Comparison of Polymer Based Porous Bone Scaffolding Materials for Regenerative Engineering

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Abstract

Regenerative engineering has emerged as a major topic of interest in the medical field. Its potential has yet to be fully achieved as its uses are still being discovered through research. One of the many potential uses of regenerative engineering is found in Bone Tissue Engineering (BTE). Today, people experience various problems with bone tissue caused by aging, disease, or trauma. Generally autografts from the patient's own body or allografts from other biocompatible materials are used to promote local cell regeneration, however, these materials are used permanently in the body. Though these materials are meant to be used for extended periods of time, when they fail or malfunction they require follow up operations. To propose a solution to these dangerous exposures to anesthesia based procedures, biodegradable scaffolds engineered using various biomaterials have become increasingly apparent as potential options. To limit the scope of the study, this research inquiry only focuses on polymer based scaffolds. This study compares the mechanical strength of PLAGA (poly(lactide-co-glycolide)) and Polyphosphazene scaffolding materials. Both materials were researched using a systematic literature review. After compiling data into an Excel spreadsheet, the data sets were compared using a two-tailed t-test. Statistical analysis provided evidence supporting the acception of the null hypothesis which stated there was no difference between each material's structural integrity. However, to further contribute to the search of one optimal biomaterial for BTE, this study evaluated the degradation byproduct of each material. Consideration of acid accumulation in PLAGA scaffolds post degradation contributed to the conclusion which states that with the acception of the null hypothesis, additional research is needed to identify one optimal material with potential for use in BTE.

Introduction

The human body struggles to maintain healthy bone tissue over time due to complications related to aging, disease, or trauma. When significant portions of bone tissue are lost due to these problems, the remaining tissue may struggle repairing itself. In this case, a scaffold is required to bridge the gap from the adjacent bone to heal the affected tissue (Borden et al., 2002). Today, many of the commonly used treatments for these issues lead to donor site morbidity, infection, postoperative pain, and complications that can lead to potentially harmful follow up surgeries (Zhou et al., 2018). Research in the field of regenerative engineering has utilized advancements in biomedicine to help reduce these follow up surgeries and thus limit unnecessary exposure to dangerous procedures and anesthesia.

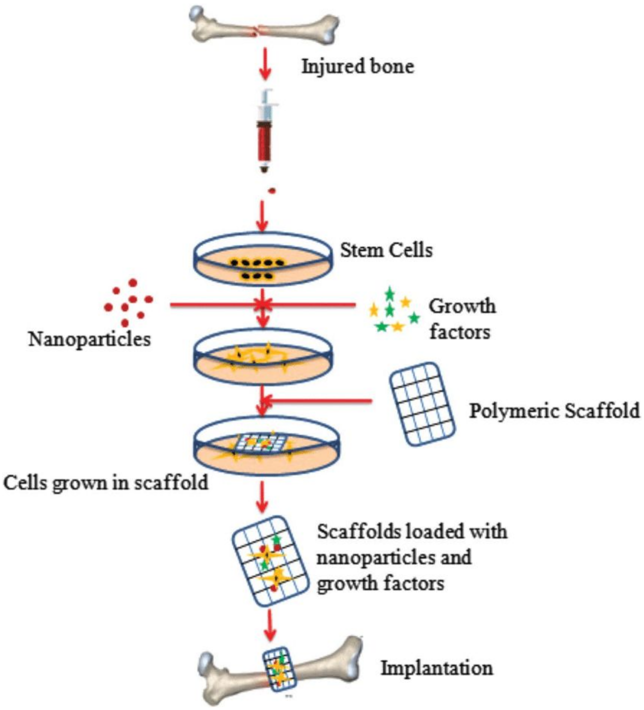


Figure 1: Displays overall process involved in scaffold technique including application of growth factors, stem cells, etc., and then implantation within affected bone tissue. Provides visualization of notion of a porous scaffold that can promote cell regeneration.

Bone Tissue Engineering (BTE) is one predominant field of regenerative engineering. BTE uses scaffolds that act as biodegradable templates for cell adhesion and tissue regeneration (Shuai et al., 2013). To best support treated areas, these scaffolds must provide the necessary qualities that constitute ideal scaffold characteristics. The scaffold should not only remain biocompatible to negate potential rejection of the material, but it must provide the tissue ample porosity levels for blood vessel formation to support cell regeneration with necessary nutrient flow to the cells. In doing so, the scaffold should also remain mechanically stable to match host tissue weight bearing characteristics (Shuai et al., 2013). Determining an optimal material for BTE requires analysis of the ideal characteristics for scaffolds. Like all components of the body, bone tissue is complex in balancing the relationship between stability and functionality and therefore demands certain essential qualities for ideal scaffold formulation. These critical characteristics include:

Biocompatibility: Scaffolds should support normal cellular activity without harming host tissue (Nitschke et al., 2002). An ideal scaffold must also be osteoconductive, allowing the bone tissue to adhere to the scaffold, proliferate, and form an extracellular matrix throughout the pores of the scaffold. Similarly, blood vessels also need to form to provide nutrients and oxygen, while transporting waste from the regenerating tissue (Akao et al., 1993).

