Investigating 3D Bioprinting as a Solution to the Kidney Shortage in the United States

Thousand Oaks High School

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Abstract:

Currently there are over 100,000 people in the United States on waiting lists to receive one of the approximately 16,000 kidneys that are donated per year. During this same one year period, over 5,000 people on these lists will have died while waiting for a donor kidney, and more will get added to the lists every day. For a number of reasons that will be discussed later in the paper, the primary method in use today for providing kidneys to patients in need is harvesting from deceased donors. However, deceased donor kidneys have a much shorter life expectancy than living donor kidneys, leading to them often to be only short term solutions and resulting in the kidney crisis to continue to compound with no donor-based resolution in sight. And while living donor kidney donations have better life expectancies than deceased donor kidneys and the number of living donor kidney donations has been gradually increasing in recent years in the United States, these two methods of kidney donation are projected to remain at a level well below the needs of patients with kidney disease into the future. This paper will examine the use of the new 3D Bioprinting technology, which has already been proven using bioinks to precisely print less complex living structures, as a potential solution to this kidney shortage in the United States.

Kidney Shortage:

The United States kidney shortage continues to become more problematic despite an increase of willing donors. As of 2017, “There are currently 121,678 people waiting for lifesaving organ transplants in the U.S. Of these, 100,791 await kidney transplants” (National Kidney Foundation, 2018). In the United States alone, approximately 5,000 people die per year waiting for a life saving kidney transplant, and another 5,000 are removed from the transplant lists each year because they are no longer healthy enough to receive a donor kidney (LKDN, 2019).

Because of several factors to include the National Organ Transplant Act of 1984, the main method used today for providing kidneys to patients is through the use of deceased donors (UNOS, 2017). The National Organ Transplant Act (NOTA) banned the acquisition of human organs in exchange for money, primarily to prevent the exploitation of socioeconomically disadvantaged people, who were most likely to sell their organs. Many people believed it was unethical to “buy life”, however many other people who are not willing to potentially wait for years for a kidney donor continue to leave the United States to acquire live donor kidneys from the overseas black markets. For those patients who do chose to remain within the United States, the live donor kidney transplantation (LDKT) still account for one-third of kidney transplants performed in the United States. In fact, there has been a remarkable 265% increase in the annual number of living donors from 1988 to 2004. In each year during this time period, there was an increase in living donations relative to the previous year. This increase in living donation has been attributed to several factors, including advances in histocompatibility testing, new laparoscopic surgical techniques, findings of comparable graft survival outcomes with genetically related and unrelated living donors, and greater public awareness about the need for organ donors (Rodrigue, 2013). However, even with this positive live donor kidney donation trend, available kidneys are still failing to keep up with the number of patients needing life saving transplants.

Current Methods Of Treating Kidney Disease

There are two major methods of treating people with chronic kidney disease in practice today, dialysis treatment and kidney transplantation. Dialysis is a recurring treatment process that filters waste and extra fluid from your blood when your kidneys are unable to adequately perform their jobs. In hemodialysis, the blood of a person is purified through the use of a machine that cycles the blood from a person, removes the blood waste and free water from it, and then returns it to the body. In peritoneal dialysis, a thin tube is inserted into the patient' abdomen that fills their abdominal cavity with a solution that collects waste and excess fluids. The "dirty" solution is then drained from the body, removing the waste and free water along with it. Although both types of dialysis can be effective temporary solutions for patients with kidney disease, they can also cause many other potentially life threatening problems in a patient such as, sepsis (blood poisoning), low blood pressure, insomnia, bone and joint pain, and hernias (NHS 2018). So while it has been shown that dialysis treatments can treat the symptoms of some forms of kidney disease to keep a patient alive, dialysis does not actually address the patient's underlying kidney disease and will not be a focus of this paper.

