MJoSHT
Malaysian Journal of Science, Health & Technology
[mjosht.usim.edu.my]

USIM

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One printed heart, please – 3D Bioprinting in Medicine: Applications and Ethical Issues

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***Abstract*— Background: Organ bioprinting is only two decades old but has made tremendous progress in advancements of synthetic implants, reconstructive surgeries, prosthetic developments, and medical education. These are made possible due to the increasing affordability of bioprinters and their capability for tailor-made applications. However, the ethical considerations of bioprinting research and applications are still in its infancy. This article summarises the current literature on 3D bioprinting applications in medicine and its ethical concerns. Methods: EBSCOhost service search using related terms was applied on four databases (PubMed, EBSCOhost eBooks, Medline, and Academic Search Complete). Inclusion criteria consisted of any publication or academic article in electronic media discussing the use of 3D bioprinting in medicine and its ethical concerns. Results: A total of 41 articles were identified from the aforementioned databases discussing the applications of 3D bioprinting in medicine, screening of which left only 35 articles that met the inclusion criteria. 24 articles discussed the applications of 3D bioprinting, nine articles discussed the ethical concerns related, and two articles discussed both bioprinting and its ethical implications. Conclusions: 3D bioprinting offer limitless opportunities in the field of medical education but face limitations in real clinical application. Specific guidelines on ethical use of 3D bioprinting are urgently for its appropriate regulation.**

***Keywords*— 3D bioprinting, 3D printing in medicine, ethical issues**

I. INTRODUCTION

The concept for three-dimensional (3D) printing started in 1984 when Charles Hull created models using layer by layer application of resin known as stereolithography. The biomedical application of this technique was built upon Gabor Forgacs' discovery of how cells can be combined into completely new spatial structures. The world's first synthetic organ was constructed using a spatial scaffold in 2000; the recipient's host cells were coated on the scaffold to reduce the possibility of 'rejection' by the patient's immune system.

Four years later, Forgacs presented his bioprinter that allowed 3D directed biodegradation, i.e. printing using live cells but without the use of a scaffold. The first biodegraded blood vessel was created using this bioprinter. Since then, companies have been racing to produce a plethora of bioprinting machine, some as cheap as only $5,000 [1]. At present, 3D bioprinting is mostly used for simulating and reconstructing hard tissues while the fabrication of complex organs is still at an exploratory stage [2].

Although bioprinting is still in its infancy, the technology is advancing rapidly to create many things from organs-on-chips [3] to patient-specific surgical plates [4]. Figure 1 depicts the 3D bioprinting system schematics. The model design begins by collecting precise information of the target tissues and organs. A standard CT or MRI scan is used to get the exact dimensions of the tissue. The server then conveys the information to direct the printer for printing the tissues (Figure 1B). The cell viability is maintained by the printer during the fabrication process (Figure 1C). Typically, a tissue is composed of several types of cells, and the cellular fusion is facilitated by the use of bioinks (Figure 1C) [5]. Bioinks are a combination of living cells and a compatible base like collagen, gelatin, silk, alginate or nanocellulose. The complete substance is patient- and function-specific.

The 3D printing process deposits the bioink layer-by-layer thinly (each layer is 0.5 mm or less). The number of nozzles and the type of tissue being printed determines the rate and size of the deposits. The bioink layer starts as a viscous liquid and solidifies to hold its shape. This continues as more layers are deposited. Application of UV light, specific chemicals, or even heat is used to promote crosslinking in the blending and solidification process.

3D printers have been used to fabricate certain types of hard tissues in clinical trials [6]. However, complex tissues have not been successfully constructed by 3D bioprinters. Perhaps in the future, 3D bioprinters could be utilised to print organs for repairing damaged body parts and to imitate functional tissues for therapy, research, and drug testings.

The cost of tissue replacement treatment could be reduced as 3D bioprinting can be used for personalised therapy. The incompatibilities caused by combining biocompatible and

biodegradable materials can be reduced with 3D bioprinting [7]. Thus, 3D bioprinting can lead to a novel technology revolution in medicine and eliminate the issue of tissue shortages or incompatibilities in organ donations and transplantations.

