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3D and Bio-printing as an Efficient and Safe Alternative to Traditional Methods and Materials in Cardiovascular Diseases

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3D AND BIO-PRINTING AS AN EFFICIENT AND SAFE ALTERNATIVE TO TRADITIONAL METHODS AND MATERIALS IN CARDIOVASCULAR DISEASES

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ABSTRACT

Background: Cardiovascular diseases are the leading cause of death globally. Therefore, there is the need for more resources to be poured into the research of more treatment options, diagnostic methods and preventative steps for patients. Though several technological advancements are being made in the world of medicine, it is not a bad idea to look at other avenues that have great potential to improve patient outcomes in cardiovascular diseases. 3D and bioprinting, though a relatively new technology in the world of medicine, is showing a promising future. It is already being applied in the field of orthopedic surgery and other specialties are jumping on this band-wagon as well.

Purpose: The question at hand that this literature review seeks to answer is that, can 3D and bioprinting serve as an efficient and safe alternative to traditional methods and materials in cardiovascular diseases?

Methods: In an attempt to answer this question, a comprehensive literature review was conducted via Google Scholar, Google and Trip Database by using the search terms, 3D printing, bioprinting, tissue engineering, cardiovascular diseases, and orthopedic implants, to name a few. Inclusion criteria were primary research, clinical trials, and exclusion criteria were studies before 2017 and systematic reviews.

Conclusions: Looking at some of the marvelous already performed and ongoing studies, there is a strong potential for 3D and bioprinting to become a potential alternative to traditional methods and materials in cardiovascular diseases in the near future. This new technological advancement

just needs time, dedication and hard work to bear relevant fruit in realm of cardiovascular diseases.

Keywords: 3D printing, 3D bioprinting, applications, cardiovascular diseases

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INTRODUCTION

According to the World Health Organization (WHO), cardiovascular disease is the leading cause of death globally, claiming an estimated 17.9 million lives per year and with coronary artery diseases alone afflicting more than 16 million American adults. Looking at the encouraging advancements in the field of medicine globally, the treatment of cardiovascular diseases is getting better, but there is still more room for improvement. Current traditional methods and materials used in treating cardiovascular diseases have shortcomings as is expected with almost any treatment method. As such, there is the need for safe and efficient alternatives especially in medical situations where the traditional routes are not as beneficial to the patient. This is where 3D and bio-printing have promise in becoming effective alternatives. 3D printing is basically the creation of three-dimensional objects from a computer aided design (CAD) model or digital 3D model.[1,2] 3D printing and its variety of applications are no strangers to the world of engineering and it is amazing to see 3D printing rearing its head in the field of medicine through medical engineering. Its uses are seen in a number of ways in specialties such as orthopedics, plastics/dermatology, cardiovascular, surgery etc. Therefore, 3D and bioprinting has great potential to serve as an efficient and safe alternative to the traditional methods and materials in cardiovascular diseases.

In the field of medicine, the priority is to prevent or fix medical problems with little to no harm to the patient. There have therefore been years of work and dedication put into research and experimentations in order to come up with established standard methods and materials to fulfil this priority. These traditional ways of doing things in the medical world seem to work most of the time with little to no complications (given that everything goes as planned). But in cases where these traditional ways are not optimum for the patient, it important to have other safe and efficient options to present and have available for patients. In the field of medicine, the application of 3D printing can be seen in radiology to create a 3D model of a patient's spine to aid in surgical planning, or even in dentistry to produce tooth crowns that fit perfectly in a patient's mouth.[3] Another current application of 3D printing is in the field of orthopedic surgery, where 3D joint implants for the knee and ankle are being used in joint replacement surgeries instead of the standard biocompatible artificial joints such as titanium, stainless steel or cobalt joint implants and encouraging results are being observed and recorded.

