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Review

Porous NiTi for bone implants: A review

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Abstract

NiTi foams are unique among biocompatible porous metals because of their high recovery strain (due to the shape-memory or superelastic effects) and their low stiffness facilitating integration with bone structures. To optimize NiTi foams for bone implant applications, two key areas are under active study: synthesis of foams with optimal architectures, microstructure and mechanical properties; and tailoring of biological interactions through modifications of pore surfaces. This article reviews recent research on NiTi foams for bone replacement, focusing on three specific topics: (i) surface modifications designed to create bio-inert porous NiTi surfaces with low Ni release and corrosion, as well as bioactive surfaces to enhance and accelerate biological activity; (ii) *in vitro* and *in vivo* biocompatibility studies to confirm the long-term safety of porous NiTi implants; and (iii) biological evaluations for specific applications, such as in intervertebral fusion devices and bone tissue scaffolds. Possible future directions for bio-performance and processing studies are discussed that could lead to optimized porous NiTi implants.
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Keywords: Nitinol; Cellular metals; Biocompatibility; Chemical modification; Bioactive surfaces

Contents

1. Introduction

The near-equiatomic nickel–titanium alloy (NiTi or Nitinol) exhibits unusual mechanical properties (e.g., the superelasticity and shape-memory effects which are related to a thermo-elastic phase transformation near ambient temperature, martensite twinning and inhibition of slip by fine Ni_4Ti_3 precipitates) that enable multifunctional applications involving high recovery strain, high strength as well as a relatively low Young's modulus [1,2]. A few years after the unusual shape-memory properties of NiTi were discovered, a porous form of NiTi was introduced [3]. Porous NiTi – because of additional benefits common to other porous or foamed metals such as low density, high

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surface area and high permeability–was proposed in many applications, including bone implants [4–6], energy absorption [7], light-weight actuators [8] and hydrogen isotope separation [9].

Biomedical applications remain the main target for NiTi with open porosity given the following properties: (i) good biocompatibility, comparable to conventional porous stainless steel and titanium (Ti) implant materials [10–12]; (ii) a combination of high strength (important to prevent deformation or fracture), relatively low stiffness (useful to minimize stress shielding effects) and high toughness (essential to avoid brittle failure); and (iii) shape-recovery behavior facilitating implant insertion and ensuring good mechanical stability within the host tissue. The biocompatibility of NiTi and its unusual mechanical properties make it a superior alloy in monolithic, non-porous form for many bone implant applications. These include maxillofacial and dental implants, cervical and lumbar vertebral replacements, joint replacements, bone plates, bone tissue engineering, spine fracture fixation, anchorage and repair [4,13–17], and many review articles have been published on the biological performance of monolithic, non-porous NiTi [18–20].

In the early stages of research on porous NiTi, the main objectives were to develop fabrication processes for creating foams with desirable architectures and microstructures, and to understand the resulting mechanical and transformation behavior [13,21,22]. It was not until the last decade that many studies were performed on the biological performance of porous NiTi [23–28]. In these studies, the consensus was that porous NiTi exhibited biocompatible behavior *in vitro* and *in vivo*. In 2001–2002, Shabalovskaya et al. [29,30] published an exhaustive review on biological performance of NiTi, focusing primarily on monolithic NiTi but also addressing porous NiTi implants. They pointed out the need for continued research on surface design, characterization of corrosion behavior (especially under load or mechanical deformation), the effects of surface condition and sterilization procedures on biological response, and long term *in vivo* and *in vitro* studies. Following this review, more work has been dedicated to the combined study of the biological evaluation of porous NiTi in parallel with studies on the development of new processing methods [31–33], more in-depth mechanical properties (including fatigue and damping) [34], and modeling [35–37].

In the present article, we review recent progress on the biological performance of porous NiTi in four sections. The first section is a summary of processing methods and properties of NiTi with pore sizes and fractions suitable for implant applications. The second section covers surface modifications of porous NiTi to create surfaces with low and acceptable Ni release levels, improved corrosion resistance, and bioactive properties. The third section addresses the biocompatibility of porous NiTi (with and without surface treatment), including *in vitro* and *in vivo* studies for cytotoxicity, genotoxicity, cell culture, bone apposition, and tissue ingrowth. The fourth section reviews biological studies of porous NiTi in practical applications. Given the reviews by Shabalovskaya et al. [29,30], this article will mostly survey work spanning the six years from 2002 to 2007, with an exclusive focus on fully porous NiTi materials, rather than NiTi with surface porosity (which has been shown to encourage bone ingrowth, e.g., Refs. [38–40]). In each section, the review will provide general observations, a summary of past work, and a future outlook.