Pore Size: Ideally, a bone scaffold should also have interconnected porosity with a minimum pore size of 100 μm in diameter to provide sufficient space for diffusion of nutrients and oxygen to the regenerated tissue (Gao, Niklason, and Langer, 1998). Additional research has indicated that optimal pore size ranges from 200 to 350 μm (Peter et al., 1998). However, one critical characteristic of scaffolds is the relationship between mechanical strength and pore size. For instance, increased porosity will reduce mechanical strength; limiting porosity would increase mechanical strength, but would negatively influence nutrient flow to the tissue (Borden et al., 2002).

Biodegradability: Another crucial property of an ideal scaffold is biodegradability. Scaffolds should be semi-permanent without the need for follow up surgery for removal or repairment of the scaffold. Therefore, the scaffold must be able to degrade through natural biological functions within the body. With time, the scaffold should degrade and be resorbed at a controlled rate, eventually creating sufficient space for new bone tissue growth. Degradation behavior should vary based upon the implantation site and area of affected tissue; periods of structural integrity should last nine months or more (Bose, Roy, and Bandyopadhyay, 2012).

Mechanical Properties: An ideal bone scaffold will provide mechanical strength matching host bone properties to allow for proper weight load bearing (Bose, Roy, and Bandyopadhyay, 2012). In other words, the necessary mechanical properties of the scaffold depends on the tissue it is supporting. For example, a scaffold's compressive strength should be between 100 and 200 MPa for cortical bone and 2 and 20 MPa for cancellous (Bose, Roy, and Bandyopadhyay, 2012). Meeting these complex requirements has promoted research in proper scaffold design and structure.

This study will effectively compare PLAGA scaffolding material to Polyphosphazene scaffolding material. Finding one material that will meet all of the ideal characteristics for bone scaffolds is nearly impossible simply due to the variety of variables that complicate perfection. Also, there are too many essential characteristics for one functional material to meet easily. In fact, certain characteristics inhibit one material from being an all-around candidate. For example, pore size has a direct relationship with mechanical strength: when increasing pore size, the scaffold sacrifices weight bearing capabilities for improved nutrient flow and cell adhesion. The inverse is also true, smaller pore sizes will increase density and overall mechanical strength while limiting its ability to inhibit blood flow. Therefore, this study will specifically compare the two scaffold materials based on their mechanical strength as researchers have already identified the ideal range of porosity within the scaffold.

PLAGA Scaffold Material

PLAGA (poly(lactide-co-glycolide)) is a copolymer of poly(lactic acid) (PLA) and poly(glycolic acid) (PLG). In the field of regenerative engineering, PLAGA has become one of the most commonly used materials for its various characteristics. These beneficial traits include biocompatibility, tailored biodegradation rate (dependent on the molecular weight and ratio), its approval for clinical use by the Food and Drug Administration (FDA), and its ability to modify surface properties for better interaction with implantation sites (Piergiorgio et al., 2014). These properties justify the popularity of the material, but there

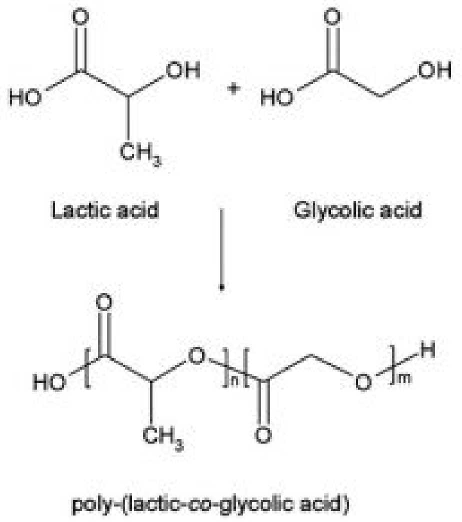


Figure 2: Lewis diagrams of the individual acids are used to visualize chemical composition. When each acid is combined to form the copolymer the material is biocompatible. These acids used to form the material are acidic in nature, but are naturally occuring and in some cases found in normal bodily functions, e.g. lactic acid fermentation.

are some limitations. In the degradation process, bulk erosion of the material can lead to accumulation of acid in the implantation sites, which could cause inflammatory responses in the body. Furthermore, these reactions could reduce bioactivity of the growth factors used concurrently with the scaffold. Fortunately, research indicates that these limitations can be minimized with buffer macromolecules that can control degradation rates (Ogueri et al., 2016). PLAGA is a synthetic biodegradable polymer that allow for hydrolytic degradation through de-esterification according to their chemical properties. Once degraded into lactic and glycolic acid, it is removed from the body using normal metabolic pathways (Shuai et al., 2013). In all, the PLAGA material is able to sufficiently supply the patient with a safe and clinically approved scaffolding material that would promote cell regeneration without potential follow up surgeries. However, it is important to evaluate each material based upon all of their respective characteristics to determine whether or not they will not only be successful, but continue to provide the advantages over leading treatment methods without harming the patient in the process. By presenting potentially harmful byproducts, its advantages may not outweigh those of the risks involved in using the new practice.

