A Review of Bone Implants and the Suitability of Porous Nitinol

Abstract

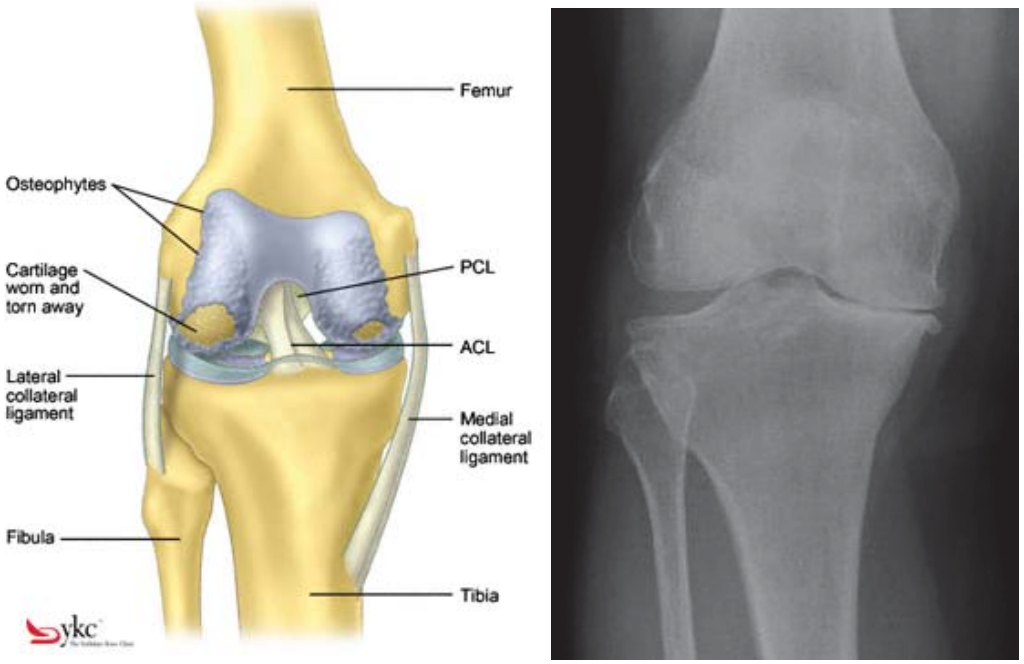
Because more people are developing bone and joint problems that can only be fixed through bone replacement surgery, the need for improved and long-lasting synthetic bone implants is increasing. Conventional implants, such as titanium and cobalt based alloys are too strong and inflexible, compared to bone. Because these implants act so differently from bone and bear most of the weight, the surrounding osseous tissue becomes weaker and may loosen from the implant. These implants need to be replaced after about 15 years, when the accumulation of wear and tear finally leads to failure of the implant. The appropriate design parameters of an implant material will be discussed, focusing on mechanical properties, biocompatibility, and longevity as an implant. Nitinol foam, a distinctive porous nickel-titanium alloy, provides an appropriate alternative to conventional implants. Nitinol is known for its high strength, low stiffness, shape memory and superelastic effects; these unique mechanical properties and the ability of porous alloys to interface well with bone make porous nitinol an optimal material for bone implants. Fabrication of porous nitinol (NiTi) is usually accomplished through a combination of powder metallurgy techniques to react the nickel and titanium powders and space-holder techniques to obtain desired pores. This is a critical step, as pore size, overall porosity, and fenestrations between pores affect not only the mechanical properties of the porous alloy, but also the biological interaction between the foam and the host tissue. Often, to optimize the tissue integration, further surface modifications are made to increase host receptiveness, decrease corrosion and minimize nickel release. Many studies have confirmed the biocompatibility of both monolithic and porous nitinol *in vitro* and *in vivo*; however, further evaluations must be done to confirm the long-term safety of porous NiTi especially considering the eventual effects of fatigue and implant wear and tear. Finally, this review will cover implant applications of porous nitinol, ranging from intervertebral fusion devices to hip implants or even as a surface coating for other implants. Ultimately, optimizing the fabrication and surface modifications for biocompatibility is the most important factor in deciding the path that NiTi implants will follow in the future.

Introduction

As our population ages, instances of osteoarthritis and osteoporosis are steadily rising. Often our bodies are not able to regenerate bone tissue effectively, especially in cases where the patient is elderly or has suffered a trauma accident. In these cases, the most effective means of fixing the problem is through bone replacement surgery. In the United States every year, approximately 500,000 people undergo total knee replacement surgery [21]. An additional 460,000 Americans undergo either partial or total hip replacement, and 300,000 patients have spinal fusions every year [21]. These implants provide

pain relief and mobility; however, these implants often do not outlive their host and need to be replaced. These implants can be designed to increase duration and performance; the demand for implants with appropriate design parameters and materials is rising.

The most common reason for these replacement surgeries is osteoarthritis. Osteoarthritis is a type of degenerative joint disease, where the cartilage which protects the joints is slowly worn and torn away and the body is unable to effectively repair and replace it (Figure 1). As the bones at a joint begin to grind against each other, movement for the patient becomes difficult and painful due to the absence of cushioning provided by the cartilage [22, 24]. Figure 1 shows a schematic and an X-Ray of a diseased knee, where the cartilage has been eroded from osteoarthritis. Primary treatment of this condition involves treating the symptoms, such as using Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) for pain relief [22, 24]. Since there is currently no cure for osteoarthritis, the cartilage breakdown eventually becomes so severe that some form of bone replacement surgery is needed [22].



1(a) (b)

Figure 1- Progressed osteoarthritis of the knee. (a) Representation of the knee, where the cartilage at the joint has been worn and torn away. (b) X-Ray of severe osteoarthritis- the cartilage shielding the tibia from the femur has been eroded, so the bones are now in contact. Images from Yorkshire Knee Clinic.