The second, and more enduring, treatment option for patients with kidney disease is kidney replacement via transplantation. Kidney Transplantation is a procedure to surgically remove a

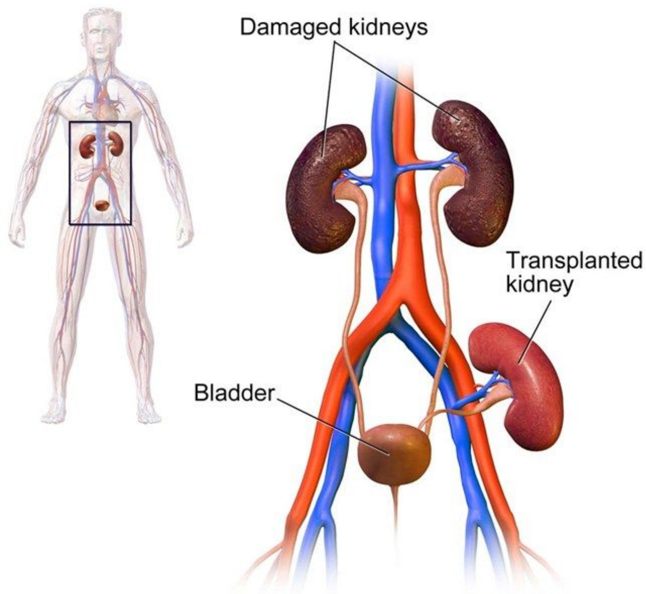


Figure 1. Kidney transplant technique and transplant location (Blaus 2019)

damaged or diseased kidney and replace it with a healthy kidney, from a compatible donor. There are two sources for donated kidneys, kidneys from deceased donors comprise approximately two thirds of the total kidney donations in the United States every year, and those from live donors that comprise the other third. However, the method of transplanting kidneys from deceased donors is not fully effective since these kidneys from deceased donors tend to fail much quicker than those from live donors, shortening the lifespan of the patients who receive the kidneys (National Kidney Registry, 2018). This is due to kidneys picking up and growing germs and pathogens that they are exposed to once they are removed from a cadaver . Despite the lower donation numbers, living donor kidney transplants continue to offer superior outcomes compared to maintenance dialysis and deceased donor kidney transplantation for individuals with end-stage kidney disease (Borislav 2017). For those patients who do chose to remain within the United

States, the live donor kidney transplantation (LDKT) still account for one-third of kidney transplants performed in the United States. In fact, there has been a remarkable 265% increase in the annual number of living donors from 1988 to 2004. In each year during this time period, there was an increase in living donations relative to the previous year. This increase in living donation has been attributed to several factors, including advances in histocompatibility testing, new laparoscopic surgical techniques, findings of comparable graft survival outcomes with genetically related and unrelated living donors, and greater public awareness about the need for organ donors (Rodrigue, 2013). However, even with this positive live donor kidney donation trend, available kidneys are still failing to keep up with the number of patients needing life saving transplants. So in summary, while more donor kidneys are available from deceased donors in the United States, living donor kidneys can be considered the most optimal method of preventing death from kidney disease or failure. As discussed earlier in the paper, only 12% of patients with kidney disease on the kidney transplant list receive a donated kidney from any source during a given year. This significant disparity between the number of patients in need of kidneys and the availability of organ donors each year had led to innovative approaches such as the use of the expanded criteria donor, otherwise known as ECD, to increase the pool of available kidneys for otherwise healthy patients. Deceased donor kidneys are considered expanded criteria if they meet the following conditions: donor age more than or equal to 60 years or donor age 50 to 59 years, with at least two of the following criteria: serum creatinine more than 1.5 mg/dL, death due to cerebrovascular accident, or history of hypertension (Sung, 2005). By expanding the donor criteria, in 2005, ECD kidneys constituted 17% of all deceased donor kidneys transplanted, or about 3,000 ECD donated kidneys that year. However, kidney transplants from ECD donors have experienced a 70% greater risk of graft failure than those from the lowest-risk non-ECD donors. Additionally, data shows that since these ECD kidneys will survive on average for only about five years, ECD kidneys are not a permanent solution (Ratner 2002). In contrast, living donor kidneys have been shown to have a 20% greater chance of surviving between 5 and 15 years after transplant than deceased donor kidneys (UNOS). So while there is a significant shortage of donor kidneys to meet patient's demand in the United States, kidney transplants have been shown to be the most effective kidney disease treatment option, especially if the kidneys are from a living donor.