In the area of cardiovascular diseases, 3D and bioprinting are being researched for their potential to produce cardiac tissues that can make up the myocardium, heart valves that can grow as the patient ages, and in vasculature with coronary arteries. Though 3D printing is fairly new and its applications still require a lot of research, clinical trials and observations, it has great applications to come. A future application of 3D and bioprinting is in the area of organ transplants. It comes as no surprise that the demand for transplant organs by patients with end stage organ failure diseases exceed the number of available organs from donors. And even with a successful organ transplant, there is a chance of rejection by the patient. This is one of the areas where an efficient and safe alternate to this traditional route might be very beneficial. Imagine if not all patients in end-stage organ diseases had to qualify and wait on a transplant list and could have access to another artificial organ that could work safely and efficiently through bio-printing. This could even benefit the patients who are not able to qualify for these very competitive transplant lists. It is obvious that this kind of medical advancement with bio-printing of organs still has a long way to go in order to be a medically approved and accepted alternative to the traditional ways, but there are still incredible uses of 3D and bioprinting that are currently being researched to pave the way for greater future medical advancements such as these. 3D printing is also showing to be quite beneficial when it comes to patient education, medical training and surgical planning.

This literature review will provide some background information on how 3D and bioprinting works as well as their current and potential applications in fields such as orthopedics, plastics, cardiovascular and in more general areas like patient education, medical training and surgical planning. Though there are currently few adopted applications of 3D printing across medical specialties, the studies presented will show that there is potential for 3D and bioprinting to be used as a safe and efficient alternative when it comes to cardiovascular diseases. In summary, 3D and bioprinting have the capability of giving medicine the upper hand to customize diagnostic/treatment plans that specifically meet each patient's anatomy and overall medical needs and this literature review seeks to delve deeper into that as it discusses some of the relevant studies.

METHODS

A comprehensive literature review was conducted using Google Scholar, Google and Trip Database using the search terms 3D printing, bioprinting, applications in medicine, cardiovascular diseases, orthopedic implants, burn patients and more. The inclusion criteria were studies with primary research, studies conducted in-vivo and clinical trials. The exclusion criteria were studies before 2017 and systematic reviews. Since studies on the application of 3D and bioprinting are relatively new, there were a limited number of experimental research and prospective studies that fulfilled all the inclusion and exclusion criteria. As such, there are some sources before 2017 and systemic review studies that were included in this literature review.

REVIEW OF LITERATURE

While traditional methods usually focus on processes like carving and molding to create a product,[3] 3D printing involves the delivery of thin layers of materials such as collagen, gelatin, alginate, hyaluronic acid (natural polymers) or PCA, polyethylene glycol (synthetic polymers) in a sequential manner and bonding them together to form a solid 3D structure.[4] 3D printing for tissue engineering is bioprinting. 3D bio-printing is a form of 3D printing whereby cells and biomaterials which form bio-inks are used instead of traditional materials like metals and plastics to create 3D constructs that used for functional 3D tissues. 3D bioprinting starts with a model of a structure which is created layer-by-layer out of a bio-ink either mixed with living cells or seeded with cells after the print is complete. Bio-ink is a hydrogel based scaffold. These starting models can come from anywhere, a CT or MRI scan, a computer generated design (CAD) program, or a file downloaded from the internet.[4] 3D bioprinting, which is basically a subset of 3D printing mostly consists of five steps: imaging or scanning of the target tissue, developing the model from the image input with computer-aided software (CAD-CAM), choosing the biomaterial scaffolds and cells according to the tissue type, printing the tissue using a bioprinter and finally allowing the bioprinted tissue to mature. Bioprinting can be applied in-vitro or in-situ settings. Most of the time, for bioprinting to be used for implantation during tissue engineering, it requires the in-vitro setting or testing.[4]