The goal of bioprinting is to imitate the actual micro- and macro-environment of human tissues and organs. This is crucial in drug testing and clinical trials, with the potential to reduce the need for animal trials. The manifold possibilities presented by the 3D bioprinting technology are the purpose of this literature review to discuss the ethical issues arising from its use.

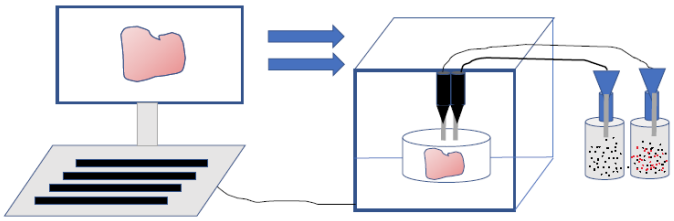

Fig. 1 A diagram depicting a common 3D bioprinting set up. A, Server; for designing the model. B, 3D bio-printer; the core facility for 3D bio-printing. C, the source for the different cell types. [Adapted from [2]]

II. Methods

Articles were searched using EBSCOhost service in four databases which were: EBSCOhost eBook collection, MEDLINE complete, PubMed, and Academic Search Complete. The articles selected were published from 2011 to 2020. The keywords used were '3D bioprinting' or '3D printing organs' or '3D printing in medicine' or 'bioprinting organs' or 'bioprinting tissues' or 'bioprinting 3D' or 'bioprinting ethics' and 'application' or 'practice' or 'approach' or 'strategies' or 'implementation' or 'utilisation' or 'use' and 'ethical issue' or 'ethical concern' or 'ethic' or 'ethical principle' or 'ethical consideration' or 'ethical dilemma' or 'ethical practice' or 'ethical problem'.

Articles were included if they contain anything related to the application of 3D bioprinting or ethics in 3D bioprinting and were written in English. Articles were excluded if they were published in other languages than English, and if they specified real organ transplantation.

III. Results

A total of 41 articles were identified from the databases discussing the applications of 3D bioprinting in medicine. Seven articles were duplicates and considered to be unrelated after the title was screened, which left 35 articles. 24 articles discussed the applications of 3D bioprinting, nine articles discussed ethical concerns related, and two articles discussed both.

IV. Discussion

Researchers are using 3D bioprinters to reshape the healthcare landscape outside of the clinics and operating theatres. Since 3D bioprinting was introduced in the medical domain in the last decade, it has been used in a variety of educational, and surgical applications.

A. Applications in medical practice and education

Medical models exhibit plays an important role in teaching basic and clinic medicine. However, the conventional process of manufacturing medical models is time consuming, complex, and expensive. With 3D bioprinters, production of medical models from digital designs to producing physical objects is faster and easier. 3D printing can reproduce highly accurate anatomical structures that can reveal normal or pathological variations at a relatively low cost compared with original specimens [8]. Realistic internal organs and tissue structures, such as the heart, can be accurately displayed to improve students' anatomy, physiology, and pathology knowledge [9].

In 2016, this state-of-the-art technology was introduced at Rhode Island Hospital (RIH) [10]. A trauma case patient suffered severe facial injuries which required multistage surgeries to correct his maxillofacial damage. The surgical team 3D printed the victim's facial skeleton as an on-table surgical reference to correct the complicated anatomic deformity during the various procedures.

Not only are 3D printers useful for medical students and residents, it can be used to facilitate patient-physician consultation. This was demonstrated in a 23-week foetus diagnosed with myelomeningocele *in utero* [10]. An individualised educational model was created to demonstrate this condition by combining MRI and CT scan data that includes bony structure, soft tissue and the anatomic defects of the foetus whose spinal canal failed to close. This printed model also helped resident surgeons to identify critical anatomical landmarks for this rare foetal surgery.

Surgical training is important to help young surgeons perfect their skills; the gold standard in developing such skills is the use of cadaver models [11]. Unfortunately, cadavers are limited in terms of cost, reproducibility, and availability [12], and the constant use of the same cadaver can destroy the normal anatomy [11]. Hence, 3D bioprinted models that create accurate facsimile of human organs can provide a viable alternative to the use of cadavers.

