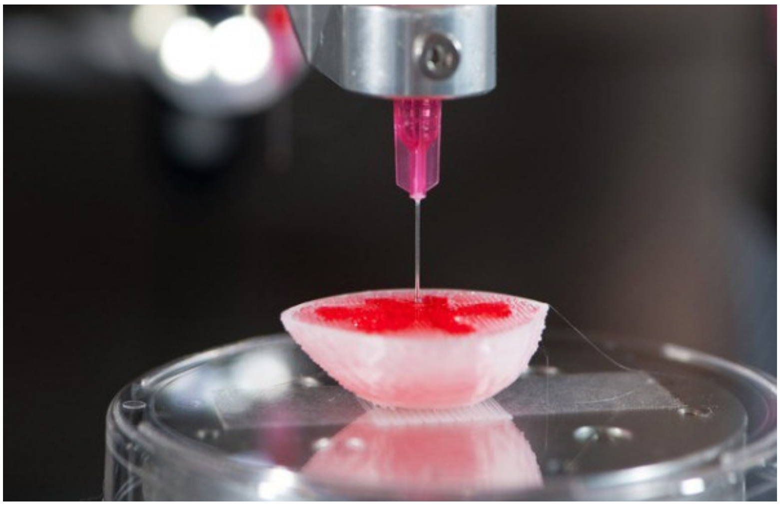

Figure 3. Prototype of kidney with 3-dimensional bioprinter [11].

The choice of these methods is based on the growth, complexity and oxygen delivery of the cells. It is not enough that these cells are only multilayered, at the same time it is also important to be able to interact with each other. In addition, the oxygen nurturance system for each organ prior to insertion into the body should be developed. During this prototyping phase, one of the most important problems is the vascularization process. Work continues to work on bioreactors, chemicals, tissue viability and blood transfusion that help preserve tissue integrity within the framework of this process [11].

Although researchers have successfully obtained more than one 3 dimensional kidney prototype, using synthetically grown kidney cells, a real kidney printing process is still in its developmental stage.

The left kidney model is produced for use in transplant surgery. In the first stage, a CT scan is performed on the receiver and a contrast CT scan is performed on the donor. A stereolithography file of the organ surface is obtained with a the multi-detector scanner. Standard images are then taken to perform morphologic analysis and analysis of the vascular and urinary tract anatomy [12]. These images are evaluated in Digital Imaging and Communication (DICOM) images and separated by OsiriX, the image processing software package.

Using the surface rendering function from DICOM data, the field of interest (donor kidney, renal artery, renal vein, ureter, recipient pelvis: iliac artery, iliac vein and urinary system) is subtracted and converted to a stereolithography (STL) file. The digital preparations of STL data are completed with the Magics software program, the Connex 3 Objet 500 is modeled by transferring to a three-dimensional printer. In figure 4, 3 dimensional printing laparoscopic left donor model is shown.

Figure 4. 3 dimensional printing laparoscopic left donor model [12].

Figure 5 shows the simulation before surgery [12]. This simulation provides ease of at the time of transplantation of a kidney prototype before surgery.

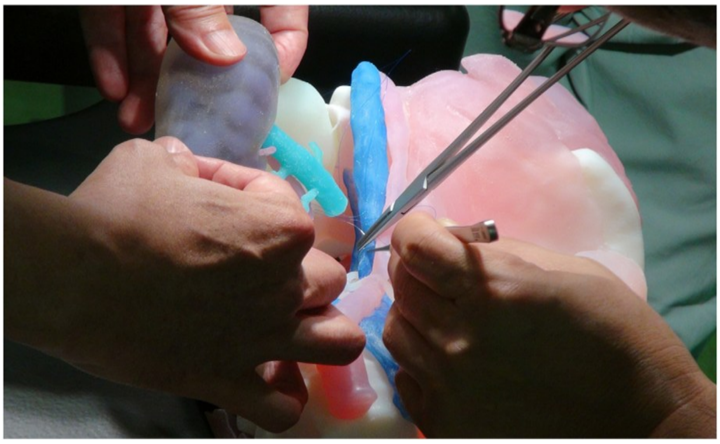

Figure 5. 3 dimensional printed kidney transplantation [12].