Introduction to 3D Bioprinting

To address the growing gap between the number of patients with kidney disease needing a kidney transplant and the number of available donated kidneys each year, a potential solution could be to utilize the new 3D bioprinting technology to "print" replacement kidneys for these patients in a lab. Bioprinting is a 3D creation technology that is already being used to construct functional human tissues, and even some living organs, with a matrix of live cells. While still in developmental stages, bioprinting has already shown its potential in regenerative medicine to create a plethora of human tissues, including skin, cartilage, and bone. Currently 3D bioprinters are able to print some complex tissue and are mainly being used to print implants and prosthetics in commercial medicine (Malik, 2015).

However, current bioprinting approaches still have mechanical challenges in terms of very precise cell deposition and controlled bioink printing. No concrete method to bioprinting large complex structures such as human kidney has emerged yet, however advances in this technology is being made at Universities and private research laboratories everyday. According to experts in the field, 3D bioprinting introduces a versatile fabrication technique that may address the growing organ shortage (Mandrycky et al, 2015) . All current methods for bioprinting start with creating sugar glass scaffolds and filling them with the desired bio inks to create functional tissues, “this approach sacrificed[s] the ability to carefully control the deposition of cells within the bulk matrix, [however] it enabled previously unachieved engineered vascular complexity in a synthetic tissue,” (Mironov et al, 2008). There are presently three methods of bioprinting; inkjet bioprinting, laser assisted bioprinting, and extrusion bioprinting.

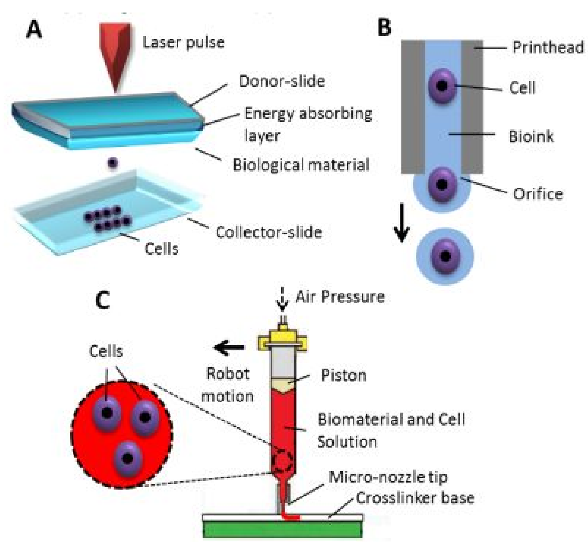


Figure 2. Bioprinting techniques including (A) Laser based bioprinting, (B) InkJet based bioprinting, and (C) Extrusion based bioprinting (Ozbolat, Yu, 2013)

Inkjet printing was the first bioprinting technology utilized and is functionally similar to regular 2D printing, where a liquid bioink is stored in an ink cartridge that is connected to a printer head

(Mandrycky et al, 2015). Inkjet printing is a "noncontact" technique that uses thermal, electromagnetic, or piezoelectric technology to deposit tiny droplets of bioink onto a substrate according to digital instructions. Bioinks are materials that replicate a human-like cell to support the adhesion, division, and differentiation of living cells. In inkjet printing, droplet depositing is frequently done by using compression or high heat to expel the ink droplets. In Thermal InkJet (TIJ) printers, increasing the temperature of the printhead creates microscopic air bubbles that will collapse, which will, in turn create pressure pulses that expel ink droplets from nozzles in volumes as small as 10 picoliters volumes as large as 150 picoliters. Droplet size can be changed between varying sizes by adjusting the temperature of the machine, the frequency of the pulse, and the viscosity of the ink. TIJ printers are very promising in the fields of tissue engineering and regenerative medicine. Due to their digital precision, versatility, and control, and benign effect on mammalian cells, this technology is currently being applied to print simple 2D and 3D tissues and organs. TIJ printers may in the future prove necessary for other complex uses, such as gene transfection during tissue construction, and drug delivery.