Polyphosphazene Scaffold Material

Polyphosphazenes are unique in the field of biomaterials, as they have large available freedom in terms of modifying the material's physical and chemical properties. They are organic-inorganic hybrid polymers that support its increased compatibility with alternating phosphorus and nitrogen atoms in the backbone; each of these phosphorus atoms bears two organic side groups as seen in Fig. 3 (Nukavarapu et al., 2008). Polyphosphazenes can utilize various organic side groups, such as amino acid ester derivatives, which allow the material to better control degradation rates which has increased interest in this material among those in the field of regenerative engineering. Researchers have also identified that, unlike PLAGA, the degradation products of many Polyphosphazenes form a buffering system (ammonium phosphate) that maintains neutral pH throughout the scaffold. In other words, the non-toxic, neutral degradation product of Polyphosphazene material make it an ideal candidate in regenerative engineering. Just as the PLAGA scaffold material provides sufficient osteocompatibility, Polyphosphazenes provide the patient with another safe alternative. However, it has not been approved by the FDA due to the limited research available on its potential health risks. Nevertheless, the neutral pH degradation can pose a health benefit compared to PLAGA scaffolds because the acidic accumulation in PLAGA uses have been reported to cause catastrophic failure of structural integrity (Ogueri et al., 2017). Research for this material is in direct response to the field’s standard for regenerative techniques and addresses the issues that PLAGA have been found to have.

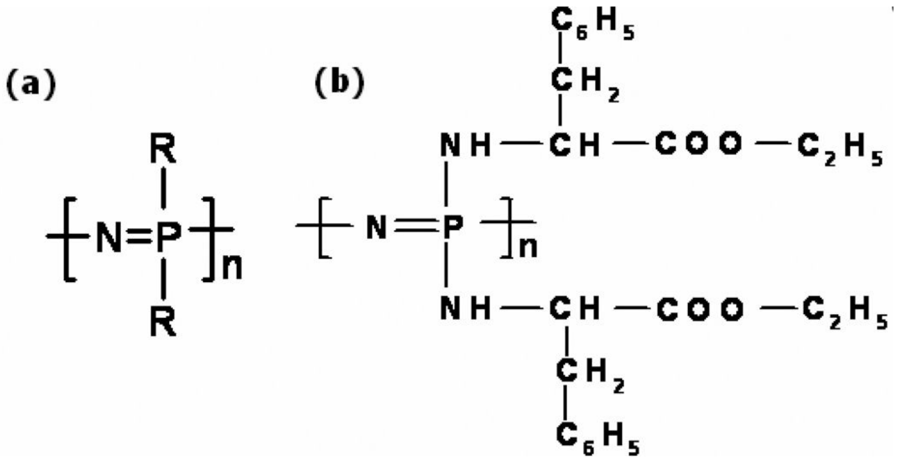


Figure 3: The diagram above shows, like the diagram of PLAGA, the chemical composition of polyphosphazenes. Notice the name given to the material is derived from its make up of its alternating Phosphorous and Nitrogen backbone. Various amino side groups (R) can be attached to the material which enhances its biocompatibility.

Purpose

The purpose of the study is to compare two different biomaterials with potential for regenerative engineering practices. Many of the field's standard methods can cause the patient risk for follow-up surgery which would expose them to excess anesthesia. This research aims to evaluate data from peer-reviewed papers to help identify one specific material that would eliminate the current treatment methods and the coexisting surgical procedures. Though researchers have identified various materials for regenerative engineering over the past few decades, these materials do not tend to address every need for an ideal scaffold. This study will compare PLAGA bone scaffolds to Polyphosphazenes by analyzing data from a statistical perspective to determine the more practical material in terms of mechanical strength

Research Question

Which scaffolding material best provides ideal scaffold properties for optimal cell regeneration success when comparing PLAGA scaffolding material to Polyphosphazene scaffolding material?

Hypothesis

Alternate hypothesis: The Polyphosphazene material will provide more structurally sound scaffolds and best support cell regeneration by matching host tissue strength.

Null hypothesis: In comparing the two scaffolding materials, neither material will provide a significant advantage in terms of their mechanical strength and structural integrity.