3.2. Design and Production of Person-Specific Biomaterials

In this section, person-specific head, face implants and tail implants are described.
First, the skull and jaw injuries were performed using a surgical saw on a human cadaver skull provided by the Institute of Anatomy and Cell Biology at the University of Wużrzburg. After producing defects,

CT scans of the skull were performed. CT data (DICOM files) were visualized as a virtual 3 dimensional geometric model and a program was written using Visual Basic 6. The virtual production (CAD) of the implants was performed and the creation of the DICOM files of the implants was monitored.

For rapid prototyping, conversion from DICOM to STL format was done using Amira software. Describes the processing and use of 3 dimensional powder-printed calcium phosphate implants for repair of injuries. Production of the implant is performed with 3 dimensional powder printing system. Printed on dilute phosphoric acid tricalcium phosphate powder, it led to the formation Brucite. The hydrothermal transformation of the Brucite matrices has been shown to lead to the formation of Monetite. Finally, virtual implant structures were completed and transferred to the printer using CAD [14].

The individual-specific implants were placed as shown in Figure 6 and showed a high degree of fit [14]. The 3-dimensional powder printing of calcium phosphate material provides a promising new method for the production of biodegradable synthetic patient-specific head and face implants.

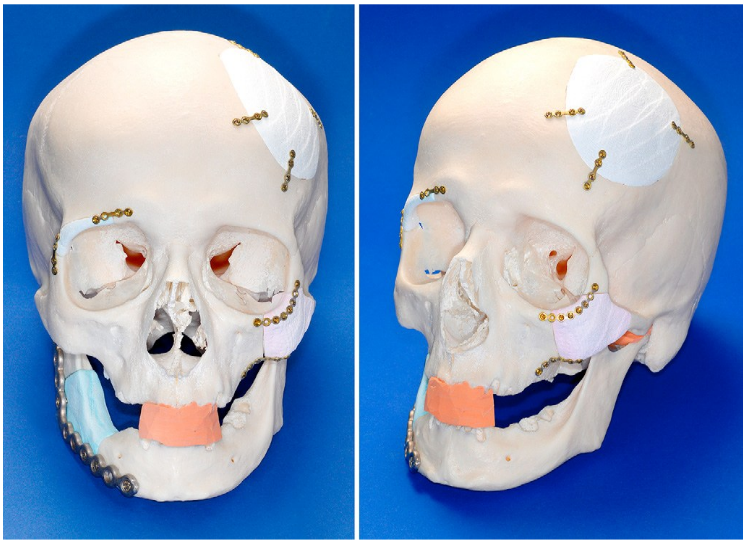

Figure 6. General view of an implant bearing skull [14].

Secondly, pelvic resonance imaging of the patient showed damage to the left side of the coccyx (sacrum). After short-term chemotherapy treatment, it was decided to perform a patient-specific implant. Examining a 3 dimensional image of Sacrum, a customized implant was designed using 3-matic materialize software. The implant is designed to be patient-specific, often resembling an anatomical structure. A couple of quick prototypes using a conventional 3 dimensional printer for review and correction was printed.

A metal printer (Arcam-EBM A1; Arcam AB) system was used for the printing of the implant. Structure The 3 dimensional printing structure made of Ti-6Al-4V (titanium 6-aluminum 4-vanadium) material in Figure 7A, the body part of the left corpus shown in Figure 7B is shown [15]. In this system, the electron beam is spread over successive powder layers, which are fed from the powder cups and roughly 50 µm thick. The structure component, is lowered to the structure section with the completion of each successive layer. Each freshly drawn powder layer is initially spread by a beam current of approximately 35 mA and each layer is preheated before to approximately 600 ° C. These layer during preheating, normally 4 mA current flows.

Melting is carried out by a 3 dimensional computer aided design program and just merely adds metal to the structure by melting the metal selected layer areas. Printed implants, revised and finally obtained.