Laser-assisted bioprinting emerged next and utilizes lasers to position bioinks. This allowed the bioprints to be more precise but still did not allow the use of viscous materials. To solve this challenge, extrusion printing was developed as a modification to inkjet printing. In order to print the viscous materials inkjet printers cannot deposit, extrusion printing uses either an air-force pump or a mechanical screw plunger to dispense more viscous bioinks (Khatiwala, 2012).

Advances in Bioprinting:

Current applications for 3D bioprinting are rapidly evolving and will revolutionize health care. Anticipated medical uses for 3D printing, both current and future, can be separated into several categories, including organ and tissue fabrication, implants, and development of customized prosthetics. The use of 3D bioprinting in medicine can provide many other benefits, including, testing medium for the customization of medical products, drugs, and equipment, and increased productivity. However, it should be known that despite recent medical advances involving 3D printing, notable scientific and mechanical challenges remain and the most complex applications for this technology will need time to develop.

Despite these challenges, bioprinting remains a very attractive technology to consider to help address the donor kidney shortage because tissues, and hopefully one day entire organs, can be printed on demand when a patient requires them. And since each bioprinted tissue, or organ, would be developed for a specific patient, the use of bioprinting could greatly reduce the chances of kidney rejection by tailoring the kidney to the patient's exact bodily makeup. But most importantly, if replacement kidneys can one day be produced by bioprinting, they would be able to supplement the number of available live and deceased donor kidneys for patients with kidney disease, and once the technology matures, could one day potentially eliminate the need for donor kidneys altogether.

Social Importance

Researching new technologies to address the kidney donor shortage in the United States is a critical social issue. With over one hundred thousand people living in the United States in need of an organ transplant, in 2018 only about one fifth of the people, about 20,000, recieved the organs they need according to the United Network for Organ Sharing (UNOS). The other 80,000 patients that remain on the donor waitlist will continue to need recurring dialysis treatment to remain alive, at a significant cost to them, the insurance industry, and society in general. In addition to the cost, the time involved for repeated dialysis treatments keeps them from being as productive as they could be in society. The ultimate goal of many bioprinting experts is to design a method to print organs in order to solve this organ crisis (Derakhshanfar et al, 2018). Bioprinting organs would provide a safe and stable way to produce transplantable organs, and eventually eliminate the organ shortage and work towards creating a future where organs can be printed on demand, and are no longer in demand.(Panduranga, 2009). It will also address the worldwide social issue of illegal or predatory human organ trafficking that led to the establishment of the United States' National Organ Transplant Act in 1984.

Limitations to Research:

The biggest limitation to this research is that science has yet to successfully 3D bioprint a viable kidney for testing. Due to this limitation, there is no data regarding how effective a 3D bioprinted organ will actually be, so several assumptions must be made based on data that is available. It is assumed that technology will continue to mature to the point that a 3D bioprinted kidney, which is printed with living cells, will perform similarly in function to donor kidneys. Another limitation that restricts this project is the inability to conduct an inclusive long-term study on the lifespans and viability of living versus non living donor kidneys, thus all data utilized in this paper was previously collected by national organizations that track the statistics on the lifespans of donor organs, viability of living and deceased donor kidneys, and populations of living and deceased donor kidneys throughout the U.S.

Purpose:

The purpose of this study was to research the current kidney shortage in United States, analyze factors causing it, and investigate 3D bioprinting kidneys as a solution. The scope of this project was limited to assessing the kidney shortage in United States since the United States the highest rate of kidney disease throughout the world and more data was openly available (United States Renal Data System 2012).

Research Question:

Are the current methods of providing kidneys effective and would 3D bioprinting provide a more efficient means of supplying organs to reduce the shortage in the United States?