Difficult surgery cases require preoperative assessment and practice to guarantee achievement and success in the surgery. With 3D printers, surgeons can reconstruct CT or MRI medical image data and print the parts involved in the surgery. The surgeons can then design the preoperative surgical process and customise their postoperative treatment using the printed models. For example, a patient with multiple liver metastases from colorectal malignancy had a 3D-printed liver model used to perform a hepatectomy [13]. The patient underwent chemotherapy before surgery, so one of the tumors shrank and was not detected by ultrasonography. Using 3D combined images, the resection line was determined, and the team changed the image data into a 3D-printed liver model to plan the hepatectomy and completed the surgery with negative cut edges. Different specialists have their own distinctive 2D comprehension of the spatial connection between blood vessels and tumours which can be overcome with the use of the 3D-printed liver model [13]. This accentuated preparation is hoped to be translated into shorter operation times and better patient outcomes.

In addition, researchers have successfully printed the world's first 3D vascularised engineered heart complete with cells, blood vessels, ventricles, and chambers [14]. The heart was made using patient's own cells and specific biological materials served as the bioinks. This proof-of-concept miniature size model is still considered a huge achievement milestone in the field of personalised regenerative medicine, and hopefully present an alternative solution to organ transplantation.

3D printing is a robotised layer-by-layer production method which presents the possibility of tailored and complex drug products. It is timesaving, has great adaptability, and exceptional assembling capacities which utilises computer-aided design. This differentiates 3D printers from traditional manufacturing processes in three aspects. First, 3D printing allows complex refinement of the 3D printed items to regulate drug targeting and release kinetics [15]. Secondly, personalisation is made possible by customising the amount of drug delivered to a patient depending on the patient's weight and metabolism [16], and the 3D printing process can further improve patients' compliance through individualised dosing by combining all of the patients' medications into a single daily dose [17]. Lastly, 3D printers can create on-demand formulation through immediate printing of drugs for patients at times of resource constraints, and for urgent consumption [18]. Drug efficacy, safety, and tolerability have been upgraded by the innovation of various 3D printing techniques and has been approved by the US FDA for commercial and industrial use [19].

3D printers have sparked homegrown innovations and spawned numerous medically related start-ups. A number of healthcare professionals and advocates working with patients to create do-it-yourself devices to meet individual medical needs have emerged. For example, a 3D printable prosthetic hand that was originally developed for a 5-year-old-boy was made freely available for download, and its parts can be reprinted for $150 [20]. Other start-up companies include Spectroplast which prints medical implants using biocompatible silicone, Colossus that sought to reuse plastic waste into huge 3D models, and many more [21].

3D bioprinting is still a recent technology that needs further development in various areas to make it a more viable option. For instance, production of a patient-specific 3D model is dependent on the quality of the original medical imaging scans; the accuracy of current imaging techniques and its data processing technology must be improved to support 3D bioprinting production. Although there is a large range of commercially available 3D printers, there are no clear gold standard to guide its manufacture, processes, and product. Available bioprinting materials include biomaterials, metal or acrylic; however each bioprinter can print only one type of material, and the ability to combine these materials by a single 3D printer remains limited. The cost of 3D bioprinting is also prohibitive; its hardware, software, and printing materials are specialised and expensive. At present, 3D printers can only be applied to structures that do not surpass certain dimensions because 3D printers are unable to produce extremely large parts, e.g. the entire human body.

The production time of 3D bioprinting depends on the complexity and size of the models. Many teams are able to perform this process within 24 hours, but this means that 3D printing can only be used in elective surgeries. In addition, because this is such a new technology, there is incomplete data on cost-benefit analysis, and objective patient outcomes.

B. 3D bioprinting ethical issues

The first ethical concern with regards to 3D bioprinting: are we free to bioprint anything? Are there anything that ought to not be bioprinted? Should we even be allowed to print any biological organ such as kidneys and use biological cells as its bioink? To answer these questions, the purpose of 3D bioprinting should be determined first. 3D bioprinting not only proposes a novel opportunity to relieve pain through custom-made treatments, it can produce individualised therapeutics at industrial scale [22]. There are a lot of parties at stake in this situation, especially pharmaceutical companies. For example, 3D printed functional islet cells of the pancreas could, theoretically, deplete the incidence of insulin-dependent diabetes patients, which is a significant burden on health care budgets of people all over the world [23]. Even better, large scale use of safe and profitable 3D bioprinting could help to upgrade the health of the population.