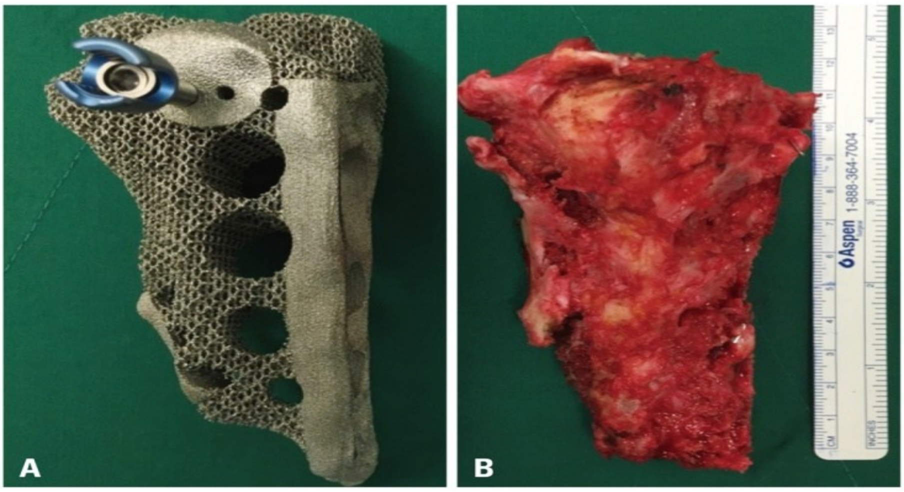

Figure 7. (A) 3D printing structure having porous titanium structure, (B) The left corpus (body), the healthy part is protected, the diseased parts are cut out [15].

3.3. Anatomically Shaped Bone Tissue Production with 3 Dimensioanal Bioprinter

This section describes the production of bone tissue appropriate to the anatomical structure. Bone tissue is a tissue that can repair itself after any damage. However, each tissue can not perform the self-renewal process. For example, large damage and multi-part fractures resulting from removal of the bone tumor may not be repairable. In these cases, the structural and mechanical support that needs to be done and filling of the area with a filling material. An ideal bone filler material should contain viable cells that will allow the bone to develop, stimulate bone formation and create centers of bone formation [16].

Temple and her colleagues conducted a study on this subject in which residual fat grains from liposuction operations were collected and stem cells derived from fat were isolated by enzymatic method. The resulting stem cells are loaded onto the hydrogel portion of the bioturbated biopurine to form this three-dimensional structure. The first of this two-titled structure is the rigid polymeric part providing structural and mechanical integrity and the second is the hydrogel part containing the cell. These stem cells, which are provided meltdown within the syringe, are compressed into filaments together with PCL (poly caprolactone) by pressure. As the filament emerges, multilayer structures are produced in biodegradable and biocompatible manner[17,18]. Figure 8 presents the upper jawbone and jaw structures produced from the anatomical model seen in the left column [18].