Methods

To begin finding appropriate and relative information for the investigation, a research inquiry first needed to be identified. To research one idea that worked to fill a gap in current studies, numerous peer reviewed papers in the general field of regenerative engineering needed to be read to keep from researching a concept that already exists. In the papers that were read, annotated, and analyzed, each had tailored their research in an argumentative style that provided data and insight that backed the material they were researching. Simply put, each researcher was dedicating their research solely on the potential of one material without truly considering other materials. The scope of this research investigation was then continuously narrowed by isolating variables to find one question that would fill the research gap. To fulfill this void in research, this study specifically compared numerous materials as opposed to individualizing the inquiry to one material. This was done in two ways: by narrowing the scope of the research into one class of material and by evaluating those based on one of the ideal scaffold characteristics.

There are many types of materials that can be used for regenerative engineering: ceramics, composites, hydrogels, bioactive glasses, or polymers. Though ceramics are more structurally sound then polymer scaffolds and can be administered as granules or injected to form a strong integration with host tissue, they are much too hard and lack optimal degradation rates. Bioactive glasses are osteoconductive and biocompatible, but they too, lack degradation control. Hydrogels can be 3D printed to mimic microarchitectures but cannot be physically manipulated easily. Polymer based scaffolds are biocompatible and can offer both natural and synthetic forms; natural forms are derived from the extracellular matrix and therefore obtain biocompatibility and synthetic forms offer improved mechanical properties (Turnbull et al., 2018). One potential problem with polymer based scaffolds is that they tend to lack mechanical properties for weight bearing; however, this can be addressed by combining certain bioactive factors that improve strength. This issue is why this study compares the polymer based materials in relationship to their mechanical strength. But perhaps most importantly, polymer based scaffolds are biodegradable and for this reason, polymer based scaffolds were studied in this investigation as opposed to reviewing all types of materials for regenerative engineering.

Once, the research question was formulated, data collection was performed through a systematic literature review to begin formulating a hypothesis that could be tested using values found in research. To find academic, peer-reviewed papers related to bone scaffold material analysis, various research outlets were used such as Science Direct, Google Scholar, Research Gate, National Institutes of Health (NIH), National Center for Biotechnology Information (NCBI), etc. Each of these search engines provided open access to information from well-established researchers at the top of their respective fields. Each of these research papers have eliminated any and all bias which in-turn makes this study's literature neutral. To identify papers that pertain to the information needed for data analysis, keywords for searches consisted of "PLAGA bone scaffold mechanical strength", "Polyphosphazene bone scaffold mechanical strength", "relationship between porosity and mechanical strength in bone scaffolds", "PLAGA biodegradability in bone scaffolding", "Polyphosphazene biodegradability in bone scaffolding", etc. Each paper that was deemed relevant and necessary was then read, annotated, and analyzed for identification of specific information related to the topic. For example, to compare the mechanical strength of each material, research that investigated the properties of both materials were examined for data compilation. In turn, each paper related to a specific property was used to provide relevant data for that individual characteristic. Data from each paper was compiled into a table for accessibility purposes; data retrieved from the literature review would then be analyzed statistically to test the hypothesis.

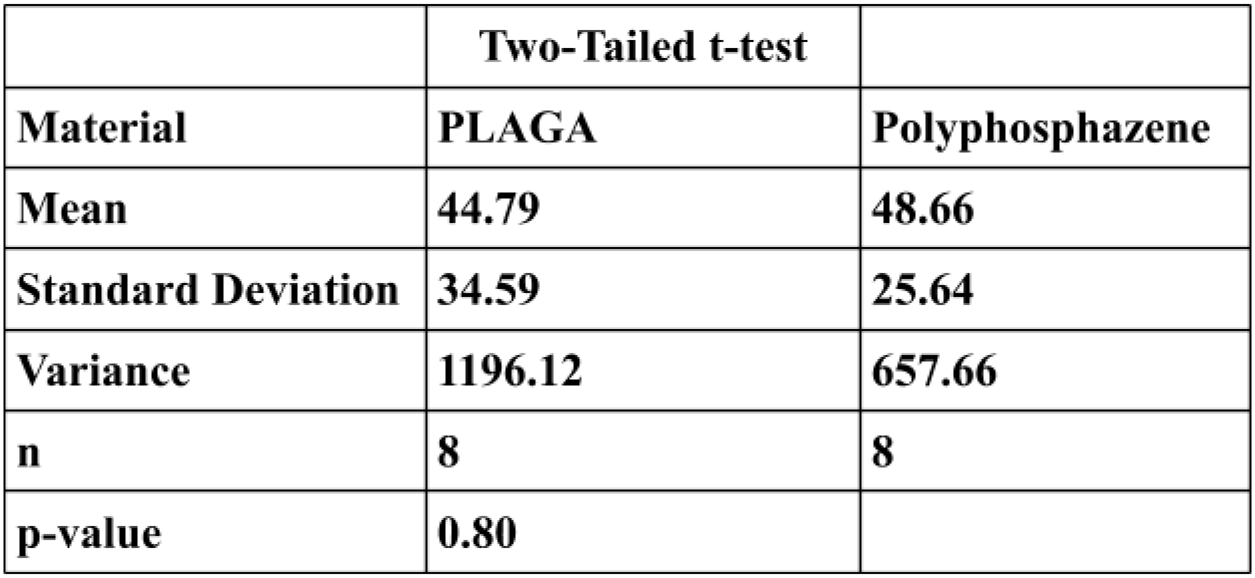
Before compiling data for statistical analysis, the initial literature review was used to formulate a hypothesis. Essentially, research needed to be gathered to decide whether PLAGA or Polyphosphazene scaffolds would be more mechanically sound. Certain factors for each material were used to formulate the hypothesis. In general, one of the main weaknesses of polymer based scaffolds is that they tend to lack mechanical strength. PLAGA based materials are FDA approved and are biocompatible, but because they are the leading material used, it can be inferred that perhaps they tend to lack mechanical strength like most polymer based materials. Additionally, Polyphosphazenes have variability; their Phosphorous-Nitrogen backbone allow for the application of various amino side groups. This variability increases opportunity for the material to be used and accepted by the implantation site. Greater interconnectivity between the scaffolding material and the implantation site would in theory lead to improved strength in the scaffold. For this reason, the Polyphosphazene scaffolding material was initially favored prior to statistical analysis.

