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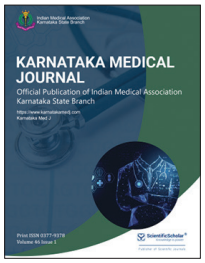

Review Article

Applications for 3D printing in healthcare system: Current trends, recent developments and future prospects

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ABSTRACT

3D Printing (3DP) has application in various fields including healthcare. As there is acute shortage of organs for transplantation in diseased patients, 3DP organs are a ray of hope. In the healthcare system, 3DP is used in surgical planning, medical education, research, drug delivery and organ printing. It widely used to test new drugs, chemical and cosmetics, etc. 3D bioprinting (3DBP) is printing implantable tissue and organs made out of living cells. Organ printing with stem cells is much in progress since the past two decades. Scientist's printed live organs such as skin, ear, orthopaedic and dental implants using patients own cells by 3DP. It has many advantages such as lifesaving, economical, time saving and no need to use immunosuppressive medications. Our primary goal is to solve the organ crisis by printing living organs such as kidney, heart and liver, so for we did not reach that stage due to the complexity of these organs, their vascularity and innervation. Each organ comes with its own complexities. Simpler organs could be seen very soon but for internal organs it may take another 15–20 years. However, 3DBP technologies are moving in the right direction at the expected rate and we are coming closer to making our dream a reality. With many collaborative studies one day, we may print them to fulfil our needs.

Keywords: Printing, Healthcare, Bioprinting, Drug delivery

HISTORY

Revolution in the world has taken when 2D printing started in Germany in the year 1450 for spreading knowledge, development of science, arts, literature, etc.[1] Similar revolutionary changes are seen with 3D printing (3DP) also from 1984. In 1960s, Francis Willems in France tried to make model of a disease by hand, taking multiple pictures from 24 different cameras. His idea was that patient and doctor can understand the illness is better by seeing models in different angles. 3DP first started by Charles Hull in US in the year 1984. He tried to make 3D models using a sophisticated computer and programing, that is he tried to convert digital data into physical objects. These models are then reformed using molten plastic or other materials. In the year 1999 – Team of doctors in Howard medical school developed artificial bladder using collagen and polymer by artificial methods for dogs by combination of ideas.[2-4]

As further in the year 2004, Dr. Antony Atalla in US prepared artificial bladder for children from stem cells using a 3D printer and transplanted with great success. It is successfully worked for

many years. With this Dr. Antony Atalla gave the idea of using 3D printer to create other organs also.[5]

With these orthopaedic doctors tried to create artificial joints, discs, prosthesis etc., using 3D printers as there was so much demand for them. Similarly, dentists used this technology in making artificial dentures and bridges, etc. Within short time, this technology is improved and expanded unimaginably.[2-4]

INTRODUCTION

3DP was first started by Charles Hull in the US in the year 1984 for preparing 3D models. Last two decades, 3DP technology is extensively used in various fields such as construction, space, automobile, food preparation and medical due to its multiple advantages.[2-4]

Dr. Antony Atalla in US used 3DP Technology in medicine in 2004. From then doctors from different part of world started using this in healthcare system. In past 10 year, its use in medicine is so expanding from 1% to 21% of total 3D budget. Now, it is growing up to a billion-dollar market. It is used extensively for the creation of bones, titanium mandible, hearing acquired immunodeficiency syndrome (AIDS), prosthesis, implants, anatomical models like ear, etc., this technology is also used in surgical planning, pharmaceutical research and in medical education, etc.[1,6] In pharmaceutical research, 3D printed organs are used to know the dosage, adverse effects and drug delivery.[1,7]

3D bioprinting (3DBP) is the construction of living tissue or organs in a 3D printer using cells, biomaterials and growth factors (bioink) layer by layer. Using 3D printing (3DP) scientists have already printed tissue, organs, windpipes, blood vessels, skin, vascular networks, ear, etc., from patients own cell cultures and stem cells,[1,2,7-9] it is most promising but in the initial stage. By using patients own cells Scientist already printed implantable tissue, ear, bone and muscle with its own blood vessels.[8]

Extracellular mesenchyme is prepared using skin fibroblasts which are more helpful to grow stem cells. Moreover, it can be used in the future for printing living organs such as kidney and liver in future that is our dream. In man, the organ already printed in 3D has good size, strength and function which can be used in patients suffering from various congenital or acquired disease, battlefield injuries, etc.[10]