However, osteoarthritis is not the only instigator of bone replacement surgery. Other common afflictions include blunt trauma accidents, such as sports injuries or traffic accidents. Severe accidents can permanently damage the joint or bone, calling for immediate replacement surgery. Other less severe accidents can plant the seeds of bone problems that will aggregate and worsen over time,

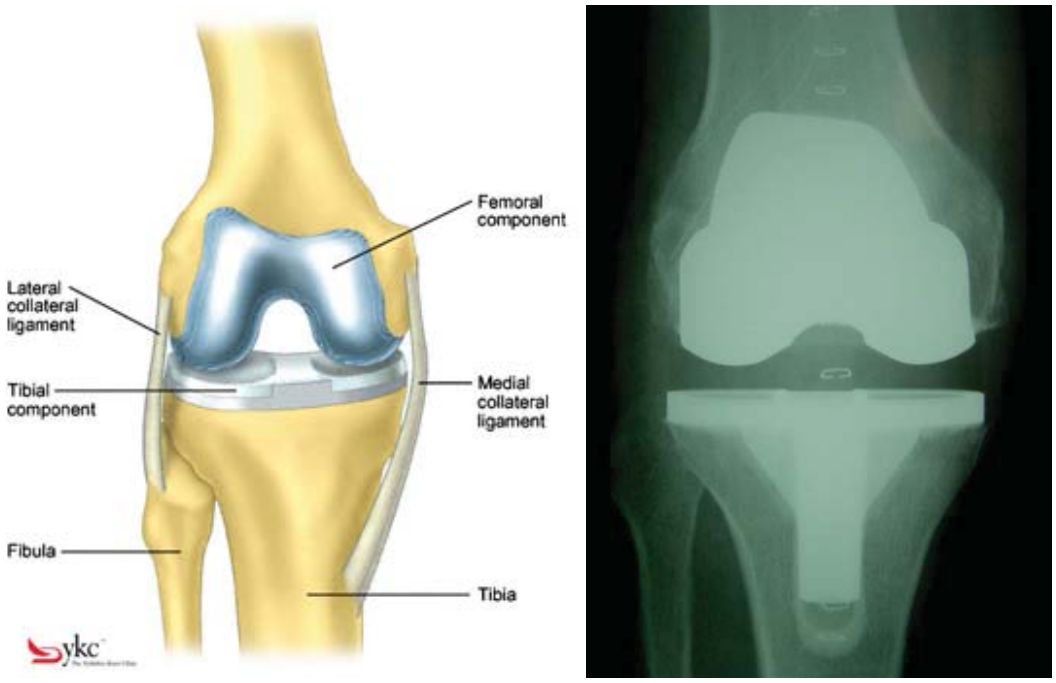
ultimately resulting in the need for replacement surgery. For example, an athlete having a joint injury early in life may lead to more serious joint problems later in life, as the injury may never fully heal and cartilage damage can accumulate. Other potential reasons for bone replacement surgery include bone cancer and dental problems (dental bone implants).

In the field of bone replacement, there are several solutions to the need for an implant, including autografts, allografts, synthetic implants and grown implants. Autografts involve taking a bone tissue sample from some other part of the patient's body and implanting it at the damaged site. This is possible for smaller bone defects, but not for total knee or hip replacements as there is not enough tissue to transplant [6]. This approach is surgically intense, since the bone must be harvested from elsewhere on the patient's body and can cause complications such as donor site morbidity, which can involve pain and scarring [2]. The site being harvested may not have the appropriate mechanical properties; for example, tissue from the iliac crest (the most common donor site [6] located on the pelvic bone) used for a knee replacement surgery does not have the desired strength and flexibility, because its original function was different. The advantages of autografts are that the graft tissue is living and will be more readily accepted by the patient's immune system than other foreign tissues. This means that the graft does not elicit an immune response, which allows for easier integration (growth of the host tissue into the graft) and healing of the entire graft site [6, 11]. Complications from autografts have been reported to be about 16% [2] (Iliac crest harvesting on 414 patients), which mainly includes infections and pain at the donor site.

Allografts are another technique, which involves taking tissue from a donor (usually a cadaver at a Bone Bank) and implanting it into the patient. After the bones are removed from the donor, they are processed and sterilized to reduce the chance of infection and host immune response. They are then frozen or freeze-dried and can be kept for 1 to 5 years [6]. While the tissue being used may have the same function (tissue from a cadaver knee can be transplanted to the patient's knee), the tissue is no longer living and will have deteriorated mechanical properties, depending on the intensity of sterilization and the length of storage [6]. The host tissue will have a less than optimal response, since a foreign tissue is being inserted, but the bone tissue may ultimately grow into the grafted bone. However, healing and incorporation of the allograft is incomplete and unpredictable due to the high number of complications [11]. When performing a bone graft, allografts are considered to be the surgeon's second choice [2] and account for 15% of all bone grafts [11]. One British study of 718 bone allograft patients recorded long-term complication rates of 46%, with the most common complications being fracture (19%), non-union at the host-allograft junction (17%), and infection (11%) [11].

Recently, advances in tissue engineering have created the possibility of growing cells on scaffolds to replace damaged tissues. One advantage of grown implants is that they could be grown from the patient's own cells, essentially minimizing immune rejection. Ideally, they would have appropriate mechanical properties, specifically designed for each implant. The downsides include an initial surgery to take tissue samples from the patient, time needed to grow the tissue, and finally another surgery for tissue implantation. However, there are no current developments, which would allow for total hip or total knee replacement surgeries [24]. The future of this field is promising, but a number of hurdles must be overcome before engineered tissue can be used in replacement for other types of implants.