2. Fabrication methods

Since NiTi has a high melting point (1310 °C), production methods for porous NiTi have been limited to date to powder-metallurgy techniques, as reviewed by Ryan et al. [41] for porous metals (including NiTi) for orthopedic applications. By contrast, implantable Mg foams [42] have a low melting point, allowing for liquid phase processing methods [43]. For porous NiTi produced by powder metallurgy, the powder can be in either elemental or pre-alloyed form. For instance, porous NiTi has been created from elemental Ni and Ti powders through self-propagating high-temperature synthesis (SHS) [44–46], spark plasma sintering (SPS) [47], hot isostatic pressing (HIP) with argon expansion [48], capsule-free HIP (CF-HIP) [49] and conventional sintering (CS) [50,51]; in this series of methods, partial powder densification and exothermic synthesis of the intermetallic NiTi occur simultaneously. Undesirable non-equiatomic Ni–Ti phases often remain in these NiTi foams, due to incomplete NiTi formation associated with the relatively low temperature achieved during the reaction between Ni and Ti (due to a modest enthalpy of formation of NiTi as compared to other intermetallics). These phases are often difficult to remove, even after lengthy high-temperature homogenization treatments. To avoid this issue all together, some researchers have used pre-alloyed NiTi powders to create porous NiTi, as demonstrated in conventional sintering [52] and sintering with Ar expansion [53]. An alternative technique was also used in some studies, where space-holder powder is mixed together with elemental (Ni and Ti) or pre-alloyed (NiTi) powders, pressed into a preform which is then densified (together with NiTi synthesis when elemental powders are used). The space-holder is eliminated during or after densification, producing pores with well-defined size, shape and volume fraction. For example, NaF was used in conjunction with HIP densification [54], NaCl with metal injection molding and sintering [55], and NH_4HCO_3 with CF-HIP [56].

Despite a variety of manufacturing routes, most porous NiTi surveyed in the present article are produced from elemental powders by the SHS process (or CF-HIP and MIM for some work) and fulfill the main prerequisites of implants: interconnected and open porosity in the range of 30–80%, pore size in the range of 100–600 μm, high strength (i.e., at least 100 MPa at 2% strain), high recovery strain (i.e., more than 2% recovery after 8% loading strain), and low Young's modulus (i.e., close to that of cortical bone, 10–20 GPa, or cancellous bone, <3 GPa). Represen-