3D printing and bioprinting are emerging as a potential for technological advancement in the various fields of medicine. By 2019, the number of US hospitals that included centralized 3D printing facility into their medical practices increased from just 3 in 2010 to over 100.[3] Specialties such orthopedic surgery, plastic surgery and even cardiovascular surgery are a few that are applying 3D and bioprinting as well as working to have them accepted and approved to be incorporated into medical practice. Though the technology of 3D printing seems to be clothed with so much potential, there is a critical need to ensure that the products made via 3D and bioprinting are safe for the patients they are intended for. Though 3D printers are not regulated by the FDA, their products are. FDA regulation is based on the type of product, its use and potential risk to patients.[3]

In 2017, there was FDA guidelines made available for customized 3D printed products for joint replacements and cranial implants. The FDA has also cleared softwares that can be used to fabricate 3D models of patient's anatomy and leaves it up to medical facilities to be responsible enough to use these softwares diligently for their intended purposes. Though it seems that FDA guidance is lacking for 3D printing in biologic domains (bio-printing) they are covered under the FDA's Center for Biologics Evaluation and Research (CBER). For the medical 3D printed products that are not directly covered under FDA regulations, the State Medical Boards may have jurisdiction if 3D printing becomes harmful to patients. The downside is that, these boards acts on filed complaints instead proactively leading investigations and hopefully in the near future this can be improved upon. The Radiological Society of North America has come out with guidelines for the application of 3D printing at the point-of-care, which ensure that 3D printed anatomical products are safe to be used for diagnostic purposes.[3]

3D and bioprinting applications in orthopedic surgery

Currently, most of the FDA-reviewed 3D medical products are in the specialty of orthopedics.[3] In orthopedics, the technology of 3D printing is being applied in surgery to make custom joint replacements for patients instead of relying on just the traditional joint replacements and encouraging results are being observed and recorded. One study conducted at the department of Graduate Medical Educations and Podiatric surgery at Our Lady of Lourdes Memorial Hospital NY, shows that the implantation of custom-made talar body for a total talar replacement (TTR) shows encouraging results. Patients who undergo total ankle replacement (TAR) due to avascular necrosis (AVN), ankle dislocation, arthritis, infections or tumors are compared to those who undergo customized total talar replacements instead. In one instance, an increase in total joint motion from 21.3° +/- 14° to 32.2°+/-11° was observed in 33 arthritic patients when they were treated with total ankle arthroplasties using custom long-stemmed talar components after their traditional TAR failed.[5] Another instance showed that a patient-specific total talonavicular replacement in a professional rock climber after a fracture showed good restoration of rotation and no evidence of changes to neighboring joints of the foot during a 30-month follow-up with a full body gait analysis and 3D joint kinematics.[5]

Recently published in the JAMA journal is the approval by the FDA of 3D-printed implants designed to treat patients with avascular necrosis of the ankle joint. According to the journal, data supporting the approval of this treatment of AVN of the ankle included results from 32 talus replacement surgeries. A 3-year follow-up from these patients through a standard subjective scoring system showed a decrease of pain from moderate or high levels to mild levels, as well as an overall improvement in the range of motion of the ankle joint.[6] The common adverse effect observed was only pain and scar tissue at the surgery site, which is to be expected for almost every, if not all surgical procedures. The FDA, using the humanitarian device exemption process found this treatment method to be beneficial with relatively low adverse effects.[6] Since this is a relatively new form of treatment, there is the unavailability of years of observation among patients undergoing these procedures and future results will show if there are other complications or adverse effects associated with 3D printed implants for AVN of the ankle. It is great to see that 3D printing is making a positive impact in the world of medicine but it is still a relatively new medical advancement. Though the studies have shown positive results so far, it is hard to efficiently conclude how it would still be accurately applied in the future of medicine in cardiovascular diseases.