When considering partial or total joint replacement surgery, synthetic implants are the most commonly used since the tissue damage is too severe to treat with other methods [24]. Synthetic implants are commonly metal alloys, such as titanium or chrome alloys (Figure 2). The damaged cartilage at the surfaces is surgically removed and then covered with the metal components [22]. In total knee replacement a femoral and a tibial component are installed, as seen in Figure 2 [22, 24]. Synthetic implants also include man-made ceramics, such as tricalcium phosphate (TCP) and hydroxylapetite (HA),



2(a) (b)

Figure 2- Knee after complete replacement surgery with a traditional metal alloy implant. (a) Representation of the knee after complete knee replacement surgery, the defective cartilage is removed and replaced with a metal alloy which protects the joint. (b) X-Ray of complete knee replacement – the metal implant is much darker than the surrounding bone tissue. Images from Yorkshire Knee Clinic.

both of which are calcium phosphate ceramic scaffolds [6]. TCP-ceramic and HA are both similar in composition to bone and are capable of being resorbed and reconstructed by the surrounding bone [6]. However, ceramics are brittle and unable to support intense mechanical stress by themselves, so they are best used in filling bone fractures rather than replacing weight bearing joints [6]. These artificial implants are advantageous and common in joint replacement surgery. Because they are predesigned and fabricated, only one surgery per patient is required and the implant can be installed immediately. Their shape, mechanical properties, and composition are all controlled by traditional manufacturing techniques. Thus, they can be easily manufactured, stored and shipped, unlike tissue samples. Both porous metal alloys and porous calcium phosphate ceramics are able to promote osseointegration, a process where the native bone tissue actually grows into and integrates with the implant (Figure 3) [1, 3, 6, 20, 23]. This is very important, because if the tissue integrates into the surface of the implant, there is a tighter bone-implant connection and less chance of the implant becoming loose [23]. Osseointegration helps to distribute stress more evenly between the implant and the bone, decreasing the likelihood of bone weakening [3]. The main disadvantage of metal alloy implants is that the body is unable to fully integrate with the implant; the surrounding tissue cannot tear down and rebuild the implant in the same manner as it would if bone tissue was implanted [6]. Ultimately, since the body cannot rebuild the metal alloy implant, wear and tear accumulates and eventually the implant must be replaced in another surgery. The average lifetime of current total hip replacements is 20 years, while total knee replacements last about 10 to 15 years, depending mainly on the activity level of the patient [27]. Traditional implants are attached to the bone and held in place using cement (which can erode and break down over time) and screws (which can cause bone fracture) [23]. Newer implants with porous surfaces have the potential to last longer, because there is a more solid interface developed by the bone tissue growing into the implant [3].

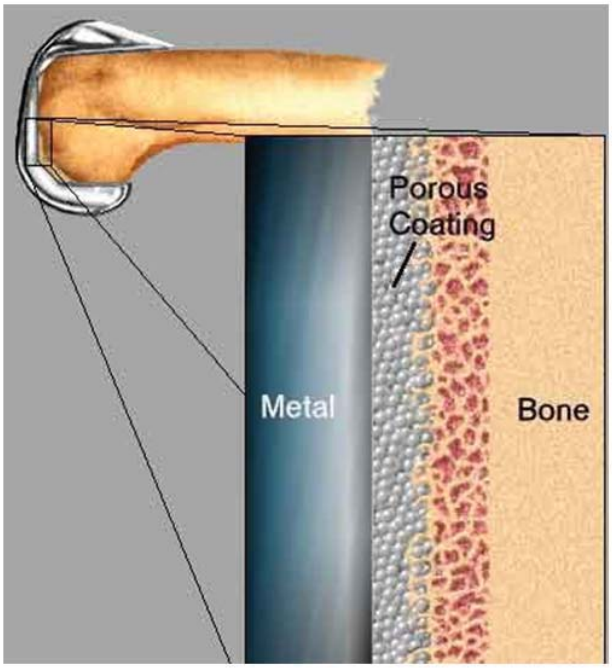


Figure 3- Schematic of Osseointegration [23]. The porous coating of a metal implant alloys for the bone to grow into the implant, creating a tighter junction.

There is a need for new types of long-lasting synthetic implants, since current bone grafts are limited and the field of tissue engineering is not yet capable of providing the tissues necessary for full joint replacement surgeries. Nitinol, a nickel-titanium alloy, has the desired strength provided by the other biomedical metal alloys, as well as a distinct ability to retain its original shape [3]. The shape memory and superelastic effects allow nitinol to effectively flex in and out of shape, through fatigue and cyclic loading/unloading. While other titanium and cobalt alloys are able to endure cyclic loading and unloading, the strain eventually disrupts the atomic bonds, causing the metal to either plastically deform or break. In either case, the implant eventually fails and must be replaced. Nitinol can last longer under these conditions [3] and its porous form has the ability to provide sufficient osseointegration [3].

Qualities of an Appropriate Implant

The desired characteristics of an implant include 1) mechanical behavior similar to bone, 2)generic qualities (size, shape, and weight) which will allow for optimal performance and comfort, and 3) biocompatibility and integration with the host tissue.

When implants, especially metal alloys, are being designed there are several important properties for the material to have. It must have high strength and low stiffness, so it must be able to withstand high amounts of force and be able to endure deformation. Essentially, the implant should behave similarly to or better than bone, and it must be able to undergo cyclic loading and unloading. If the implant is brittle, then it is liable to break, causing serious problems. The implant also cannot take on the entire load of a particular joint, because that can lead to the surrounding bone becoming weaker and increase the risk of fracture [7].

The size and shape of the implant is highly dependent on the bone or joint being replaced, as well as other patient characteristics, such as gender, height, weight, and age. Generally speaking however, implants can be mass-produced based on a few parameters, so synthetic implants are immediately available for use and not custom-made. Generally, the shape for a hip implant will remain the same but scaled into different sizes. During the surgery, the host bone tissue is cut away so that there is a tight fit with the implant. The weight of the implant is important for integration with the bone and for patient comfort, but it is often overlooked in favor of other characteristics. If the implant is too heavy, then it can be made into a porous metal throughout; however, completely porous metal implants are uncommon among traditional metal alloys due to their diminished mechanical properties and increased likelihood to break [7]. With the traditional metal alloys it is more common to have a dense center (providing the original high strength properties) with a porous coating (to enhance bone

ingrowth) [1]. Porous nitinol behaves differently from traditional porous metals, because it is flexible and able to regain its shape, where conventional metal alloys would become brittle and break.