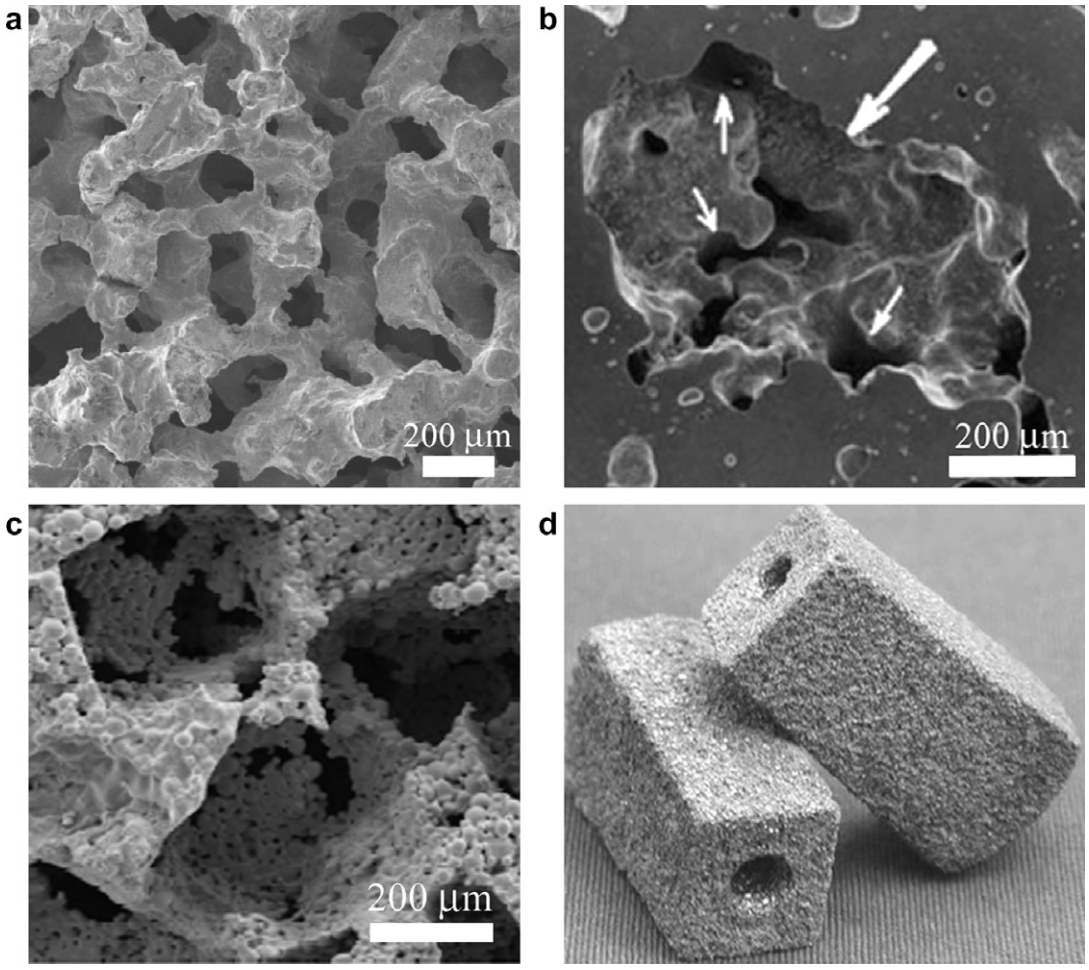

Fig. 1. SEM micrographs of porous NiTi produced by three different methods: (a) SHS process (65 ± 10% porosity, 100–360 μm) [27]; (b) CF-HIP with argon expansion (42% porosity, 50–400 μm) [64]; (c) MIM and sintering with NaCl space-holder (pre-alloyed powders, 70% porosity, 355–500 μm) [55] and (d) Photograph of commercially available porous NiTi implant produced by SHS process (Actipore™, Biorthex, Canada), used in a study for intervertebral fusion application [78].

tative foams produced by these three processes are provided in Fig. 1a–c. The most widely used porous NiTi (Fig. 1a and d) in biological studies is Actipore™, a commercially available product made by Biorthex (Canada) through the SHS process, which offers porosity of 65% and average pore size of 215 μm. A detailed analysis of the structural and mechanical aspects of these porous NiTi materials will be provided in a separate article and is thus not reported here.

Further advances on processing of NiTi foams for implants are needed in the following areas. First, while the pore size can be reasonably well controlled with the space-holder technique, this is not true of the fenestrations (windows or throats) connecting the pores. If these fenestrations are too narrow, they may inhibit bone ingrowth. Fenestration size to a certain extent may be manipulated by controlling space-holder shape, size and packing, and they may be enlarged after creation of the foam by dissolution in acid. Second, the roughness of the pore inner surface may have an impact on bone ingrowth, and may be controlled during foam synthesis, e.g., by judicious choice of space-holder powders and initial Ni and Ti powders. Third, the pore aspect ratio may be increased, and elongated pores may be aligned so that the NiTi foams better mimic the structure of bone. This has been achieved in titanium foams but not yet in NiTi foams, except for one study where continuous zone melting under pressurized hydrogen created elongated pores in NiTi [57]. Fourth, gradients in pores size, shape, fraction and orientation may be designed in the implant to specifically enhance its mechanical (i.e., low interior porosity) and biological performance (i.e., high surface porosity). Finally, ternary or higher alloying additions to NiTi, such as Cu, Zr, Nb or Pd which have been studied extensively in bulk NiTi alloys to modify the transformation temperatures or stresses, have to date not yet been studied for porous NiTi and would provide a further approach to manipulating the properties of NiTi foams.

3. Surface modification to produce biocompatible and bioactive surfaces

Nickel is a main component of NiTi, and somewhat Ni-rich compositions (ranging from 50 to 51 at.% Ni) are very

commonly used, especially to induce superelasticity. Although this nickel is in a tightly bound intermetallic form, Ni release due to corrosion in the biological environment is unavoidable. Excessive Ni exposure can cause adverse symptoms, from asthma through allergic response, to cellular hypersensitivity, cytotoxicity and genotoxicity, leading to serious health problems [58,59]. Nickel leaching from porous NiTi is of particular concern due to the large exposed surface area, which is in direct contact with adjacent bone and tissue at the implant site. For example, the amount of Ni release from porous NiTi was found to be two orders of magnitude greater than that from a solid implant [60,61]. Moreover, the amount of Ni released is affected by both the stoichiometry of the equiatomic NiTi phase (which can vary between ~49 and ~52 at.% Ni), and by the presence of non-equiatomic phases (e.g., Ti_2Ni, Ni_3Ti and Ni), which are often present after incomplete synthesis by the elemental powder methods.