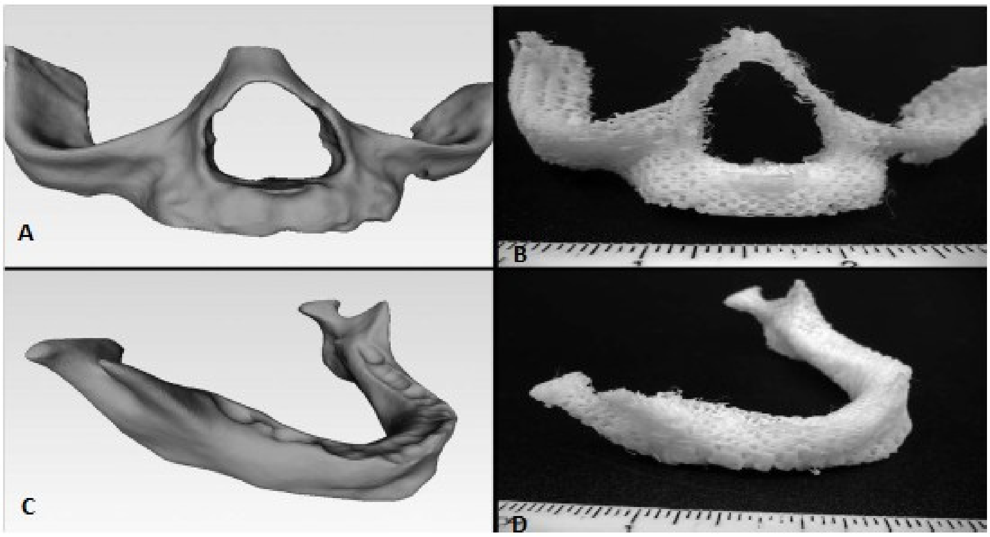

Figure 8. A-B: Upper jawbone, C-D: Jaw (Structures produced from biocompatible and biodegradable polymeric materials) [18].

3.4. Artificial Breath Pipe with 3 Dimensional Bioprinter

Regenerative medicine is a branch that provides tissue and organ restorations through different methods. The first of these methods stimulates resident stem cells, surgical and chemical signaling mechanisms to heal damaged tissue or organ itself. Second, the stem cell taken from the appropriate donor is replicated in the laboratory environment. Later on transplantation of 3 dimensional organ structures or transplantation is carried out with the help of tissue engineering. In this project, which was organized not only by tissue engineering but also by many branches, it was decided to construct artificial organ of the patient who was diagnosed with cancer in the breathing tube [19].

In the construction of the breath tube, the CT scan is performed and the image is taken first so that the measurements are closest to the actual size. A mold is obtained and a duplicate is produced. In this study, silsesquioxane-polyurethane, which is a nanocomposite material based on silica, was used because, usually other used materrials can't melt in the body. This construct was implanted with 200 milliliters of bone marrow taken from the patient for two days and 40 milliliters of mesenchymal stem cells obtained therefrom. The resulting structure was matured in a specially designed bioreactor at Harvard. Since heparin is used besides this material and it is desired to obtain a porous structure, the salt crystals placed in the structure are melted and the structure is finally made. In the proliferation process of the cells, the immune system did not react because the upper part contained the own tissue of the patient. This artificial respiratory tube is shown in Figure 9 [20].

Figure 9. Artificial respiratory tube [20].

3.5. Embryonic Heart Formation with Suspension Hydrogel Technique

In this section, an embryonic heart formation process will be explained. The only place where a new heart muscle can be formed in the human body is known as the embryonic period. In this method, fluorescence-labeled three-dimensional optical imaging data is used to generate embryonic chick heart. Macro and microstructures displayed in the embryonic period are examined in detail.

This technique; fibrin comprise soft materials such as collagen and polysaccharid alginate. The materials are contained in a dense slurry of gelatin microparticles and water in the petri dish. Gelatin, semi-liquid mixture of the microparticles, in the case of leakage during operation, the soft biomaterials released at the same time are firmly implanted with the pressure technique during the layer. After completion of the procedure, the dish is heated to 37 °C, gelatin taken and an organ or tissue scaffold structure is obtained as shown in figure. 10 using the suspension technique [21].

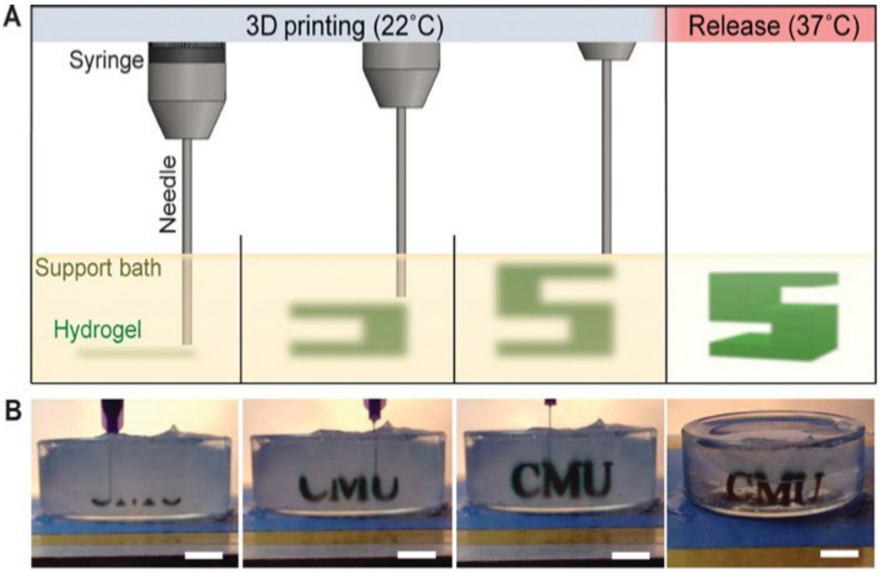

Figure 10. Suspension gel technique [21].