It is critical that the implant is biocompatible, causing few or no adverse effects to the patient. The human body is a rough neighborhood for foreign objects, and the immune system does not always accept the metal alloy implant. Up to 13% of the population is hypersensitive to nickel, cobalt, or chromium [13], which means they may develop an allergic reaction to their implant. Other key factors, besides the composition of the implant, include the metal ion exposure and release. The host reaction depends upon how much tissue is in contact with the metal alloy surface and how much of the toxic metal ions are being released into the system [3]. The more common cobalt based alloy contains chromium and molybdenum (Co-Cr-Mo), while the more common titanium based alloy contains aluminum and vanadium (Ti-6Al-4V). Both cobalt and titanium based alloys have passive oxide layers that form on their surfaces, which allows for corrosion resistance and limits metal ion release [13, 16]. Ultimately, it is important to use implant alloys that will not release large amounts of metal ions, and whose surface modifications make it conducive to tissue growth and not to tissue inflammation.

In this paper, we will judge the appropriateness of an implant based on three parameters: mechanical properties, biocompatibility, and longevity as an implant.

Titanium Implants

In order to better understand how nitinol fits into the mold of an appropriate implant alloy, we will look at more commonly used titanium alloys for comparison. Titanium's superior weight to strength ratio and high resistance to corrosion makes it an especially useful material for orthopedic implants. Grade five, the most commonly used titanium alloy, is a blend of 90% titanium, 6% aluminum, and 4% vanadium (Ti-6Al-4V). The composition of this alloy is important, since it contains none of the commonly allergenic metals: cobalt, chromium, and nickel. While Ti-6Al-4V's properties make it a suitable implant alloy, cells do not adhere to it well without special processing such as surface powder sintering. During sintering, a fine layer of titanium powder is attached to the surface of the implant; the resulting uneven surface provide the bone cells a much better medium on which to adhere [1]. Unfortunately, the boundary between sintered beads and the base alloy is a potential starting place for cracks and other defects [1]. Grade 5 Titanium is used because it is very strong and relatively light; however, it does not bond well to the bone tissue without further surface modifications, which can compromise its strength.

Porous Nitinol

Nitinol is a binary Nickel Titanium alloy, also known as NiTi, whose superelastic and shape memory properties have made it an important and useful alloy. Currently, its wire form is commonly used in stents, but other forms such as monolithic (dense) and porous (foam) are also gaining recognition as being useful for other biomedical purposes.

Nitinol's shape memory effect is dependent on the transition between two equiatomic crystalline structures, martensite and austenite. Deformation occurs through a transition from the inflexible austenite to the more pliable martensite [29]. After deformation has occurred, the original structure can still be recovered through a martensite to austenite transition [29]. The shape memory effect (SME) is primarily dependent on temperature; so the nitinol is deformed from its parent shape at a low temperature and remains in the deformed shape [29]. Once it is heated above a certain temperature (known as the A_f temperature or Austenite formation temperature), the martensite to austenite transition is induced and the nitinol returns to its original parent shape [29]. The superelastic effect occurs when the environmental temperature is above the A_f temperature; the nitinol wants to revert to the austenite structure [29]. This effect is primarily mechanical in nature and manifests as an elastic response to temporary stresses. Superelastic nitinol samples can be deformed under an applied load, but will spring back to the original shape as soon as the load is removed. When used as a biomedical material, nitinol with an A_f temperature at or below body temperature is used, so that the nitinol always acts superelastically *in vivo*.

Mechanical Properties

It is important that the implant is able to endure the cyclic loading and unloading weight put on it through everyday use. This means that it must act similarly to the surrounding bone, if not better. Conventional implants, such as titanium alloys have a stiffness of ~110 GPa, while cobalt alloys have a stiffness of ~210 GPa [7]; both of which are much higher than that of compact bone (12-17 GPa) or cancellous bone (<3 GPa) [7] (See Table 1 for a summary of stiffness). Stiffness is a measure of how flexible the implant is, or how much it deforms under stress. A large difference in stiffness between the implant and the surrounding bone tissue can result in stress-shielding, where the implant absorbs most of the applied force [7]. The stiffness mismatch causes bone weakening and implant loosening, since the bone and implant respond differently to applied forces [7]. Monolithic nitinol has a much lower stiffness of 55-80 GPa [7], which is much closer to the stiffness of compact bone. One of the more common ways to match the properties to those of bone is to make the metal alloy porous, rather than dense. Since

dense nitinol has a relatively low stiffness, a lower degree of porosity (16%-30%) is required to match compact bone (12-17 GPa), where titanium alloys require porosity around 50% [7].

One of the reasons titanium and cobalt alloys must be so stiff is because they do not regain their original form very easily. Nitinol, on the other hand, has unique properties allowing it to be deformed while under stress, but regain its original shape once the stress is removed. Strain is a unitless measure of how much the sample has been deformed; recoverable strain measures the amount of elastic deformation that is able to be recovered once the stress is removed. Grenier *et. al.* (2005) produced 16% porous nitinol with high recoverable strains (6%), while Zhang *et. al.* (2008) created 27% porous nitinol with recoverable strains of 6% as well. Compact bone has a recoverable strain of approximately 2% [26]. Xiong (2007), as well as Shape Change Technologies have recently created more porous foams, but with lower recoverable strains. There is a relationship between porosity and strain recovered: as the porosity increases, the ability of the material to recover strain decreases. Table 1 summarizes the stiffness and recoverable strains of traditional dense metal alloys, bone, and nitinol with varying porosity.