Lack of regulation means that anyone can own and operate a 3D printer. Almost anyone can buy a 3D bioprinter, bioinks and cells, a computer, a good connection to the Internet, and use freely available data to bioprint tissues in the comfort of their own home [24]. Nevertheless, even if one can bioprint a whole organ at their home, it would not go far without a surgeon and the whole medical team to actually implant it. Still, it is imaginable that anyone can use a 3D bioprinter to develop a bioweapon that could threaten mankind [25]. This is usually seen primarily in institutional settings, which leads to the question of proper regulation of 3D bioprinting.

Should there be ethical limits to the types of bioinks that we can use? What if it is possible to print an organ using cells that were derived from non-human sources to be implanted in a human patient? What about the danger of zoonosis, i.e. diseases that can be transmitted to humans from animals? Would it be more morally complicated than administering a patient's own cells to print a replacement organ for that same patient? Would it pose bigger risks of harm to the patient such as teratoma formation induced from the manufacturing autologous induced pluripotent stem cells (aIPSC) [26]?

Should criteria for the origin of cell lines used in bioprinting be a definitive factor on whether it is ethical to print using that bioink? While the probable health outcomes for the patient is one of the concerns, there could be patients who protest the use of cells originated from animals, be it from religious or lifestyle choices [27]. Some institutes or patients may think it is unlawful to use human embryonic tissues as the cellular ink for 3D printed organs [28]. If some cell line sources that can be acquired in other countries are forbidden by regulation in another country, it could lead to medical tourism, e.g. stem cells therapy tourism operating an ambiguous economy of hope without appropriate regulatory ground rules [29]. The speed of 3D bioprinting growth is outstripping regulatory authorities capacity to make laws to address the risks to patients.

There are other issues that may affect the moral acceptability of using bioinks from non-autologous cells. For instance, using stem cell bioink sourced from donors who were pressured to donate, or donors who do not have the capacity to give informed consent for the use of their cells, e.g. unconscious patients in intensive care units. On account of this, a trustee such as the family members may agree on behalf of a powerless participant. In any case, potential donors and their families should fully understand the risks, and have sufficient information to manage their expectations.

The use of bioinks from autologous cells can be often seen as ethically clear because they are derived from the patient's own body [30]. Even so, the behaviour of the cells remains unknown after being printed and implanted. Will it migrate away to other parts of the body? Will it stay in its original printed form or will they mutate into vicious cancerous cells? There have been reports of lesions developing within the kidneys of patients following marrow-derived cells treatment for lupus nephritis [31], and components of bone developing around a patient's eyelid who received a stem cell boosted facelift [32]. These reports raised concerns for the safety of using autologous cells.

3D bioprinting is a device within the more extensive arena of stem cell therapy and tissue engineering. Any harm from these two fields can be carried over to bioprinting. The more complicated the bioprinted tissues, the more potential for harm. This is a particular concern for artificial organ bioprinting in the long term [33]. Since 3D bioprinting treatment is patient-specific, preceding randomised safety trials on other patients are not needed because it will not produce similar applicable findings. Thus, it would be immoral and of little clinical value to test the safety of organ bioprinting in a randomised clinical trial on a heterogenous population of non-specific subjects; how is it ethically acceptable to test the safety of an organ which has been specially customised for person A with person A's own stem cells on another person?

On that point, a patient waiting for a biofabricated organ would likely be their own 'lab rat' for their 3D printed organ. In contrast to standard Phase I of clinical drug trials where risks are managed by dosage testing, patients in 3D bioprinting assessment trials do not have the privilege to withdraw from the trial subsequently after implantation. Furthermore, this treatment trial may be irreversible, and any attempt of reversing the implantation may result in further harm. Dropping out of the trial is almost impossible since patients who want to be transplanted with a novel and experimental organ choose to do so because of a life-threatening condition. Consequently, these patients may lose the opportunity and eligibility for future treatments if anything goes wrong with the trial [34]. Hence, lack of access to a cure because of the possible damages and its irreversibility is immoral. The risk of harm could be bigger if the tissue targets a neurological condition [35] or worse, exacerbates pre-existing neurological problems [36].