3D bioprinting application in skin tissues

Another area that 3D and bioprinting is growing is in the specialty of plastic surgery. There is an ongoing research in the process of using 3D bioprinting in the reconstruction of skin tissues that can be used in the treatment of burn wounds in patients. According to the burn and trauma article in BMC, there are two ways of skin bioprinting which are in-situ and in-vitro.[4] To quote the source, "In the in-situ form of skin bioprinting, there is the direct printing of pre-cultured cells onto the injury site for wound closure which allows for skin tissue maturation at the site of the wound. This allows for precise deposition of cells on the wound, elimination of the need for expensive and time-consuming in-vitro differentiation and the need for multiple surgeries. In the case of in-vitro skin bioprinting, maturation of the bioprinted skin tissue is done in a bioreactor and transplanted to the wound site after maturation.[4]" Other skin appendages (like hair follicles, sweat glands, melanocytes etc.) are being evaluated in recent studies to ensure that these bioprinted skin, function as close to natural skin as possible.[4] There is still a great need for clinical trials to ensure that 3D bioprinting can serve as a safe alternative to the traditional donated skins for these burn patients. Though these studies are still in the testing in-vitro stages, it gives an idea of how 3D and bioprinting can be implemented in cardiovascular diseases.

3D bioprinting application in myocardial tissues

Cardiovascular surgery is also showing huge interest in this relatively new technology. The technology of 3D printing is in the process of being studied to fabricate tissues of the cardiovascular system such as the myocardium, heart valves and even in vasculature like coronary arteries. In diseases such as congestive heart failure or coronary artery disease some of the cardiac tissues get damaged. There is loss of cardiomyocytes and this permanently affects the contractility of the myocardial tissues. This thus, leads to an overall decrease in cardiac output, which eventually can lead to ischemia and then death. Traditionally, an approach to treat damaged heart tissues is via cellular therapy. This treatment regimen is dependent on the implanted cells' ability to survive implantation and be incorporated into the patient's heart tissues. Unfortunately, the use of cellular therapy alone has not been as effective in heart tissue regeneration due to the inability to keep up with functions of the heart.[7,8] This is where the technology of tissue engineering which includes 3D bioprinting seems to be a helpful and promising alternative.

One study evaluates the combination of tissue printing (TP), human cardiac-derived cardiomyocyte progenitor cells (hCMPCs) and biomaterials to investigate their cardiogenic potential for in-vitro and in-vivo use. Human fetal cardiomyocyte progenitor cells and alginate (biomaterial) were included in making a porous bio-scaffolder for 3D bioprinting of the tissues. The study was able to generate a homogenous distribution of cells in the scaffolds in-vitro and showed a cell viability of 92% and 89% on days 1 and 7.[8,9] It showed that a porous structure which is only achieved via tissue printing (bio-printing) preserved the viability of the hCMPCs and could potentially lead to effective cardiac tissue regeneration. To simulate an in-vivo environment, the printed hCMPCs were placed on a Matrigel layer to stimulate cell growth from the matrix. A few cell growths were observed after one day and tubular structures were observed after 1 week. Viability of migrated hCMPCs was demonstrated through a live/death assay after 3 weeks in culture and few cell deaths were observed.[8] This study, though it was mainly performed in-vitro/ex-vivo, had a good control of comparing a porous scaffold to that of a non-porous (solid) scaffold in terms of cell viability. It showed that, cell viability was preserved and free of influence in the porous scaffold as compared to that of the solid scaffold.[8] But it fails to compare the effectiveness of tissue printing for cardiac cell regeneration to that of the traditional cellular therapy. Another study done in-vivo involving rats with infarcted hearts was able to show that the use of bioprinting for cardiac tissues, improved blood vessel formation, increased capillary density and an overall improvement in the function of the heart when using spatial cell arrangments.[9]

3D and bioprinting application in heart valves

Currently there are two options for heart valve replacement surgeries which includes using a mechanical heart valve or a biological heart valve. The advantage of mechanical valves is that they are robust and last a relatively longer time as compared to biological valves. The disadvantage of mechanical valves is that, since they are technically a foreign material in the body they have a tendency to trigger clotting and as such, patients are required to be on a lifelong anticoagulants. On the other hand, biological valves which are from allographic or xenographic sources do not require a lifetime of anticoagulants from their patients, but do tend to have a shorter life span and increase the chances of the patient having to go through another surgery to replace their valves.[7] This is where 3D bioprinting of heart valves stand to have potential of being an alternative to these traditional materials and might even prove to be more beneficial for patients in the long run. They have the potential to remove the need for anticoagulants of patients with artificial heart valves and even have the ability to grow as the patient ages. This will be very helpful in younger patients.