	Material	Author	Stiffness (GPa)	Recoverable Strain (%)
Traditional Metal Alloy	Titanium Alloys	Greiner et.al., 2005 [7]	~110 GPa	<1% [26]
	Stainless Steel	Greiner et.al., 2005	~190 GPa	<1% [26]
	Cobalt Alloys	Greiner et.al., 2005	~210 GPa	<1% [26]
Bone	Cancellous Bone	Greiner et.al., 2005	<3 GPa	<75% [26]
	Compact Bone	Greiner et.al., 2005	12-17 GPa	2% [26]
Nitinol (varying porosity)	Dense Nitinol	Greiner et.al., 2005	55-80 GPa	8%
	16% Nitinol	Bansiddhi and Dunand, 2008 [4]	16 GPa	6%
	27% Nitinol	Zhang et. al., 2008 [19]	13 GPa	6%
	66% Nitinol	Shape Change Tech [26]	8.6 GPa	5%
	71% Nitinol	Xiong et. al., 2007 [17]	8.6 GPa	5%
	80% Nitinol	Xiong et. al., 2007	3.1 GPa	4%
	87% Nitinol	Xiong et. al., 2007	0.3 GPa	3%

Table 1 shows the stiffnesses and recoverable strains of traditional metal alloys, compact and cancellous bone, and experimental data on nitinol (dense and porous). Porous nitinol is much closer to the characteristics of bone than the other metal alloys.

Thus, porous nitinol is a suitable implant because its material properties are able to match those of bone in stiffness, while having higher strength and high recoverable strains (see Table 1). Nitinol is able to last longer under cyclic loading and unloading because the material regains its original shape after the force has been removed. Conventional alloys are harder to deform, but once they have been

bent, they do not return to their original shape. Nitinol's superelasticity thus contributes heavily towards the appropriateness of this alloy as a bone implant based on mechanical properties and longevity as an implant.

Fabrication of Nitinol Foams

Designing an implant with appropriate mechanical properties and durability, begins with the fabrication of the base alloy. Making monolithic, or dense, nitinol is a difficult process, because the melting point of nitinol is relatively high (1310 °C). There are a variety of ways to make nitinol, the most common involves powder metallurgy, where powdered nickel and titanium are mixed together (in approximately equiatomic proportions) and then heated to form the alloy. There are a number of powder metallurgy routes, which have been used successfully to create nitinol. However, self-propagating high-temperature synthesis (SHS) is the most commonly used method [3] and so shall be discussed here. SHS is a way to manufacture compounds in a propagation reaction, where the combustion of one layer initiates the combustion of the next layer [10]. After nickel and titanium powders are mixed together, a small portion of the sample is heated to the reaction temperature [10]. Since the reaction is exothermic, enough heat is provided to the surrounding area to cause it to react and form nitinol as well [10]. In this way, the reaction propagates until all of the powder has been formed into the metal alloy.

In order to make porous nitinol, pores must be generated during the formation of the alloy. The common methods for obtaining pores within the nitinol are through either Argon gas expansion or using a salt space holder. Argon gas expansion has been successfully used to create porous nitinol [7], although the resulting porosity was uneven and rather low (17% closed pores). Closed pores indicate that there is little or no connection in between pores, while open porosity means that there is high connection between pores. The salt space holder technique is a better way to produce porous nitinol as it is easier to perform and provides more consistent and open porosity [3, 4]. This technique depends on adding non-reactive salt granules to the powdered nickel and titanium [3]. This salt holds the space, forming pores while the alloy hardens around it [4]. Once the alloy is completely formed, the salt is washed away with water. Using salt granules is useful because pore size can be controlled through the size of the salt grains and the level of overall porosity can be controlled by the relative volume being dedicated to pores.

Choosing an appropriate salt is harder than it may seem at first glance, and various space holders have been used including NaF, NaCl, and NH_4HCO_3 [3]. The melting temperature of sodium

fluoride is higher than that of sodium chloride (993 °C compared to 801 °C), so it was initially preferable as the reaction to form nitinol can be carried out at temperatures around 950 °C [3, 4]. It seemed that melting the space holder would lead to more difficulties in the formation of the pores, but it has recently been shown that sodium chloride can still be used as a space holder even though it does eventually melt during the process [4]. The molten NaCl did not react with the NiTi and was able to be washed away using aqueous solution afterwards; thus, they were able to successfully create porous nitinol (40% porosity, 75-250 µm) [4] as shown in Figure 4. It is apparent that they were successful in creating pores in the nitinol using NaCl space holders; however their technique was unrefined, creating blocky pores and inconsistent pore fenestrations (white arrows). Sodium chloride is a much better choice than sodium fluoride, due to its low cost, solubility in water, and low toxicity. Additionally, when the NaF salt was washed away with water, a hydrofluoric solution is created which is corrosive to the porous nitinol [3]. The most important aspect, especially when the foam is to be used in biomedical applications, is the lower toxicity of a slightly salty implant (using NaCl) compared to an implant with trace fluoride (from using NaF).