To analyze the mechanical strength of each material, this study examined peer-reviewed research that determined the compressive strength of each scaffold material in terms of megapascals (MPa). Over the course of the investigation, data was compiled in an Excel spreadsheet to be used for statistical analysis. Researchers tend to analyze their data either using chi-squared analysis or a t-test; in this study, a two-tailed t-test was used because of the relationship between independent and dependent variables in the data sets. With the data compiled, a two-tailed test was used because the distribution of the data could not be determined at face value. In order to identify a statistically significant difference between the results, the t-test compared the two data sets using a p-value of 0.05. An Excel spreadsheet was used for analysis because the program uses integrated formulas to calculate various mathematical terms. Each data set was analyzed by finding its mean, standard deviation, and variance. Finally, each data set was ran through the t-test using each of the subsequent values found to output a p-value; the t-test compares the two data sets by essentially evaluating the discrepancy between their individual distributions. This resulting p-value would be compared to the critical value of 0.05 to determine whether or not the data indicates a statistically significant difference between the mechanical strength of the two materials. Despite acknowledging the hypothesis in support of Polyphosphazenes before testing, this study continued to eliminate any bias by compiling data from respected researchers that understood the shortcomings of their respective arguments in favor of either PLAGA scaffolds or Polyphosphazene scaffolds. Following the conclusion based on data analysis, more factors and information were evaluated to help further the discussion towards an optimal scaffolding material that best encompasses all ideal characteristics; to continue evaluating the materials, certain characteristics such as post-degradation products and their pH levels were addressed so as to introduce their biocompatibility into the evaluation.

Results

Preliminary research indicated that pore size was an independent variable that dictated the scaffold's resulting mechanical strength (Borden et al., 2002). When the porosity is greater, there are larger pores and more of them which decreases the structural integrity of the scaffold.

Similarly, if the scaffold has lower porosity there are smaller pores and less of them which increases the strength of the scaffold. Additionally, one of the primary issues with polymer based scaffolds is there lack of mechanical strength. Considering both of these factors, PLAGA and Polyphosphazene scaffolding materials were evaluated based upon their respective mechanical strengths. For each material there were 8 different values in the data set: PLAGA values ranged from 22.24 MPa - 126.30 MPa; Polyphosphazene values ranged from 13.7 MPa - 84.83 MPa (Borden et al., 2002; Shuai et al., 2012; Ma and Choi, 2001). At face value, these numbers would indicate that PLAGA values were significantly greater, however their averages are more telling.



	Two-Tailed t-test	
Material	**PLAGA**	**Polyphosphazene**
Mean	**44.79**	**48.66**
Standard Deviation	**34.59**	**25.64**
Variance	**1196.12**	**657.66**
n	**8**	**8**
p-value	**0.80**	

Table 1: Table shows variety of values found to further t-test process. The t-test requires mean, standard deviation, variance, and total values (n) for computation of p-value. Each of these values were calculated using an Excel spreadsheet which computes the values using integrated formulas within the program. They work to determine discrepancy between PLAGA and Polyphosphazene strength data values and their respective distributions (Sethuraman et al., 2010; Saito et al., 2010; Nukavarapu et al., 2008;Borden et al., 2002; Shuai et al., 2012; Ma and Choi, 2001).

PLAGA values averaged to 44.78 MPa and Polyphosphazene values averaged to 48.66 MPa (Sethuraman et al., 2010; Saito et al., 2010; Nukavarapu et al., 2008).