To reduce the release of Ni ions from NiTi surfaces, many surface treatments have been used to create uniform, homogeneous, and thick TiO_2 films (thicker than the natural surface oxide layers, and those formed during processing, which are typically only nanometers thick) on NiTi surfaces [30]. For porous NiTi, surface treatments such as ion implantation, oxidation, heat treatment, and surface coating have been reported. Commonly in these studies, nickel release levels were measured by immersing porous NiTi in simulated body fluid (SBF) solutions, prepared with ionic concentrations comparable to those of human blood plasma in order to promote the creation of the apatite layers expected to form *in vivo* on the porous surfaces.

Thermal annealing is a convenient method for surface treatment of porous NiTi as shown by Wu et al. [62], who oxidized porous NiTi in air for 1 h. They found an optimized annealing temperature (450 °C), with lower temperatures (300–450 °C) still reducing Ni leaching by a factor of two as compared to untreated NiTi, but higher temperatures (550–800 °C) increasing Ni leaching by a factor of 12–25 as compared to untreated NiTi, due to thick Ni-rich layers formed under the thin TiO_2 surfaces.

A non-abrupt Ni-depleted surface layer with the same range of thickness was achieved by performing oxygen plasma immersion ion implantation (PIII) [63] on porous NiTi. This method was claimed to allow a relatively uniform plasma implantation, despite the non-planar surfaces and complicated internal geometry of porous NiTi. The resulting barrier layer helped reduce Ni release from porous NiTi to about a third of the level in untreated material. The layer is stable in SBF for 28 days without signs of chemical reaction, and treated porous NiTi has strong corrosion resistance, comparable to (or even better than, in the long term) dense NiTi without plasma treatment. Porous NiTi produced using similar starting materials and methods (capsule-free HIP-based), and surface treated by PIII, shows the same magnitude of Ni release concentration after 70 days in contact with SBF as the previous study [64]. Compression test results show that porous NiTi after PIII treatment exhibits superelasticity, with almost the same mechanical behavior as the untreated material.

TiN and TiO_2 coatings were also deposited on porous NiTi by physical vapor deposition (PVD) [65]. The coatings covered the entire exposed surface area, even in the center of $8 \times 17\ mm^2$ samples with $210 \pm 110\ \mu m$ pores. Nickel ion release was decreased relative to an untreated sample by factors of 10 and 14 for TiN and TiO_2 coatings, respectively. Although these factors seem large compared to those of the other surface treatments, one must take into account that the untreated, non-homogenized control foam in this work had a much higher initial Ni release concentration than that of untreated foam used in the works previously discussed. The effect of pre-soaking in SBF solution (for 1 month at room temperature and for 5 cycles of 1 h at boiling temperature) was also investigated in the same study [65]. These treatments resulted in very low Ni ion concentrations, comparable to those achieved by TiN and TiO_2 coatings. The authors suggested that the effect of pre-soaking was due either to depletion of Ni from the near-surface regions of the NiTi, or possibly to the formation of a protective Ca–P layer which insulates the NiTi surfaces from the SBF. Furthermore, the authors demonstrated another interesting alternative, consisting of TiN- or TiO_2-PVD coating followed by SBF pre-soaking for 1 month. The additional SBF treatment further reduced Ni release rates for the TiN-coated foams (by about a factor 2), but no improvement was achieved for the TiO_2-coated foams.

Following a similar double coating approach to enhance bioactivity and also lower Ni release, Jiang and Rong [60] reported crystalline hydroxyapatite (HA) layers on porous NiTi by chemical treatment (32.5% HNO_3 solution followed by boiling in 1.2 M NaOH solution) and subsequent immersion in SBF. The resulting HA layer uniformly covered the porous NiTi, both on the surfaces and within the pores, after 5 days (which is faster than natural HA formation), and Ni release was even lower than in untreated dense NiTi (up to 50 days). Gu et al. [31] reported similar results, but at the early stages of apatite layer formation (1 day after 1.5 SBF soaking) on porous NiTi. The main difference in this latter work was their use of nanocrystalline Ni and Ti powders in the SHS process which resulted in changes to pore geometry (nearly circular or elliptical pore shapes, rather than mostly elongated channel structures) while keeping porosity and pore size, and to a reduction of non-equiatomic phases which was expected to reduce Ni release (no Ni release results were, however, reported). In another study, after chemical treatment (8.8 M H_2O_2 and 0.1 M HCl) followed by annealing (400 °C for 1 h), a TiO_2 layer consisting of many nanoscale spheroidal crystallites and pores, acting as preferential nucleation sites for apatite, was present on the surface of porous NiTi [66]. After SBF immersion, bone formation was observed in the form of a nanocrystalline apatite structure (whose crystallographic orientation with respect to