As we know for transplantation, organs are taken from donors or cadavers. Acute shortage of organs, its high cost, ethical issues and adverse effects of immunosuppressive and other drugs used are all its limitations.[1] If we uses the patient's own cells to create organs for self-transplantation, all these problems are answered.[1]

Our primary goal is to solve the organ donor crisis by printing living organs and other body parts. We are not yet at the stage we can implant 3D printed organs, due to the complexity of our bodies. Each organ comes with its own complexities but 3DBP technologies improving is moving in the right direction at the expected rate and we are coming closer to making this dream a reality. Simpler organs could be seen very soon but for internal organs such as heart and kidney that it may take another 15–20 years it need lot of research works.[9]

3DP PRINCIPLE

3D printing (3DP) is a process that joins materials layer by layer to create objects based on digital data. Similar to how a 2D printer uses ink and paper, a 3D printer deposits material over material or uses supporting media such as gel. The materials used in 3DP include metals, plastics, liquids, ceramics, wax, resins, and even living cells.[6,11]

The process relies on computer software, integrating computer-aided design (CAD) with computer-aided manufacturing (CAM). CAD software assists in designing components like circuits and slices the 3D model into thousands of layers (approximately 0.1 mm thick) using slicing software. The sliced model generates data representing the object's design. These data created, analysed and improved by geometric parts of software are transferred to CAM Software. CAM is software that controls the coordinates of manufacturing equipment and facilitates the printing process. High end 3D CAD is used in 3DP. High-end 3D CAD creates three-dimensional object from two-dimensional sketch then cut at different planes to create required shape.[12,13]

PROCEDURE OF 3DP

3DP is also called as additive manufacturing because it is deposition of material layer by layer as thin slices under computer control. These materials join and solidify to form a three-dimensional object. The volumetric 3DP principle is different.[14]

3DBP

Bioprinting is creating living tissues and organs using 3DP technology. The process involves creating a three-dimensional scaffold, or structure, made of biocompatible materials such as hydrogels, and then depositing living cells onto the scaffold in a precise pattern using a specialised printer. Cell growth may be facilitated by growth factors.[15]

3DBP is printing the organs by layer-by-layer deposition using different types of biomaterials, stem cells and biomolecules in perfect regulated form. It has multiple steps such as (1) create blueprint of organ to be printed with the help of X-ray, computed tomography (CT) and magnetic resonance imaging (MRI). (2) Creates its plan (biomimicry). (3) Create 3D scaffold from hydrogel, etc. (4) Isolate and differentiate and

grow stem cells convert them to induced pluripotent stem cells. (5) Prepare bioink (natural or synthetic ECM containing living stem cells, that is organ cells, supporting cells and vascular cells). (6) Load the bio ink into cartridge of the printer. (7) Print the organ using printer (placing the living cells on scaffolds in particular manner). (8) Promoting cell growth and function by providing growth factors and receptors. (9) Place it in a bioreceptors. (10) Exite the cells using laser.[15,16] (11) Use the tissue, organs for implantation or for *in vitro* testing.[15,17]

First is to create scaffolds which provide mechanical support, nutrition and microenvironments to biomaterial and cells. Scaffolds like cellulose based biomaterials are good for this.[18-20] Next step is to seed the living stem cells. The extracellular mesenchyme for the cells are either created by cell itself or provided by synthetic ECM. For soft tissue, synthetic biodegradable polymers may be used as ECM. Hydrogel is better than synthetic ECM as chances of rejection is less. For hard tissue like bones, hydroxylapatite may be used as ECM.[21,22] Stem cells extracted from patient, modified as pluripotent stem cells and culture them on media to grow. These stem cells are mixed with bioink and processed to make it is like a printable ink. Load this mixture in to one or more print cartridge. Set the parameter program it and start the printer. Layering of the stem cells on scaffold like hydrogel is seen. Once it starts growing maintain its size with growth promoting colony stimulating factors. After bioprinting keep the organ/tissue in ionic solution or UV light for the structure to cross link and organ becomes stable. These tissue/organ typed can be used for medical purpose[7,18-20] [Figure 1].