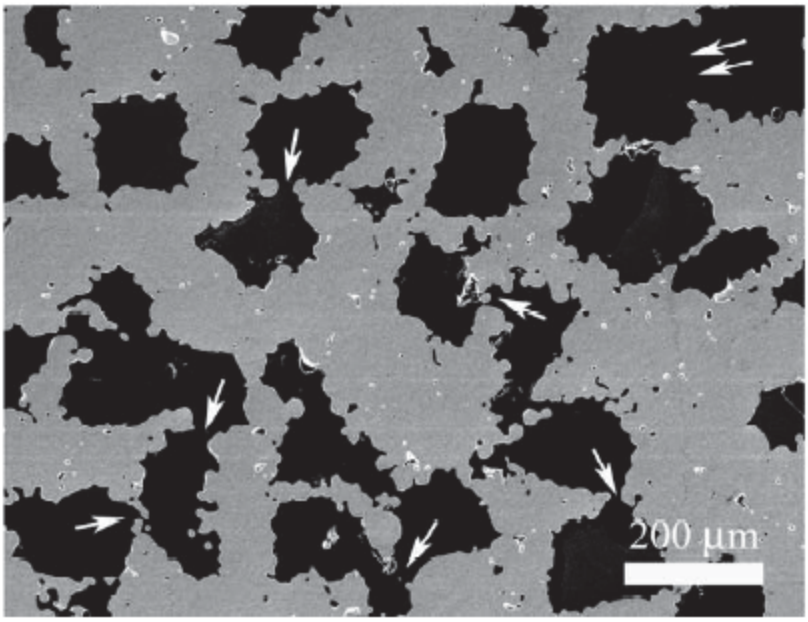


Figure 4 shows porous nitinol created by Bansiddhi and Dunand (2008) using the NaCl space holder technique. Black blocky areas indicate where the NaCl granules once were. Arrows show fenestrations between open pores.

Through the use of powder metallurgy and space holder techniques, one is able to make fairly consistent nitinol foams. These porous nickel titanium alloys have both specified pore sizes and known overall porosity. The target range for pore size is approximately 100-600 µm [3], and the expected porosity is 30%-80% [3]. Determining the ideal porosity of the nitinol implant is a difficult process, since

the promotion of osseointegration and ideal mechanical properties must be balanced. As previously shown, 16%-30% porous nitinol show stiffness match to compact bone [4, 7, 19]. However, overall porosity below 30% usually results in mostly closed pores with fewer fenestrations, which makes it less ideal for bone ingrowth [3]. The number and size of fenestrations between pores remains one of the less controlled aspects in creating porous metals [3]. Fenestrations are the windows which connect pores together, and they are exceedingly important to osseointegration of the host tissue with the implant alloy [6, 7]. Being able to control the fenestrations in between pores, in addition to overall porosity and pore size, would facilitate the creation of porous nitinol with appropriate mechanical and osseointegration properties. Gradients of porosity and pore size could also enable both superior osseointegration at the surface, and desired mechanical properties overall [3]. Gradients would be a better alternative to the current dense implants with porous outer coatings, since it been shown in titanium implants that the boundary between the porous coating and the base alloy is a potential starting place for cracks and other defects [18]. Bansiddhi (2008) also points out that additional processing techniques need to be implemented to control the shape of the pores, namely that they are aligned and elongated to imitate the structure of actual bone. There is room for refinement of current processes and/or development of new processes that create porous nitinol appropriate for bone implants.

Surface Modifications

The surface of the implant is crucial as it serves as the interface between the implant and the bone. This interface determines how the immune system responds as well as to what extent the bone tissue grows into the porous metal alloy. The most prominent reason for surface modifications of porous nitinol is to reduce the amount of nickel released into the body. Excessive nickel release in animals and humans can cause adverse allergenic or immunogenic responses including swelling, inflammation, cellular hypersensitivity, cytotoxicity, and genotoxicity [3, 25]. Nickel release appears to be the main cause of inflammation following surgery, when porous nitinol has been tested in animals [3]. Nickel leeching has been reported to be two orders of magnitude greater for porous nitinol compared to dense nitinol [3], since nickel leeching is related to the surface area in contact with the surrounding tissue. It has been extensively shown that nitinol in wire, film, and dense form is not cytotoxic [3, 5, 15]; however, porous nitinol still raises biocompatibility arguments ranging from hypersensitivity to adverse immune response [3]. For this reason, it is important that surface modifications on porous nitinol are two-fold:

effectively decreasing the nickel leeching, while inducing a more positive response and growth from the surrounding osseous tissue.

There are a variety of surface treatments used to enhance the suitability of porous nitinol; these treatments are usually tested by submerging modified and unmodified porous nitinol samples into simulated body fluid (SBF) and then measuring the nickel released into the solution [15]. These surface treatments include thickening the natural oxide layer (TiO_2), heat treating the metal alloy (aging or annealing), or coating the surface with another material. It has also been found that the nickel release from nitinol follows a logarithmic curve; since most of the nickel is released at the beginning, presoaking the porous alloy in SBF, can reduce nickel release [3]. Table 2 shows the experimental results of several different types of surface modifications, including their treatment type and the total nickel released (ppm) into the SBF [3]. Since the experimental setups by each author were so different, the effectiveness of each surface modification has been determined based on the fractional reduction in release levels (treated nitinol release ppm/untreated nitinol release over the course of the experiment). Thus a 75% Reduction level means that the surface treatment cut the nickel release rate to a fourth of the original level being released into the SBF solution.

Author	Porosity (%)	Pore Size (μm)	Time	Treatment Type	Release Levels (ppm)		% Reduction
					Treated	Untreated	
Ho *et. al.*, 2007	40	-	28 days	Oxygen Plasma	0.05	0.18	72%
Wu *et. al.*, 2006	42	50-400	70 days	Oxygen Plasma	0.08	0.3	73%
Wu *et. al.*, 2007	48	50-500	6 days	Oxidation at 450°C	0.20	0.45	56%
Lemaire *et. al.*, 2007	65	100-320	16 days	TiN PVD Coating	0.09	0.3	70%
				TiO2 PVD Coating	0.07	0.3	77%
				SBF Presoak	0.07	0.3	77%
				TiN+ SBF Presoak	0.04	0.3	87%
				TiO2+SBF Presoak	0.07	0.3	77%
Jiang *et. al.*, 2006	61	200-600	50 days	HNO3/NaOH with HA Coating	0.48	6.7	93%

Table 2 shows the experimental data and nickel released from several porous nitinol surface treatments. Treated and untreated release levels have been presented for comparison. Derived from comparison of processing methods by Bansiddhi *et. al.*, 2008.