After that, 3-dimensional heart skeleton images printed with computer-generated images are compared as shown in Figure 11 [21].

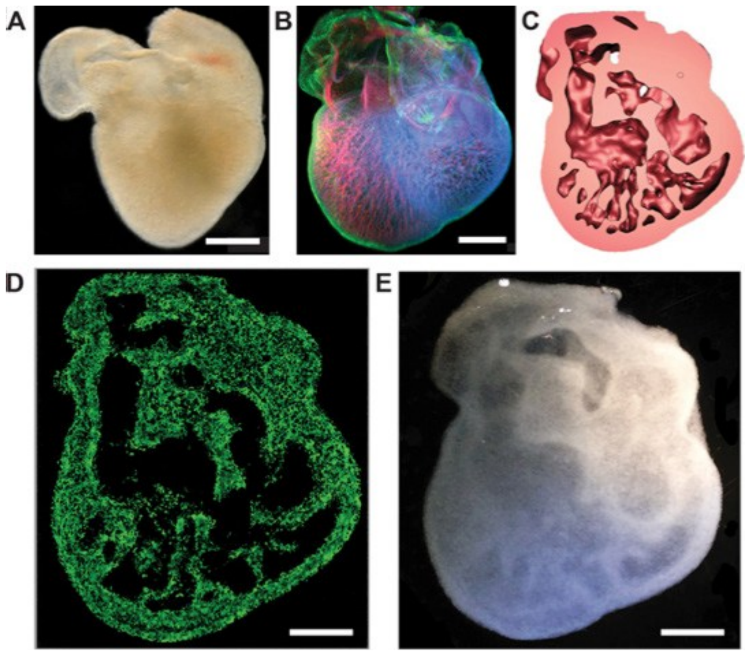

Figure 11. Comparison of 3D-printed embryonic heart skeletons and computer generated images [21].

3.6. 3 Dimensional Pelvis Formation

In this section, the formation process of the pelvic bone model is explained. It is known that it is difficult to surgically interfere with the acetabulum fractures, which are referred to as troughs, in which the femur and the hip bone are articulated. Auxiliary tools for the evaluation and classification of fractures accelerate this process. Using 3 dimensional printers, 3 dimensional model of the pelvis bone will be made to match the actual dimensions. Computer-aided design and rapid prototyping is used to obtain the product.

Firstly, Using a 64-line multi-detector CT scanner (Aquilion; Toshiba Medical Systems), a 0.5 mm cross-section CT scan was obtained before the operation of the pelvic bone. After 3D reconstruction of the images (OsiriX application), the relevant bone area is removed from the DICOM data using surface function and the STL data is transferred to the computer aided design software and processed. This data starts the layered production process in a 3D printer (Connex500 Objet) that uses inkjet technology.

After that, it is hardened by ultraviolet irradiation and the formation of the 3-dimensional model of the pelvis bone is ended. Once this model has been sterilized with gas and used in the desired area, no infection has been observed. The information of the 3 dimensional model of the produced pelvis bone is shown in Figure 12 [22].