There are mainly four different types of bioprinting techniques such as inkjet printing, extrusion, laser-associated printing, stereolithography all having its own advantages and limitations. Extrusion based is most popular.[15]

Stem cells are of three types. (1) Unipotent type which is gives to one type of cells. (2) Multipotent is one which gives rise to some restricted type of cells. (3) Pluripotent is giving extra embryonic tissue. Unipotent stem cells can be taken from the bone marrow, skin or fibroblasts and converted to pluripotent using genes. Best among them are fibroblasts. This is called as induced pluripotent stem cells. The induced pluripotent stem cells can give mature to any type of cells depending on the condition and stimulation factors.[23,24]

APPLICATIONS OF 3D PRINTING IN HEALTH CARE

The common applications of 3DP in healthcare are surgical planning, medical research, organ printing and medical education and training, pharmaceutical research, drug delivery, etc.

SURGICAL PLANNING

Any problem in the heart, brain, pelvis, spinal cord, etc., before surgery if surgeon study anatomy, physiology and disease in model has better in making surgical decision so prognosis of disease. If it is explained to the patient with 3DP, it increases the patient understanding the disease than explaining in

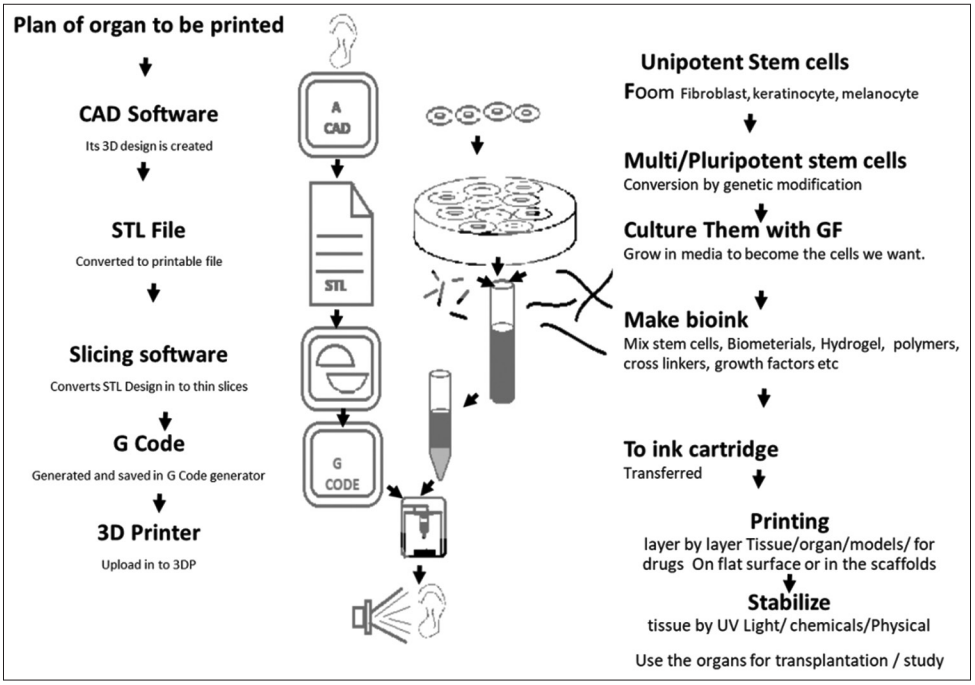

Figure 1: The diagrammatic representation of 3D bioprinting of an organ like ear. CAD: Computer-aided design, STL: Stereolithography, GF: Growth factors, UV: Ultraviolet.

2DP such as radiographs and MRI. It increases patient's confidence, doctor-patient relation. With this duration of surgery may be reduced.[25,26] Taking 3D model in brain disease, colonic cancer, etc., if surgeons know the anatomical relations between a lesion and normal tissue [Figure 2].[27-29]

PROSTHESES (ARTIFICIAL BODY PARTS AND IMPLANTS)

In the developing world, only 5% of the needy people are able to offer prosthesis such as arm, hand and leg, due to availability, expense and time needed to prepare traditional made prosthesis. Traditional made prosthesis is so expensive and time consuming because every time to make moulds, it takes a lot of labour works. With 3DP once programmed, any number of prosthesis can be made in short time with less expense.[30] And also some modification is easy. 3DP prosthesis is more comfortable and cosmetically more acceptable.[30]

In congenital, accidental and war fed deformities in any organs 3D printed prosthesis can help the patient to lead near normal life. Similarly, hip implants, cranial plates, limb implants, dental implants, etc., are very much used in health care system for comfortable life.[25,26,31]