Comparison of the fractional reductions of various treatment methods is illustrated in Figure 5. The percent reduction in nickel release from the untreated to the treated samples is shown (calculated from Table 2). It would appear that the last treatment by Jiang *et. al.*, the HA coating, is the most effective with a 93% reduction; however, they had a high release rate to begin with and their treated

sample releases more nickel (0.48 ppm) than any of the other untreated samples. Ultimately, the TiN PVD coating with SBF presoak was the most effective treatment method, causing the treated sample to release only 0.04 nickel ppm (87% of the nickel released by the nontreated sample). It is obvious based on the wide range of nickel release from untreated samples (0.18-6.7 ppm), that there is a need for standardized production of nitinol foams as well as a standard method with which to test them. Nevertheless, treatment uniformly decreased the nickel leeching, and all levels were below average daily dietary intake of nickel (170 µg/day) [25].

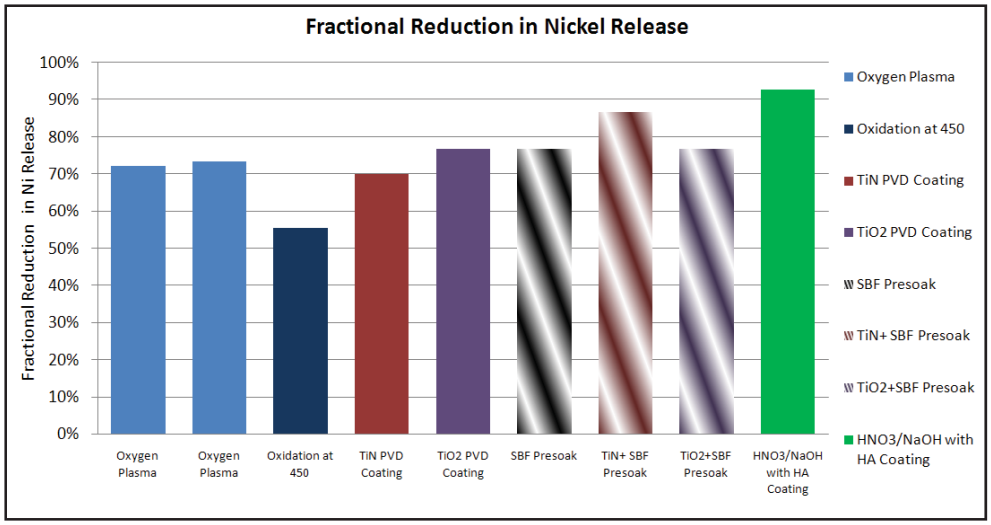
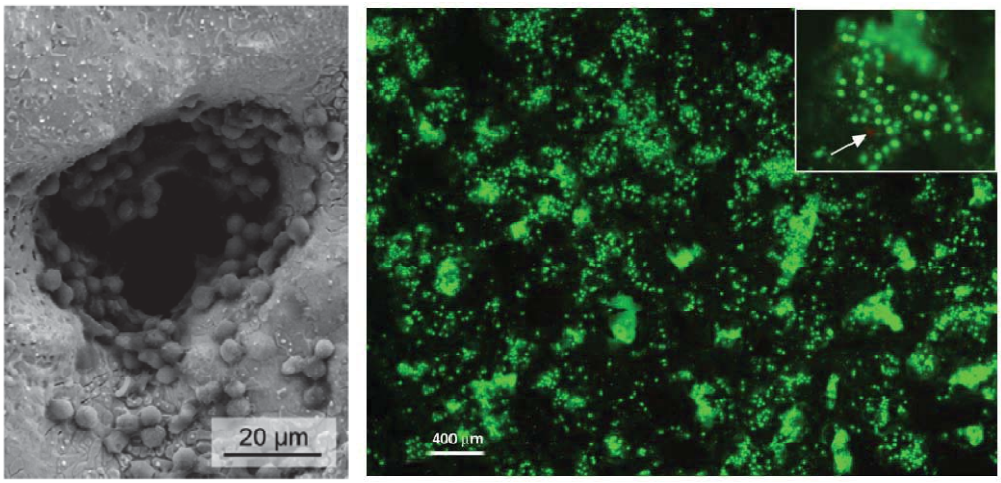


Figure 5- Fractional reduction in Nickel release. The various treatment types from Table 1 visualized here using the information on the amount of nickel released before and after surface treatment. 50% fractional reduction indicates that the surface treatment resulted in reduction of Nickel release by 50%. Solid colors indicate surface treatment alone, striped colors indicate SBF presoak with or without surface treatment.

Reducing nickel release is the first step in making porous nitinol into a biocompatible implant; the following steps involve enhancing the growth of the osseous tissue into the implant. Being a porous alloy is not enough to elicit growth from the tissue. The porosity, pore size, and pore fenestrations are all important indicators that the alloy is conducive for bone growth. Completely optimal pore conditions are currently being researched, but generally accepted ranges for porous implant alloys are 30-80% porosity (depending on whether it is compact or cancellous bone), 100-500 µm pore size, and many fenestrations (open porosity) [3]. Finally surface modifications, such as the hydroxyapatite coating [28] or other embedded bone growth factors, can make the implant more conducive to bone ingrowth, although more research needs to be done to exactly identify and optimize these.

Many studies on the *in vitro* and *in vivo* biocompatibility of porous nitinol have been done, with mostly favorable results. *In vitro* cell cultures have shown that on surface treated porous nitinol, blood leukocytes and osteoblasts adhere and proliferate within the alloy scaffold [3, 12] (See Figure 6). Cellular

assays have confirmed that treated porous nitinol is not cytotoxic or genotoxic [3, 5, 12]. *In vivo* experiments have been successfully performed on sheep, rabbits, and rats. The implants in sheep were long-term (3 to 12 months) and measured acceptable levels of nickel released into the surrounding tissue, blood, and organs (<1 μg/g for tissues and organs, 5 μg/l of blood) [3]. In rabbits and rats, osseointegration of the implant and no signs of loosening were recorded; there was up to 78% success rate of the implant integration after 6 weeks in rabbits [3]. Figure 6 shows biocompatibility of porous nitinol with human blood leukocytes; the cells attach themselves to the pores and remain alive.