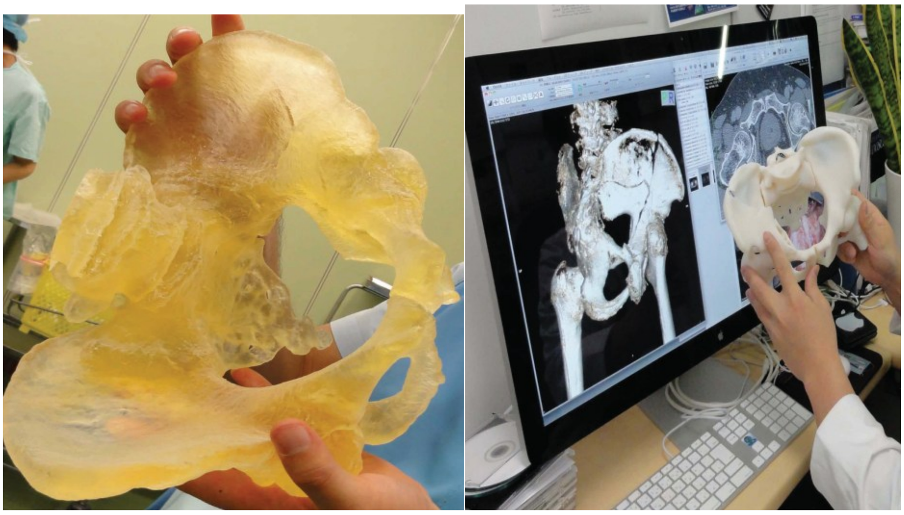

Figure 12. The 3D model of the pelvis bone provides information in every sense [22].

4. THE FUTURE OF 3 DIMENSIONAL PRINTERS IN THE HEALTH SECTOR

3 dimensional printer technologies are getting new places every day in human life. The development started with the production of the products we used daily (glasses, shoes, telephone boxes). Later, textiles, architecture is highly advanced with modeling. At this time, artificial organ printing experiments in the health sector, completion of missing bone parts and researches such as making private prosthesis has become a branch of importance for the future human health.

It is seen that the prostheses, artificial organ tests, and the preoperative model formation that will be produced from 3 dimensional printer will find the definitive solution to many diseases which are seen as problems in the future. It would be a glimmer of hope in patients' organ transplant period, it is understood that many operations carried out today. Some of these examples are the production of a synthetic skull in the Netherlands, produced in the United Kingdom by a 3 dimensional printer and carried in transplant. In these two cases, patients showed more positive results than the other methods. It is expected that complex heterogeneous tissues, such as the liver and heart organs, which can fulfill the full function of the 3 dimensioal press in the future, are successfully produced.

A toolkit is being developed to provide the formation of replacement tissues and organs for a child's lifetime use of stem cells from the baby's teeth. In this way, during operations of implants or living organs it is foreseen that the printing method (in situ printing) printed on the human body will be used in the future. Thanks to the use of 3 dimensional bioprinting cells for repairing lesions, growth factors and biological material scaffolds can be obtained. Precision digital control is attempting to perform on-site bioprinting to repair external organs of various types and thicknesses. This approach can be used for on-site repair of partially damaged, diseased or defective internal organs. A portable 3d printer for on-site use for direct tissue repair can be an innovation in this area. The developments in robotic bioprinter and robot assisted surgery are also seen to be an integral part of the development of this technology.

5. RESULTS

In this research, tissue engineering, regenerative medicine and collaborations with many other fields were examined and 3 dimensional bio printer technology was introduced. The process of obtaining artificial organs and models produced by this developing technology consists of certain stages. Firstly, if the pressure to be done is an organ, images of diseased tissue is taken. Then, for the printing tissue to be made, the person-specific design is created. Appropriate materials are selected for biocompatibility. After these steps, one of the ink jet, micro extrusion or laser assisted printer methods is selected. With the latest version of the product, transplantation is performed.

In this study, bioprint technology was used to successfully produce the kidney model, face implants, tail bone implants, jawbone formation, artificial breathing tube, embryonic chick heart and pelvic bone. Embryonic chick heart was produced in one of the studies. This production is in the beginning of a real embryonic heart formation in a short time within the research.

Biological printing process often depends on the tissue engineering. Approximately 10 different tissues have been examined in this context. In the future, more comprehensive and diverse tissue and organ examinations will be made.

NOTES

The third International Congress was presented at the 3 Dimensional Printing (Additive Manufacturing) Technologies and Digital Industry conference (3D-PTC 2018) and the summary was printed.

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