MEDICAL EDUCATION AND TRAINING

3D printed organs are helpful in medical education to teach anatomy and physiology. Students can understand better like plasticized specimens.[32] Another example is 3D printed that the polypeptides structure students can understand protein structure better which are not visible even under a microscope. Organ created by 3DP can be used in simulation surgical training for surgical instructors, trainees and less experienced doctors especially in cardiovascular surgeries.[1,6,31] Study conducted proves that students preferred physical interaction with the 3D printed models preferred in dental education. The natural elastic properties of the 3D printed models mimic human tissue are ideal for students for dissection, cutting, suturing, etc., for rapid learning and developing motor skills.[33,34]

HEALTHCARE RESEARCH AND DEVELOPMENT

Organ created by stem cells can be used to see the effect and adverse effects of drugs.[6] New drugs can be tested on 3DP tissues instead of clinical trial and animal experiments to avoid ethical issues. Ex new drug is tested for alpha 1 AT deficiency which is tested on 3DP tissue. Tissues created by 3DP are used in medical research such as gene pig and albino rat.[17] 3D Printed models can be used to study best surgical technique and procedures for disease. It also helps in the development of new surgical instruments for any innovative surgical methods apart from drugs.[35]

DRUG DELIVERY

Medicines with inactive ingredients such as cellulose and surfactants glycerine printed in 3D. 3D printed CPM, dexamethasone tablet in cellulose are effective in very small dose, this drub release in small quantity for a long time. Similar 3D printed levofloxacin as implantable drug for low release of it. These implantable tables act locally, so there are not much adverse effects. Like rifampicin, INH is bone infection.[36] 3DBP organs are used *in vitro* models for testing pharmaceutical drugs, which minimise these lengthy and expensive clinical trials and save billions of dollars for pharmaceutical companies.[37]

ORGAN PRINTING

Organs created using 3D printer are artificial ear, heart valve, re-absorbable tracheal splint, spinal disk, bones, orthopaedic and dental implants, hearing AIDS and cartilage, which are all of great success.[7,20,24,38]

One of the challenges facing by healthcare system is shortage of organs such as kidney, heart, lung and liver for transplantation. To overcome this, the scientist community is working hard and trying different methods such as xenografting and stem cell research, 3DBP is one showing more hopes in this aspect. The challenges are more complex structures of tubular hollow organs, preparation of supporting scaffolds for them, etc.[39] With scientific efforts and the involvement of many start-ups and pharmaceutical companies, many of the obstacles are overcome and already printed lung and heart are implanted to animals to know the results. Even though positive results are coming, we have to wait for some years so that it is functioning in human yet to prove so 3D printed organs will come to our help.[38]

LATEST DEVELOPMENTS BY APPLICATION

Collaboration from Harvard University, Stanford University, Massachusetts Institute of Technology, etc., printed a functional network of capillaries. In future, they can help in printing functioning glomeruli.[8] *In situ* printing of skin has already done using stem cells and growth factors to repair the skin by digital control.[5]

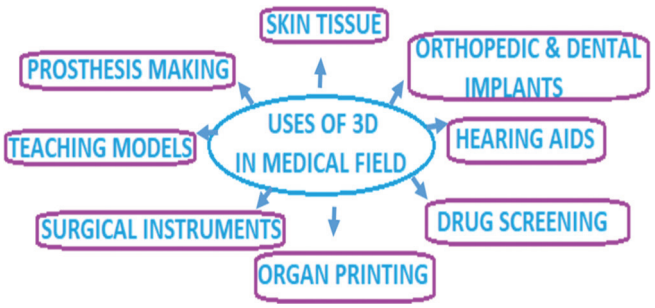

Figure 2: Multiple uses of 3D printing in medical fields.