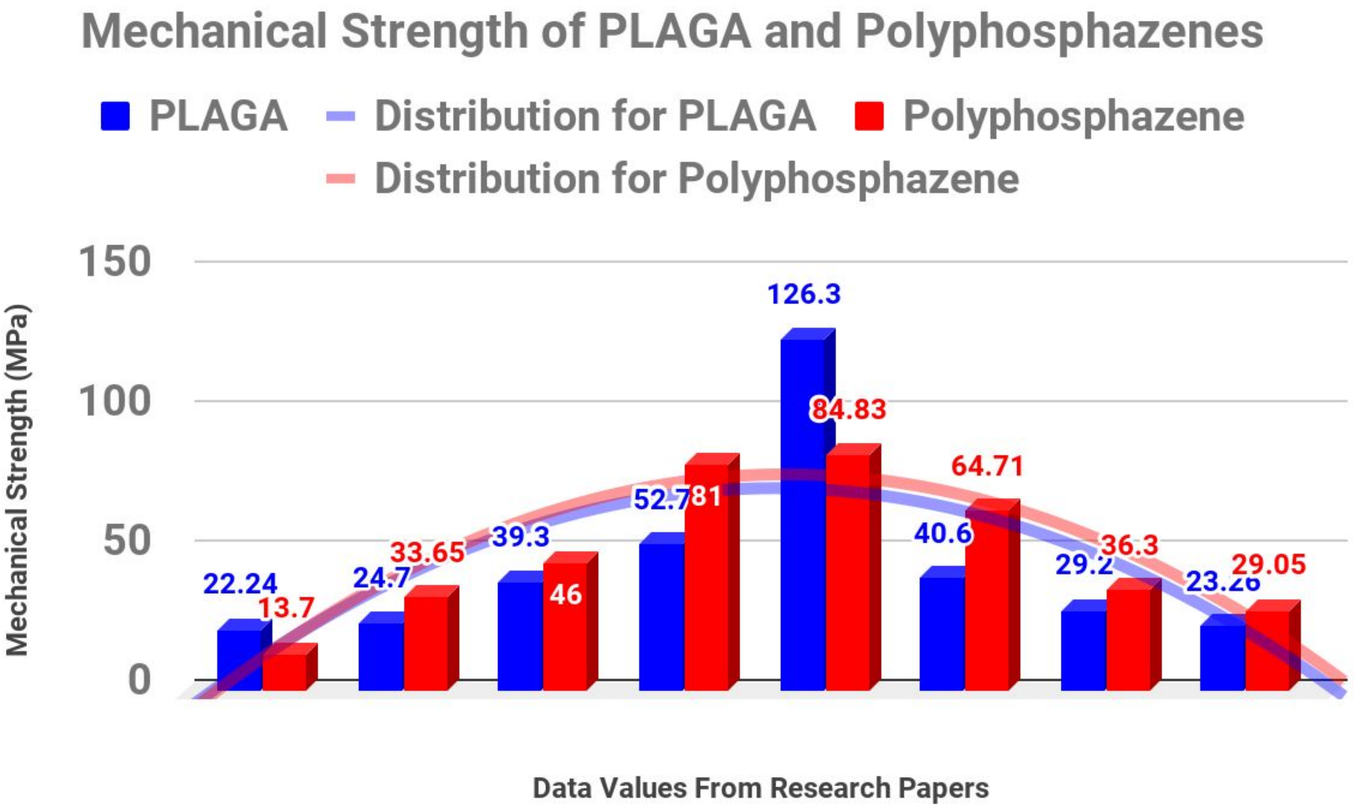


Figure 4: The graph shows the overall data used for the statistical analysis. The t-test is used to test the hypothesis that Polyphosphazenes are more structurally sound than PLAGA scaffolds; to do this, the t-test uses statistics to essentially determine the difference in the two data sets' distribution. If one data set has much greater mechanical strength, their distribution would be much greater. In this case the test would output a low p-value to prove the alternate hypothesis. In this study, the distributions were very similar resulting in a high p-value that proves the acception of the null hypothesis. The graph displays this similarity in distribution with the blue and red arcs.

The results were displayed in a graph to show the distribution between the strength of the two materials to show the function of the t-test. Following data collection through the systematic literature review and data analysis, results were compiled in graph to show the distribution of the data values. Interestingly, when analyzing the graphs and their respective distribution curves (seen in light blue and red in the graph below) there is little to no discrepancy. The graph is simply displaying the results found when conducting the t-test; the two-tailed t-test resulted in a p-value of 0.803. Comparing the resulting p-value to the critical value of 0.05, 0.803 is much greater than the critical value.

Discussion

This study aimed to design a research question that would further the overall field of regenerative engineering by comparing two different materials that can be used for BTE based upon their respective mechanical strengths. Each of the materials are polymer based which have both advantages and disadvantages for their use in regenerative engineering, their main disadvantage being their general lack of mechanical strength. So, PLAGA and Polyphosphazene based scaffolds were both analyzed in terms of their mechanical strength because structural integrity was the weakest of the essential qualities in each material. Before statistical analysis, it was hypothesized that Polyphosphazenes would provide greater mechanical strength because of their relationship between their various amino side groups and the chemical composition of the implantation site. However, after compiling data and analyzing it using a two-tailed t-test, the resulting p-value of 0.80 was much greater than the critical value of 0.05. Thus, it can be concluded with 95% confidence that there is no statistically significant difference between the structural integrity of the two materials.