Researchers from the Technical University of Munich and University of Western Australia, are in the process of developing 3D printed artificial heart valves seeded with the patient's own cells and are able to grow as the patient ages. They made use of a melt electro-writing 3D process to create porous scaffolds made up of the patient's cells. The testing phase was done ex-vivo by creating a mock circulatory system with exposure to the same pressures and flow rate of a natural heart valve. An in-house melt electro-writing 3D printer was used to create heart valve implants that mimicked an individual patient's aortic valve. The resulting product was capable of withstanding the demanding functions of a heart valve while still remaining porous enough to allow the patient's cells to colonize the scaffold and proliferate.[10] Though promising results were observed according to ISO (International Organization of Standardization) standards, it is not the best way to explore the long-term functionality of these 3D artificial heart valves and there is the need for actual in-vivo studies and clinical trials to be conducted.[10]

3D bioprinting application in vasculature

Coronary artery diseases are still a burden despite the improvement in treatment therapies. In a procedure like a CABG which is usually indicated in patients who present with blocked coronary arteries due to thrombosis or stenosis, blood needs to be diverted to the heart via a different route. A conduit is often used where other vessels such as the internal thoracic artery, radial artery or the saphenous vein is used. Though the CABG can significantly improve the health in the cardiovascular disease patients, about 30% of these patients are ineligible for this surgical procedure due to a lack of suitable autologous vessels. And with patients who are fortunate enough to have a patent vessel for the bypass there is still a risk of damage during harvesting or graft failure.[7]

Earlier studies have explored the potential of artificial coronary grafts in place of native vessels. In order to replace the native vessels efficiently, the synthesized grafts should be biocompatible, anti-thrombogenic, durable and possess similar compliance and density as the native grafts. The use of Gortex (expanded polytetrafluoroethylene) and Dacron (polyethylene terephthalate), both of which are no strangers in the aorta and peripheral vessel areas have shown disappointing results when used for small diameter and low flow coronary grafts. These synthetic grafts showed a lack of flexibility for its intended purpose in the heart and were also found to trigger some inflammatory responses upon exposure to blood which then led to thrombogenesis.[7] Vascular tissue engineering is the new avenue being explored for artificial CABG grafts. To engineer biomimetic vessels, a scaffold guided approach is used (which involves the use of natural, synthetic biomaterials or decellularized matrix as scaffolds to support cell attachment, infiltration and proliferation during the in-vitro tissue development) or a cell sheet based approach is used (which involves a monolayer of cells being cultured and rolled on a mandrel to produce a tubular conduit mimicking the media and adventitia of an artery). 3D printing comes into the process of tissue engineering through the generation of scaffolds that are patient specific in terms of geometry.[7]

3D printing is showing to be a potential tool that allows for the direct printing of synthetic biomaterials by making use of differentiated endothelial cells, fibroblasts, mesenchymal and hematopoietic stem cells, which can be used in the engineering of biomimetic vessels.[7] Unfortunately, research of 3D printing has not yet been applied directly to the creation of patient-specific coronary artery bypass grafts. Another study demonstrates the power or permeable hierarchical microchannel networks to facilitate mass exchange in tissue exchange constructs through the maintenance of metabolic functions of heart cells in-vitro that will in turn, facilitate angiogenesis and tissue integration, thus efficiently incorporated into the treatment of myocardial infarction.[11] This study is also done in-vitro and is yet to be applied in an in-vivo setting.