6 a) b)

Figure 6 shows the biocompatibility of nitinol foams in vitro cell culture. (a) Peripheral blood leukocytes adhere to the porous nitinol surface. (b) Flourescent microscopy of peripheral blood leukocytes. Green indicate living cells, and the arrow points to one red (dead) cell. Photos from Prymak et.al., 2005.

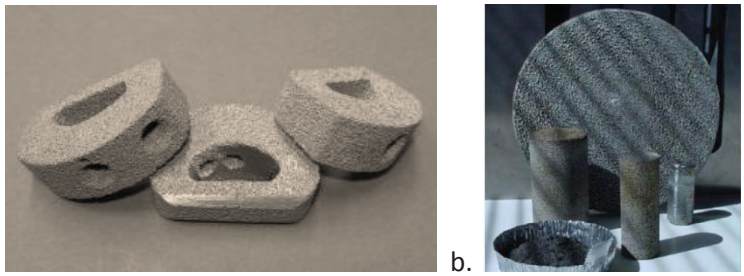
Applications in Bone Implants

Porous nitinol is suitable as a bone implant, because as it has the appropriate mechanical properties (high strength and recoverable strain), potential for biocompatibility (surface modifications reduce nickel leeching and encourage osseointegration), and can be a long-term implant (osseointegration prevents loosening and its mechanical properties prevent failure). Porous nitinol is better than other porous alloys, since traditional alloys have a greater potential for fracture. Porous nitinol is better than other dense alloys, since there is more osseointegration and less implant loosening. Ultimately, nitinol foams are capable of lasting longer than traditional synthetic alloys, because they accumulate wear and tear until they become loose or break.

Current applications in human bone implants have been commercially pioneered by Biorthex (Canada). They have produced the product Actipore, which is a porous intervertebral fusion device see

Figure 7. Shape Change Technologies is a more recent company which produces custom nitinol foam as per request, see Figure 7b.

a. b.



c. d.

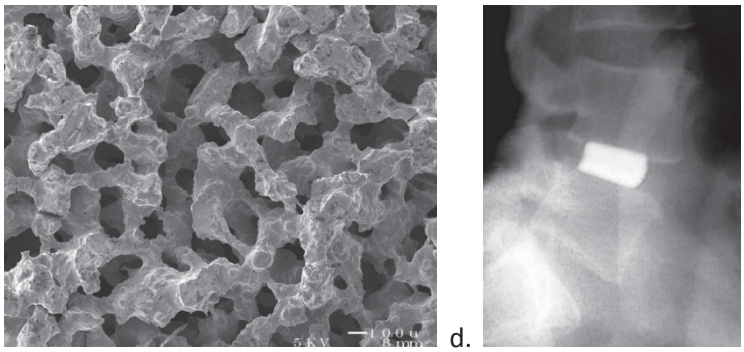


Figure 7 shows some commercially available nikel-titanium foams. (a) Actipore Anterior Lumbar Fusion System from Biortex (Canada). (b) Variety of nitinol foams from Shape Change Technologies. (c) SEM photo of Actipore, showing its 65% porosity and excellent fenestrations. (d) X-Ray of Actipore after being implanted as a spinal fusion device. Photos are from Biorthex Inc. and Shape Change Technologies LLC.

Porous nitinol has the potential to be a superb synthetic bone implant, with high bone integration and durability. Current technologies already permit its use as an intervertebral fusion device [3, 20], but more research on optimizing geometry and surface modifications is needed before it can be used as knee or hip replacements.

Nitinol foams have come a long way in the past few years; however, research on them is still in a relatively early stage [3]. Porous nitinol has the ability to fulfill the design parameters specified earlier in this review:

1) Mechanical properties- Porous nitinol has the ability to perform similarly to compact bone in stiffness (12-17 GPa), while maintaining high recoverable strains (6%). This reduces stress shielding, bone weakening, and implant loosening which reduces implant failure and increases longevity. Fabrication techniques need refining to create more predictable pore fenestrations and porosity gradients.
2) Biocompatibility- Nitinol foams have met the low standards for biocompatibility, including low levels of nickel release, minimal immune response, and not being cytotoxic. Porous nitinol has also met some of the higher standards for biocompatibility (which involve promoting tissue growth) including cell adherence, osseointegration, and minimal inflammation. More research needs to be done on various surface modifications and their

ability to enhance biocompatibility of porous nitinol *in vitro* and *in vivo*. Additionally, more studies need to be done on the long-term fatigue effects *in vivo*.

3) Longevity as an Implant- How long the implant lasts in the human body depends on a number of factors, such as its ability to resist wear and tear, maintenance of tight fit between the bone and the implant, and the patient's physical activity level. Wear and tear is common to all synthetic implants, but it can be reduced by using strong and flexible materials that can endure cyclic loading and unloading. Nitinol does not accumulate plastic deformation in the same manner as traditional metal alloys and performs superiorly over time. Osseointegration and growth of bone cells into the porous implant keeps the implant from becoming loose and needing to be replaced. Since porous nitinol is able to match the stiffness of bone and effectively bind to the osseous tissue, stress-shielding and bone weakening are minimized, again increasing the duration of the implant.

Nitinol foams currently fufill the appropriate design parameters specified; however, there is room for improvements in all aspects, especially surface modifications and fabrication. More research is required before porous nitinol can be fully implemented as a prominent and reputable synthetic implant.

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