Though there may be no difference in the mechanical strength of the two materials, there is much more to consider when evaluating materials to find one optimal for BTE. For instance, biocompatibility is another of the many characteristics needed to meet the requirements of an optimal bone scaffold. Both of the materials are biocompatible, but when degraded, each produces different byproducts. When Polyphosphazene based scaffolds degrade, ammonium phosphate remains, while when PLAGA scaffolds degrade, lactic acid and glycolic acid are formed (Gentile et al., 2014). Glycolic acid is not found in the body, but is found in plants; lactic acid is found constantly in the body when exercising. Lactic acid is formed in the body during anaerobic activity (without oxygen) when lactic acid fermentation occurs to convert glucose into cellular energy. In other words, though lactic acid is naturally occurring and formed during normal biological activities, it is an area of concern for the material as it can cause negative

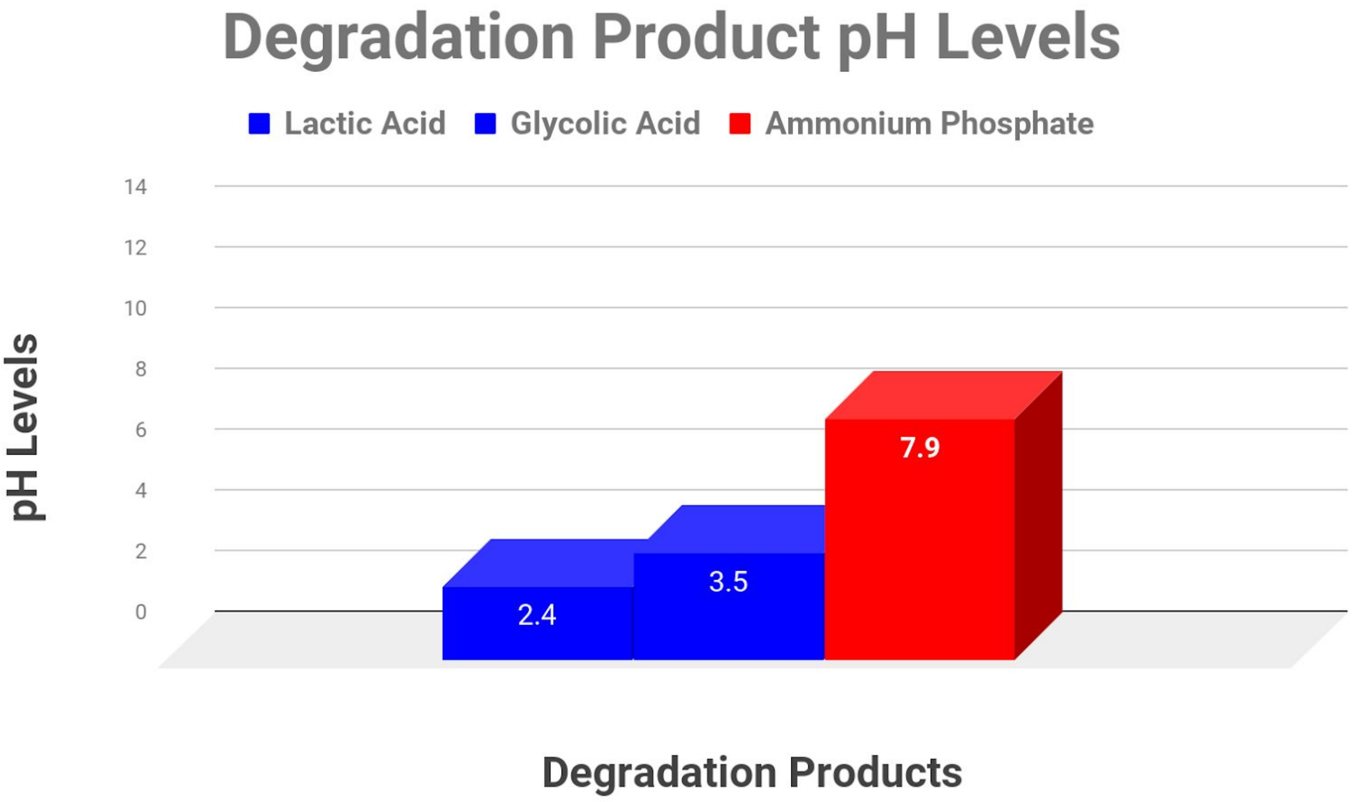


Figure 5: Though both materials are biocompatible, they have different degradation by-products that have different effects on the implantation site. Optimal pH levels in the body is around 7, but the acids are much lower. When degradation leads to bulk erosion of the acidic co-polymer, acid accumulation can lead to inflammation at the implantation site which could cause problems such as lack of biocompatibility, failure of structural integrity and rejection of the scaffold (Gentile, et al., 2014).

responses post degradation. For instance, when degradation leads to bulk erosion of the scaffold, the resulting acid accumulation can cause inflammation and lead to complications such as failure of structural integrity or rejection (Ogueri et al., 2017). This potential problem should be considered when evaluating both materials, but despite these problems, the PLAGA scaffolding material remains FDA approved. This is because there are certain regulations placed on the concentration of glycolic acid (10%) in applications within the body. Ultimately, pH level of degradation byproducts was not the focus of the study, but simply a concern addressed to increase the validity of this contribution to the search of an ideal material for BTE.