Hypothesis:

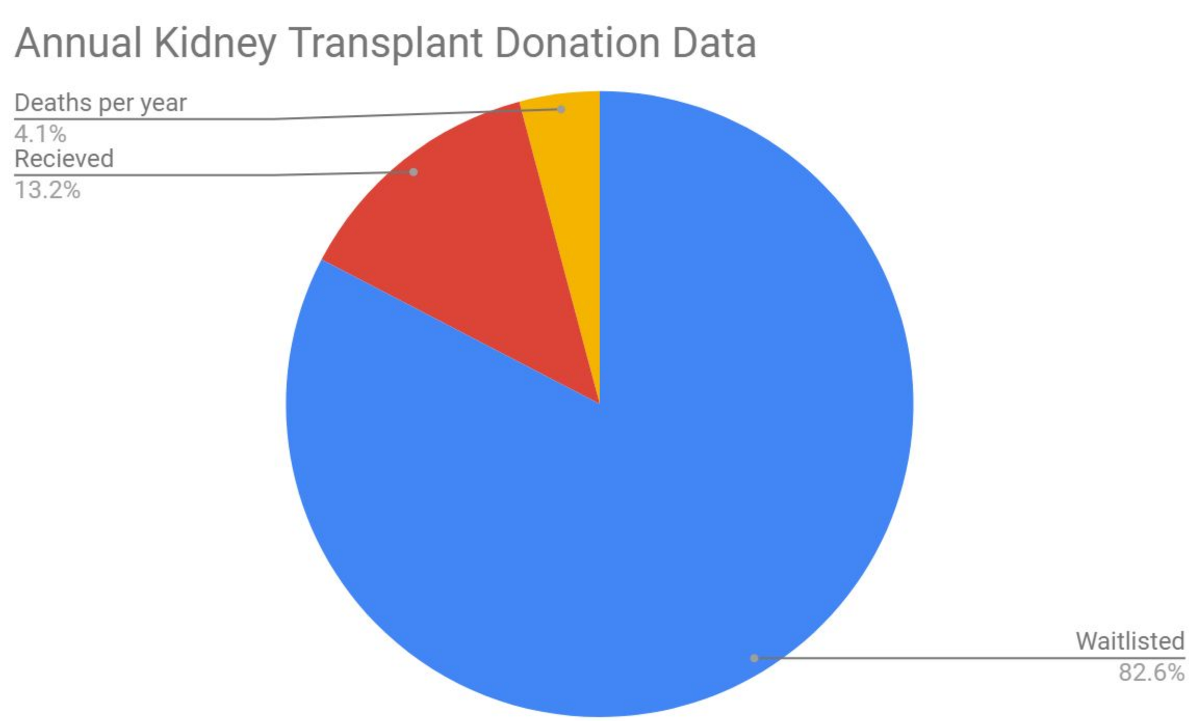
Hypothesis: The current methods of providing kidneys to patients are not effective and 3D bioprinting will be the most effective way of providing donor kidneys to future recipients in the United States.

Methods:

Due to a lack of primary sources able to support my research topic, I used systematic literature review and secondary data analysis to guide my research. Sets of data from a collection of articles will be gathered and analyzed, in order to draw a conclusion. Since the design of this study is systematic literature review as well as secondary data analysis, the most efficient source type would be scholarly peer reviewed research articles gathered from various databases such as PubMed and EbscoHost, or analyzing data presented on websites such as The United Network for Organ Sharing (UNOS) and the National Kidney Registry (NKR). The databases used will provide a plethora of valuable information regarding my topic. I also used programs such as excel to gather and plot my data into graphs that are discussed in this paper.