One study looks at the potential of 3D printed sugar based stents, that helps in vascular anastomosis in various surgery such as cardiovascular surgery. Vascular anastomosis is used in several surgical procedures such as organ transplant surgeries. The traditional approach to microvascular anastomosis involves stopping the blood flow using a clamp and holding the sides of the vessels next to each other while connecting them by using microvascular sutures (8–0 or 9–0 nylon) under a microscope.[1] This takes a lot of skill and speed for if the anastomosis fails, it can lead to thrombosis thus failure in that particular surgical procedure. This process even becomes more challenging when the vessels being connected together are of different sizes. This is where a temporary stent to keep the vessels opened is very useful.[1]

A recent solution is the use of thermo-poloxamer gel to keep the vessels open during suture-based anastomosis, but with this method, vessel blockage has not been able to be eliminated. The use of sugar based stents for temporary stenting during such surgical procedures show promise due to their potential to prevent thrombogenesis. The challenge with the existing sugar based stents are the molding technique used to make them are not robust enough to produce different dimensions to fit different patients.[1] Blood vessels dimensions differ from patient to patient and even in the same patient, the dimensions of the vessels being connected might be different. This makes an already challenging surgical procedure more complicated as the surgical team has to deal with fiddling with these stents to try to make them fit perfectly in order to get the anastomosis done. 3D printed sugar based stents makes it possible for each patient undergoing such procedures to have a customizable sugar based stent that prevents clotting and eliminates the issues of connecting two unequal vessels.

In this study, the goal was to develop a 3D printed sugar based stent that was non-brittle, had the ability to dissolve following the restoration of blood flow after the surgical anastomosis procedure and had anti-clotting abilities. Previous designs for sugar based stents that used glucose and sucrose only, formed a more brittle glass and broke upon the exposure to mechanical loads which made them less suitable for vascular stents. Therefore, in this study, dextran which is medically approved by the US FDA, was added and significantly improved the ductility of the formed sugar glass. The sugar based stents were also incorporated with sodium citrate (calcium chelator) that helps to prevent clotting.[1] This experiment was performed ex-vivo using the femoral arteries of pigs. The study was able to show an increase in dissolution time following blood flow, an improvement in the prevention of clots and fabricating them via 3D printing increased production time and allowed the dimensions to be easily customized to fit specific dimension of blood vessels. These 3D sugar based stents were also shown to have a reduced amount of leakage when placed in the vessel which is very important during the surgical procedures where surgical glue is used in combination to suturing.[1] The downside is that, this has not yet been performed in-vivo in humans and as such has quite a bit to go before it can be approved as a safe and efficient alternative to the standard methods and material in surgical anastomosis.

When it comes to 3D and bioprinting of whole organs, the technology is still in its infancy and has a long way to go. Recently, researchers from the Chinese Academy of Sciences were able to 3D print a cardiac tissue that kept rhythm (labeled alive) for at about 6 months. A six-axis robotic arm was converted into a 3D bioprinter, allowing the printing of the complex-shaped blood vessel scaffolds from all angles. In addition to the converted bioprinter, the researchers added an oil bath to replicate a more natural organ development process. They then printed mono and multilayer cells onto the printed blood vessel scaffold and cultured them for a period of time to elicit cell-to-cell contact which they achieved via hydrophobicity (water repelling) and thus, enhanced the formation of new blood vessels. These scientists are working on developing this novel approach of bioprinting to be incorporated into the creation of functional artificial tissues and organs in an in-vitro setting and soon in in-vivo settings as well.[12] Another study in Zurich is works on 3D printing to create a soft artificial heart with two ventricles using a silicone mold that was able to beat for about 30 minutes. Using a hybrid mock circulation, a blood flow rate of 2.2L/min against an afterload of 1.11mm/Hg s/mL was able to be achieved.[13]