A major concern with 3D bioprinting is that it seeks to homogenise and upgrade personalised medical treatments that do not meet any present regulation. Before 2016, regulatory agencies and bodies were undecided on how to address possible and unpredictable harms linked with 3D bioprinting [37]. In December 2017, the U.S. Food and Drug Administration (FDA) published the Technical Considerations for Additive Manufactured Medical Devices: Guidance for Industry and Food and Drug Administration Staff. This framework is a guide for the design and manufacturing considerations of medical devices created with 3D printing, which is a type of additive manufacturing (AM). However, the document stated only on design, manufacturing, and testing considerations of devices. There are other works in progress on policies specific to AM of drugs and human tissue, for instance, the Emerging Technology Programme which was developed by the FDA's Center for Drug Evaluation and Research (CDER). Under this programme, pharmaceutical companies can partner with the FDA early in their research efforts, which include use of 3D printing to manufacture drugs. The document, while bounded in its extent of application, did mention regulatory classification defining common terms used such as "custom device" versus "patient-specific device," and citing proper consensus standards for manufacturing both "standard-sized" and "patient-matched" designs [38, 39]. This coherence of terminology is an important starting point for manufacturers to standardise research and production in 3D bioprinting.

It is urgent that relevant authorities and stakeholders engage in a detailed discussion on the key risks of significant harm linked with testing 3D bioprinting for humans. This discussion should delve into concerns such as whether limits should be imposed on what can be allowed to be bioprinted in medicine, the ethical questions of the irreversibility of the procedure, the gold standard for clinical trials to test 3D bioprinting, strengthening the regulatory framework, and testing of 3D bioprinting treatments.

C. Islamic views on 3D bioprinting

Generally, Islamic laws concerning 3D bioprinting are similar to the case of stem cell research [40]. Islamic jurisprudence are bound by the principle of al-Maqsad which is sourced from the principle of al-Umur bi maqasidiha, i.e. matters are judged by intentions [41] to avert harm and to preserve the essential value of human life. These purposes are in congruence with the principle of al-Dararu yuzal (preventing harm) which says that it is a responsibility to get rid of any harm that is prohibited in religion [42].

The main objective of 3D bioprinting of human organs is to print new tissues and organs, which can be used either for medical treatment or for cosmetic purpose. If the aim of bioprinting is for the sake of preserving human life, e.g. to reconstruct damaged skin or to replace organs, it is considered as permissible. In this case, when it involves the harm of death because of the dangers of rejection from organ transplantation, donor shortage, and exorbitant medical expense to care for the new organ, another possible solution is to use the 3D-bioprinting which might remove any known harm.

Another issue that has been considered by Islamic laws is the use of autologous stem cells as a base substance for the 3D-bioprinting process for an individual. Under the maxim of injury (al-Dararu yuzal), any process to derive stem cells should incur a lesser injury than the first injury (i.e. the disease or pathological condition to be corrected with 3D bioprinting itself), in line with the maxim which is al-Dararu la yuzal bi mithlih, i.e. harm cannot be fended off with the same degree like it. In such an event, if one of the processes to

obtain the stem cells has a bigger potential to injure the body, it should be avoided. However, this is only an early review in this novel field of technology. Another area to be concern from the Islamic point of view are the ingredients used in the whole 3D bioprinting process including the bioinks. Therefore, more research is required to ensure that 3D printing of human organs are safer, stable, and its developments are in line with the Islamic faith [43].

IV. CONCLUSIONS

3D printing is indeed a game-changer, especially in medicine since its introduction in 1984. 3D bioprinting has been applied to produce almost every human tissue tested for clinical application, from blood vessels to neural tissue. It is only a matter of time before we could print a functioning biological human organ that could solve the decades long problem of inadequate organ donation. 3D bioprinting can be the future of better healthcare, not only as a treatment option but also to better educate and train residents, surgeons, and patients. Making 3D bioprinting available in developing and underdeveloped countries to ensure accessible healthcare for all should also be a goal. All stakeholders should work together to create and support regulatory mechanisms for 3D bioprinting, including religious bodies, regulatory authorities, and professional organisations. All these findings should be formulated and disseminated appropriately to educate greater society on the practical and ethical use of 3D bioprinting.

ACKNOWLEDGEMENT

We would like to thank the Faculty of Medicine and Health Sciences, Universiti Sains Islam Malaysia (USIM) for supporting this manuscript submission.

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