Limitations

Ideally, a complete and thorough evaluation of materials with potential for use in regenerative engineering would test all types of materials and investigate each of their respective characteristics. However, this study was limited to a narrower scope to make the research less broad, but in doing so it introduced limitations. The two main ways this study was narrowed was by controlling both the class of material (i.e. ceramics, composites, hydrogels, bioactive glasses, polymers, etc.) and area of characterization (i.e. pore size, biocompatibility, biodegradability, mechanical strength etc.). By narrowing the scope of the investigation, it allowed for the necessary information to be retrieved. Furthermore, if it were to study all classes of materials and all of their characteristics, the research would not have been completed efficiently and effectively. However, in presenting only one class of material and comparing two materials based on their structural integrity, a complete evaluation of all known materials in the field of regenerative engineering was not accomplished. Instead, this research project contributed to work of others to further the identification of one optimal material for BTE.

Conclusion

Prior to data collection and statistical analysis, Polyphosphazenes were believed to provide a more structurally sound scaffold due to its improved interconnectivity with the implantation site available because of its unique organic-inorganic Phosphorous Nitrogen backbone that attaches various amino side groups. However, after analyzing the data values for each material using a t-test, the resulting p-value of 0.80 was compared to the critical value of 0.05. Had the p-value been less than the critical value, then there would have been a substantial difference between the two materials' mechanical strength. However, the p-value was much greater than the critical value. Therefore, with 95% confidence, the t-test indicates that there is no statistically significant difference between the two materials' mechanical strength. Considering the statistical analysis, the data provides evidence that supports the acception of the null hypothesis: neither material will provide a significant advantage in terms of their mechanical strength and structural integrity. Essentially, this study found that there was no difference between the two materials' mechanical strength. Nevertheless, there are other characteristics of each material that were considered; both of the polymer based scaffolds were unique in that they had controllable degradation rates. Though these rates of biodegradation can be controlled, the consequential byproducts produced were much different in terms of their respective pH levels. When the PLAGA scaffold degrades, it produces two acids which can cause inflammation at the implantation site potentially depleting its biocompatible state and compromising its overall structural integrity (Ogueri et al., 2017). Therefore, the research provides evidence to support acception of the null hypothesis while contributing to the search for one optimal material that can be used for the future of regenerative engineering.

Further Work

Today, researchers in the field of regenerative engineering focus their work on their respective material and evaluate its potential directly. To contribute to the development of an understanding of one material best suited for BTE, this study focused on the mechanical strength of polymer based scaffolds. By focusing the research specifically on strength of polymer based scaffolds, the research inquiry was narrowed which allowed for a complete investigation of the subject at hand. However, to identify one particular material that best supports tissue regeneration in BTE, further work must be conducted. Current research has already identified ideal pore size to best balance the relationship between nutrient flow and scaffold stability, so additional research should be focused on other variables that contribute to the effectiveness of the scaffold. For example, additional research should be oriented around control of degradation rates to best foster cell regeneration while maintaining optimal structural integrity for proper weight bearing. Controlling the rate at which the scaffold degrades is unique to polymer based scaffolds due to their characteristics, but perhaps consequently there is more to consider in terms of class of material. Research showed that polymer based scaffolds tend to lack stability in mechanical strength; for this reason, perhaps other materials such as ceramics which provide a strong integration with host tissue should be evaluated (Turnbull et al., 2018).

If additional research on the classes of materials supports the notion that polymer based scaffolds are best for BTE, then other variables should be researched for each material. For instance, both PLAGA and Polyphosphazene scaffolding materials have different versions. PLAGA is a copolymer between lactic acid and glycolic acid and in this relationship various ratios between the two acids exists. Generally, PLAGA exists from anywhere between 75:25 (lactic acid:glycolic acid) to 85:15, but considering that the material is a synthetic polymer (as opposed to natural polymers such as collagen and chitosan) the ratio can be manipulated to test which best supports ideal scaffold characteristics. Similarly, with the Phosphorous Nitrogen backbone found in the Polyphosphazene based scaffolds, there are various amino side groups that can be attached to increase variability. Again, these side groups should be manipulated in a test similar to that of some researchers who have already began working in this direction to identify the optimal variation of the Polyphosphazene scaffold.

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