Finally, an area where the application of 3D printing is beneficial to medicine is in patient education, medical training and surgical planning. Customized 3D models can be made for patients to have a more vivid picture of where the medical problem is and how it is going to be fixed surgically. This might make it easier for patients to understand what is going to be performed on them in surgery instead of having to listen to a bunch of technical terms and explanations. It even makes it easier for patients who require translations to have a better understanding when they do not have to rely totally on their imagination but have a physical model to look at and handle. 3D printing is also helpful for the surgical team in surgery planning to make sure they are all on the same page with their surgical approach and steps. This benefit is not only limited to patient education or surgical planning but in some areas of medical training like anatomy and vascular access as well. A study showed that, 19 trainees undergoing femoral artery access training, preferred the use the 3D models compared to the use of commercially simulators. The model was created to look realistic on ultrasound imaging and even had a palpable pulse.[14] Another study sought to demonstrate the accuracy and reliability of 3D printed models in the treatment of congenital heart diseases and states that 3D printing is reliable and suitable for the analysis of congenital diseases of the heart. But acknowledges that these studies are still subject to the limits of 3D printing and its potential bias.[15,16] Though studies show that 3D printing could improve medical understanding, teaching or surgical training, there are inadequate studies to distinctly demonstrate these benefits for now.

ANALYSIS AND DISCUSSION

3D and bioprinting are relatively novel technological advancements in the field of medicine and as such has an inadequate amount of research on its current and potential applications. For 3D and bioprinting to be accepted as an alternative standard, there has to be the availability of concrete data to support its safety and efficiency. Fortunately, there are some studies that are able to show that 3D printing is actually being safely and efficiently applied in some fields of medicine. In orthopedic surgery, studies have been able to show that 3D printed ankle joint implants have been able to show encouraging results in patients with AVN, so much so that the FDA has actually approved the use of 3D printed joints in ankle replacement surgeries.[5,6] So far, the 3D printed implants are proving to be safe with no direct adverse effects but since this is relatively new, the study only has the performance of these implants over a relatively short period of time via patient follow-up to go off on. This is still not enough so adjustments of the safety and functionality of this new treatment option might be better deducted as time goes on. In the field of plastic surgery with burn patients, there are also studies going on with skin bioprinting to be used in reconstruction surgeries. These studies are still in their testing stage and a lot of them have not even been performed in-vivo. This makes it very challenging to deduce the effectiveness of bioprinting in the treatment of burn wounds since no patient population is currently being used for this study.

A lot of the studies above have only been able to highlight some of the possible applications of 3D printing and bioprinting in cardiovascular disease via in-vitro and ex-vivo studies. 3D and bio-printing are being studied to be used in treatments of the cardiovascular realm such as in the tissue engineering of myocardium, heart valves, coronary arteries and many more. Since the traditional method of cellular therapy for tissue regeneration in the face of myocardial injury is limited, 3D bio-printing can be a way to efficiently induce the growth of viable cell and tissues in the heart. By implementing the use of porous bioscaffolders (which allows cells to infiltrate it better than in non-porous scaffolds) from a patient's progenitor cells in combination with biomaterials/bioink like alginate, cells can have a greater chance of survival. The 3D printed bioscaffold is able to provide a cohesive mold for the seeded cells to grow and mature efficiently. This increases the chances of a successful implantation of the mature tissue into the patient and thus, enhance the integration of the implanted tissues into the patient's native myocardial tissues to help restore cardiac functions after a cardiac injury.[8] The challenge is that, since 3D printing is still fairly new it is very hard to extrapolate these studies into the patient population of interest in order to come out with reliable data.