3DP of skin and bone are tried in space by scientists showing great success.[37] Researchers at South China University of Technology developed new bioceramic scaffolds called as Gyr-Comp and Gyr-Tub which show good strength, foster osteogenic and angiogenic activities compared to conventional scaffolds.[40] As per the Researchers at Fraunhofer observation adhesive dihydroxyphenylalanine improves the lifespan of medical implants like orthopaedic prosthesis. As this adhesive naturally binds with apatite seen in teeth and bones [Figure 3].[41]

Already 4D printing and 5D printings are used in printing bone tissues in orthopaedics. They are expecting stronger and more natural. However, it is too early to comments about them.[42] In volumetric bioprinting, lights are focused from different angles to cure the tissue by removing the extra material. It has better resolution. It can create more complex structures in short time than layer by layer print.[43,44]

FUTURE TRENDS

We are expecting to print organs such as liver heart and kidney for transplantation. Ability to print the liver is underway. Stem cells can be taken from the teeth.[7,28]

In situ printing of skin has already been done using stem cells, growth factors to repair the skin by digital control. Future day, we may do it for the same to repair damaged other organs such as heart, lung, kidney and liver.[16,37]

Most expected in future days are 4D and 5D printers and its application. But let us wait for some time to know exactly pros and cons about them.[42]

DISCUSSION

Charles Hull initiated innovative 3DP in the year 1984 for the 1st time in US in using computers and programming, he tried to convert digital data into physical objects as 3D models.[2-4] It is an integration of CAD and CAM technology. As Louis Kahn said that, beauty does not emerge from design, it emerges from selection, affinities and integration. It is a great beginning, and it started utilising different fields such as building construction, automobile and space research.[2,12]

Medical doctors stated utilising this technology in healthcare system in the early 2000s. In the field of orthopaedic and dental, it is started using extensively for making prosthesis, artificial denture, etc.[2-4] Our aim is by these ideas and technology, to create organs such as liver, kidney and heart for transplantation using biological materials. There are so many hopes on it.

Dr. Antony Atalla in US prepared artificial bladder for a child from stem cells using 3D printer and transplanted with great success in the year 2004. This is called as bioprinting. With this success, bioprinting 3D technology started getting more attention, funds so improvements.[5] With this door of great treasury is opened. Extensive improvement is seen in this technology in the past two decades. Budget of the healthcare system increased from 1 to 21% of the total budget utilised for 3D technology. Hence, it is a billion dollar budget now.

In the healthcare system, 3DP technology is used in surgical planning, medical research, organ printing and medical education and training, pharmaceutical research, drug delivery, etc., in each field that it has many advantages.

Before any surgery, if the surgeon, with the help of a radiologist taking the 3DP of the disease is better than just 2D prints such as X-ray and MRI, advantages are first surgeon which can understand about the disease and surgery needed for the same. Surgical duration may be reduced and the prognosis of surgery may be increased. Surgeon can use this model to explain about the disease to the patient and his team of surgery. Patient will gain confidence, it increases patient doctor relations. Team of nursing and anaesthetic staff can help in a better way in surgeries.[27-29] Surgery will be less complicated, and safer than relying on 2D Radiology.

In case of congenital, accidental and war related deformities many patients are in need of prosthetic arm, hand, leg,

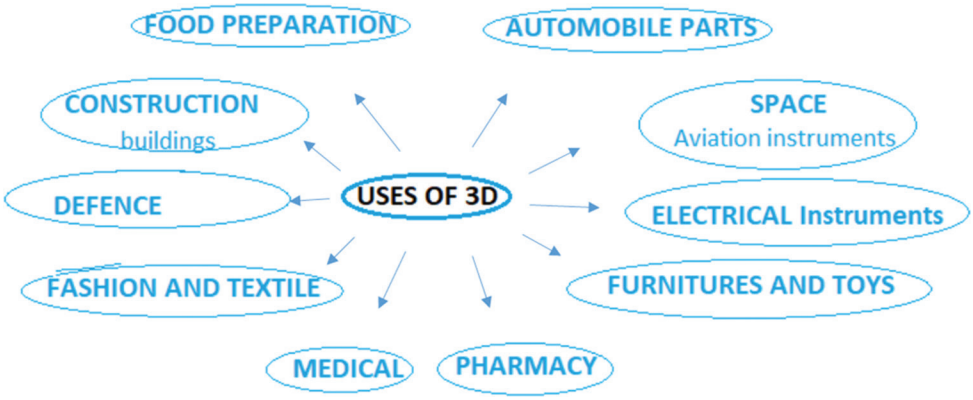

Figure 3: Multiple uses of 3D printing in different fields.

etc., only 5% of them are offered to traditional made prosthesis due to expense and availability. 3DP prosthesis are less expensive, take less time to create to make multiple prosthesis, comfortable and cosmetically accepted are widely used.[30] Like cranial plates, orthopaedic dental implants are much useful.[25,26,32] Size and shape of the traditionally made prosthesis and implants are limited but 3DP organs are modified as suited for individuals. With this increases comfort, contact area, survival of them as in joint replacement, etc. Hence, it is a great revolution in this field.