In the beginning of my research I gathered primarily articles regarding 3D bioprinting because I initially planned my project to be the prospects of 3D bioprinting in commercial medical use. I was collecting information on different types of bioprinting and their current uses in the medical industry until I hit a wall when creating my SRC document and was not able to find a suitable problem that my research would help in solving. I also discovered that there had been no successful printings of entire organs available for transplantation, however parts of living kidneys have and that lead me to shift the focus of my study to the kidney shortage in the United States and how bioprinting could aid in resolving that major issue occurring in hospitals across the country. I came to the realization that the 3D bioprinting of organs was not yet a relevant enough technology to be the focus of my research project. I decided to focus on the organ shortage because it was a way I could apply all the research I had done up to that point and have an issue that needed to be solved making my research more meaningful and giving me a sense of direction in my work. Kidney transplantation was the most viable focus of my research because the kidney shortage is more vast than the shortage of any other organ and I was able to collect more data concerning kidneys than any other organ. I collected data on survival rates after transplantation, numerical data on deceased versus living donors, data on the annual methods of transplantation to patients, including the number of kidneys received , the number of patients waitlisted and the number of deaths per year waiting for kidney transplants, and the lifespan of living versus deceased donor kidneys post transplantation in order to conclude that there is a prevalent kidney shortage in the United States and that living and living bioprinted kidneys in the future are safer, have longer lifespans, and have better graft survivability than deceased or expanded criteria donor kidneys. After the data was collected I compiled it into graphs using microsoft excel in order to graph and create tables for the collected data. I then ran t tests to check the viability of my collected data to draw my conclusions. After my data was collected, graphed, and tested I was able to compile all my data into this paper.

Results



Total Number of Patients In Need of a Kidney Transplant 121,678

Figure 3. Annual kidney transplant donation data 2013 (UNOS)(NKF)

Table 1. Number of deceased kidney donors VS amount of living kidney donors from 2007-2012

Year	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**
Deceased Donors	**7,240**	**7,188**	**7,258**	**7,241**	**7,434**	**8,250**
Living Donors	**6,043**	**5,970**	**6,388**	**6,279**	**5,773**	**5,215**

(NKF, 2018)(UNOS ,2018)(OPTN, 2018)

Since 2007 the amount of living donors has been slowly decreasing, conversely the amount of deceased kidney donors has been slowly rising.

*Table 2. Chance of living donor kidney surviving from one to fifteen years vs chance of deceased donor kidney surviving from one to fifteen years (*CIHI 2018*)*

	Chance Of Kidney Lasting One Year	**Chance Of Kidney Lasting 5 Years**	**Chance Of Kidney Lasting 10 Years**	**Chance Of Kidney Lasting 15 Years**
Deceased Donor	90%	70%	50%	40%

Living Donor	90%	90%	70%	60%

(UNOS ,2018)(NKF, 2018)

The chances of survival from one to fifteen years after receiving a donor kidney from a deceased donor are much lower than the chance of survival of a living donor kidney.

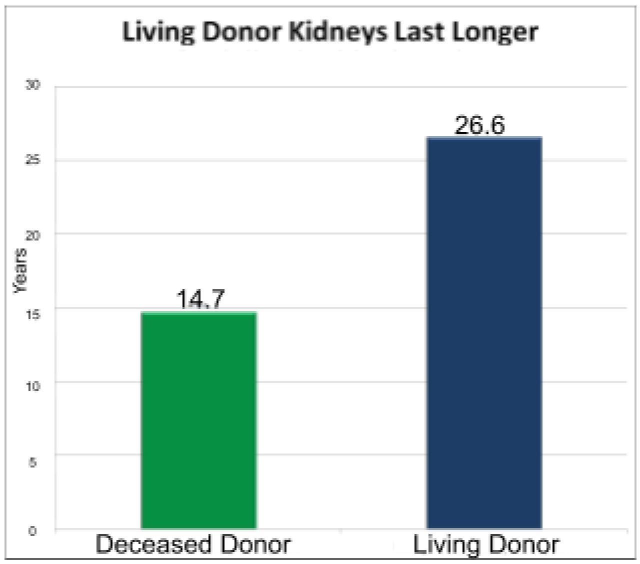


Fig. 4 Kidneys transplanted from living donors are superior because they last nearly twice as long as kidneys transplanted from deceased donors. (National Kidney Registry, 2018)

Discussion:

In recent years databases such as UNOS, NKF, OPTN, CIHI, and the NKR have released numerical data on the patients in need of kidney transplants including the number if people that receive kidney donations each year, the number of people that are put on a waiting list to receive a kidney, and the number of people who die each year in need of a lifesaving kidney transplant. In 2013 the United Network of Organ Sharing and National Kidney Foundation released statistics concerning the categories listed above, of the approximately 121,000 people in the United States included in this data, about 82% or about 100,000 people were waitlisted due to the fact that there was not enough kidneys for them to receive. According to this same study approximately 4% or 5,000 people died in need of a lifesaving kidney transplant and only 16,000 people or 13% received kidney transplants in that year. This is showing that a very small percent of a very large number of people are receiving kidney donations and only about half of them are receiving living kidneys. This further emphasizes how extreme the kidney shortage in the United States is. Over time the demand for donor kidneys has grown, causing the number of deceased donors to increase due to the higher demand of kidneys that can not be filled by more living donors. This can be seen by the fact that the number of living donors per year is on a steady decline (CIHI Database, 2018). After receiving a kidney transplant, patients with kidneys from living donors have a higher chance of their kidney surviving compared to recipients of kidneys from deceased donors. The current method of acquiring kidneys for donation, deceased donors, is causing recipients' kidneys to have shorter lifespans. After one year of receiving a kidney from either a deceased or living donor, that patients kidney has a 90% chance of surviving. Five years after a transplant a kidney from a living donor has a 90% chance of survival and a kidney from a deceased donor has a 70% chance of surviving. Fifteen years after a kidney transplant a kidney from a living donor has a 70% chance of surviving while a kidney from a deceased donor has a 50% chance of surviving. Although acquiring kidneys from deceased donors provides more kidneys for patients, the lifespan of those kidneys tends to be much shorter than the lifespan of donor kidneys from living donors. 3D bioprinting may be able to change this by providing kidneys that are functional, last a long time, and have no chance of being rejected because they will be specifically made for an individual. Table 3 shows the difference between the expected lifespan of deceased donors and living donors. Kidneys from living donors are expected to live approximately 26.6 years, where kidneys from deceased donors are expected to live around 14.7 years. This almost 10 year difference between living and deceased kidneys helps to prove that living kidneys are in fact healthier and safer transplant options for patients.

Conclusion:

Through systematic literature review and secondary data analysis of the current state of the kidney shortage in United States, it has become clear that the current methods of acquiring and providing kidneys to patients on waiting lists are ineffective and are not providing enough donor organs to resolve the organ crisis, in fact, waiting lists for kidneys grow each year despite more willing donors. In this study I was also able to come to the conclusion that deceased donor kidneys and expanded criteria donor kidneys are not as safe or as longevitious as living as well as living bioprinted kidneys. Therefore if deceased donor kidneys were to be removed from circulation of donation half of the kidneys being donated would disappear and 3D bioprinting would be able to fill this gap with living, affordable, and safe kidneys. Although 3D bioprinting technology is still a young and developing technology, in the near future it may be able to relieve the stress of the organ shortage in United States. The use of 3D bioprinting provides solutions to the two major factors causing the organ shortage, not enough living donors and grafting survivability by being alive when they are printed, and being created specifically for patients based on their specific medical needs. Overall, the current methods of providing kidneys to patients is ineffective, and in the near future 3D bioprinting may be able to take over as the primary method of providing kidneys to patients, and eventually eliminate the kidney shortage in United States.

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Further research into current uses of 3D bioprinting would provide a strong argument as to why bioprinting will be able to soon print entire organs, as well as examples for what it is currently being used for in commercial medicine. For the amount of time given, the research only allowed for the examination of the prospects of bioprinting organs and not bioprinting of other complex structures such as cartilage or artificial bone. Moreover, other possible solutions to the organ shortage such as xenotransplantation were not able to be included because of a lack of time to research that possible conclusion. Comparing the prospects of only 3D bioprinting to current methods causes there to be no other methods to compare viability in reducing waiting lists for kidneys across the United States.

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