Another area in cardiovascular diseases that 3D printing shows great promise is in heart valve replacements. Currently, the treatment of heart valve dysfunctions or failures, are limited to two options. The use of biological or mechanical valves to replace incompetent native valves. The problem with just these two treatment options is that, with mechanical valves, it has a long life span but it is susceptible to blood clots. This resigns the patient to a fate of lifelong anti-coagulants. On the other hand, biological valves, do not require the patients to be on lifelong anticoagulants, but they have a short lifespan and puts the patient at risk for multiple surgeries. 3D printing is being researched to produce patient-specific heart valves that grow as the patient ages. Since these bio-printed heart valves are seeded with the patient's cells, it is not recognized as foreign and treated as such.[9] With the valves aging with their patient, it removes the problem of the patient outgrowing their valves and standing the risk of going into surgery for another valve replacement.

As for the 3D printing of functioning hearts there are a number of studies taken place that is getting this extraordinary technological advancement closer to a foreseeable future. Research is heading in the right direction as there are 3D printed cardiac tissues that can maintain rhythm but there is still long way to go. Though 3D printing and bio-printing shows a great potential for its application in cardiovascular diseases, it is quite behind traditional approaches in terms of years and data of support. There is a lack of concrete evidence to depict the actual benefits of 3D printing in changing the outcomes of patients with cardiovascular diseases and as such there is the need for prospective clinical studies and trials. 3D printing also shows potential to be beneficial in medical training, patient education and surgical planning, but there is still the need to create well-designed studies to prove this benefit.

For tissue engineering via 3D printing to be successfully incorporated into cardiovascular diseases, there is the need to ensure that the materials used for 3D and bioprinting are safe and that biomaterials/bio-inks are not going to cause side effects to patients or negatively affect the functions of other organs of the body. There is the need for studies to show results proving that they are not just biocompatible, but in the long run, will not be harmful to crucial organs such as the kidney and liver. With 3D printed implants of joints being so new in treatment options, not enough time has passed to show that they have no long-term adverse effects in patients. Biomaterials such as silicone are used constantly in plastics for breast implants but it can still not be a concluded that the use of biomaterials as these will have no long term adverse effects.

There are so many different approaches to 3D and bioprinting that can produce different results and all these still need to be accurately studied and tested to make sure that patients who undergo these trials or even begin to use them, are not put in harm's way. We need the time and resources to explore this further in order to make sure that it is at least as safe and effective as the traditional options. There also needs to be concrete data to show the accessibility of 3D printed products to diverse patient populations and at a reasonable cost as well. It should be available and accessible to patients of various socio-economic levels.

CONCLUSIONS

Though the application of 3D printing and bioprinting seems to be growing fast and can be considered to be full of promise, they are relatively new technologies and still in need of years of clinical trials and research. Several studies conducted in various specialties in healthcare are showing a future for 3D and bioprinting applications in medicine and in cardiovascular diseases. Looking at recent studies, the specialty of orthopedics seems to be at the forefront in terms of the actual utilization of 3D printing as a safe and efficient alternative to native materials and methods. It is impressive to see that the FDA has been able to approve 3D printed ankle joint replacements for patients with ankle joint AVN. In the world of cardiovascular diseases, 3D and bioprinting still need more time in research for in-vivo studies, clinical trials and to be finally approved and accepted as safe and efficient alternatives. Having this other option for cardiovascular diseases will enable increased access for patients that may be faced with limited diagnostic and treatment options due to financial, socio-economic, language or biological barriers.

There are so many questions that need to be answered for 3D printing to be effectively implemented into the medical practice of the cardiovascular world. For 3D and bioprinting to be approved and adopted as efficient and safe alternatives in cardiovascular diseases, there has to be more research conducted in in-vivo settings that go on to be incorporated into clinical trials in order to properly assess their efficiency and safety in patients. Currently, there is a lack of such studies and research, but it does not mean that they do not have the potential to provide this medical benefit. The current studies, though having limitations as stated above, do show the applicability of 3D and bioprinting in the medical field. To conclude, 3D and bioprinting, in the near future, could serve as an efficient and safe alternative to traditional methods and materials in cardiovascular diseases, but for now, it still needs more time to get there.

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