3DP organs can be used to teach anatomy, physiology and pathology to medical, dental and nursing students. They will better understand the subject by touch, feel from different angles. Using 3DP organs for dissection, cutting, suturing and minor surgeries, etc. In training, hands on for trainees and junior doctors are good as they have natural elastic properties. Submicroscopic structure like polypeptide chain is better understand with 3DP.[1,6,32-34] As per study conducted, this is better than the traditional method of teaching in 2DP or museum specimens. This could be an innovative learning which reduces the stress in medical students

Tissues and organs created by 3DP are best used for experiment adverse effects of new chemicals, cosmetics, drugs, etc., it is better than using experimental animals and to avoid ethical issues. New drug developed for alpha 1 antitrypsin deficiency was successfully used on 3DP organs. 3DP also helpful to develop new surgical instruments.[35] Bu using 3DP organs for testing newer drugs.[37] We can avoid lengthy and expensive clinical trials to save time and money. With this cost of treatment also reduced for our patient. Field of research will improve as ethical issues and using experimental animals and be avoided.

3DP medicines such as CPM and dexamethasone with glycerine or cellulose are effective in small dosage by releasing small quantities of medicine for a long time. Like that, antibiotic 3DP antibiotics such as levofloxacin, rifampicin and INH act locally.[36] Systemic adverse effects of all these drugs can be avoided.

Most challenging in the healthcare system is the shortage of organs for transplantation. It is increasing day by day as increase the incidence of incidence of diabetes, hypertension leading to heart failure, renal failure, etc., trying to solve this by xenografting, stem cell, etc., but they are having their own limitations. 3DP is having hope. Already printed artificial ear, windpipe, heart wales, etc., printing organs such as kidney and heart liver are difficult because of their complex structure. With extensive scientific efforts, positive results are coming in experimental animals. However, we have to wait for some more years so that fully functioning organs can be printed and transplanted to save life of millions of sufferers.[16,27,28,37] It is sure the future days will come to improve our healthcare system.

ADVANTAGES 3D PRINTED BIOMETERIALS

3D printing has many advantages. Some important advantages are (1) printed model are cost effective (1000 $ is enough to build a simple 3D Printer). (2) They are all of high accuracy and resolution. (3) It is time saving procedure to prepare them than traditional (hours/days for traditional methods). (4) It create many complex structure in flexible manner. (5) We can print organ any number of times and can be shared to others also. (6) Less wastage of material in this additive manufacturing comparative substitutive manufacturing. (7) Surprising is 2D print such as X-ray can convert to 3D prints.[1,2,14] (8) They are made from patients own cells so no need to use immunesuppressant medications after transplantation.[7,37] These are much advantages as immunosuppressive drugs cause various health problems, which can be avoided.

LIMITATIONS

The use of 3D printing has few limitations also.[2] Security problems such as using this technology for illegal making of guns, master keys and ATM skimmers can be misused.[39] As it is new field need lot of experiences in it.[41] Legal regulation – FDA is approved with its regulations. As it involve both industrial and academic part may be difficult to follow them legally to regulate organ trade.[41] Highly skilled person are needed. Many times small errors such as clogging of nozzles can spoil whole procedure. Printer excrete toxic effluents may cause health hazards such as nausea, vomiting and throat irritation. Ethical issues, approval by the government and misuse of the technology, are other challenges.[37,45]

CONCLUSION

The 3DP Technology started since two decades. It is more useful in 3DBP than any other field. 3DBP is printing the organs using different types of living cells. These organs are used for surgical planning, medical research, medical education, training, pharmaceutical research, drug delivery and organ printing, etc., as more and more man and money power involvement this 3DBP is improving extensively. Our final dream is printing living organs such as kidney, heart, liver and lung, it is not for our dream will come true. So for, it is not done, it is possible in short time. So that with these organs printed using patients, own stem cells will improve our health care system. We will wait for those good days.

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Authors' contributions

SS: Conceptualization, data curation, writing, methodology; PNS: Funding acquisition, visualization, supervision; AM: Resources, software work; SSG: Formal analysis, validation; SG: Reviving and editing.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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