Table 1
Comparison of Ni release levels in SBF for recent studies of porous NiTi

Processing method (elemental powders)	Porosity (%)	Pore size (μm)	Surface treatment	Ni release levels
CF-HIP [63]	40	–	Oxygen plasma (PIII)	0.06–0.18 ppm (untreated) 0.01–0.05 ppm (treated) 7–28 days
CF-HIP with Ar expansion [64]	42	50–400	Oxygen plasma (PIII)	0.2–0.3 ppm (untreated) 0.05–0.08 ppm (treated) 70 days
CF-HIP with space-holder + homogenization [62]	48	50–500	Oxidation at 450 °C	0.45 ppm (untreated) 0.2 ppm (treated) 6 days
SHS + homogenization [65]	65	100–320	TiN and TiO_2-PVD coating; SBF soaking	0.66–0.85 ppm (not homogenized) 0.17–0.30 ppm (untreated) 0.04–0.09 ppm (TiN) 0.06–0.07 ppm (TiO_2) 0.05–0.07 ppm (SBF pre-soak) 0.03–0.04 ppm (TiN + SBF pre-soak) 0.06–0.07 ppm (TiO_2 + SBF pre-soak) 1–16 days
SHS [60]	61	200–600	HNO_3/NaOH with HA coating	6.7 ppm (untreated) 0.48 ppm (treated) 50 days

titania layer could be controlled) with a similar chemical ratio to that of natural bone.

A new, promising process for preparing biocompatible surfaces on porous NiTi was recently reported by Bertheville [50]. To prevent formation of undesirable non-equiatomic intermetallic phases (which are undesirable because they are favorable sites for corrosion) during SHS, a preform of Ni and TiH_2 powders was sintered in the presence of CaH_2. Upon decomposition of both hydrides, the Ni–Ti powder mixture sintered by SHS under an atmosphere of Ca vapor, reducing any oxide present. This method produced porous NiTi without the undesirable second phases in a single step, with pore surfaces coated with residual calcium oxide, which, if changed to $Ca(OH)_2$, might promote bone ingrowth (osseointegration and bone ingrowth information was not reported in this work, however).

Table 1 shows a comparison of Ni release levels for various coated and uncoated NiTi foams resulting from different exposure times to SBF. Regardless of processing method, surface treatment method, and initial sample properties, surface-treated porous NiTi (40–60% porosity, 50–600 μm pore size) releases Ni levels, after SBF exposures of up to 70 days, that were lower than untreated values and lower than the standard dietary intake of Ni (150–900 μg per day) [67]. This result was also seen in the investigation of Ni release following longer-term (3, 6, and 12 months) exposure to porous NiTi implants at intervertebral sites in a sheep model [68]. The Ni levels measured from either local tissue/muscle, detoxification/remote organs, or blood samples are not significantly different from those in control models, and level off at acceptable values ($<1\ \mu g\ g^{-1}$ for tissue/organ, and $5\ \mu g\ l^{-1}$ for blood). No localized corrosion or pitting on the surfaces of porous NiTi (65% porosity) was found after this *in vivo* study.

To directly compare the efficiency of various surface modification methods, porous NiTi produced by the same processing method should be used, as performed by Lemaire et al. [65]. At the same time, the effectiveness of surface treatments on foams produced by other available methods should be validated. Well-controlled processes that produce finished porous NiTi surfaces without undesirable phases and with a homogeneous distribution of surface stress should be used to minimize the need for surface post-treatment steps. The recent trend in surface modification research seems to be toward the long-term study of surface performance (i.e., of NiTi as a biocompatible/biomimetic/bioactive surface). Such studies are needed to assess the durability/stability of the surfaces (i.e., dissolution and cracking of barrier layers with time and/or deformation). Nonetheless, it is also important (for instance, in reducing operative time and guiding postoperative care) to know how quickly such stable, long-term behavior is reached. In parallel, optimization of current surface modification processes (i.e., to produce uniform and homogeneous barrier layers) should be continued. Finally, the effect of surface treatments on the overall shape-memory and superelastic behavior of porous NiTi should be studied, and the effect of cyclical deformation (e.g., during use of the implant) on the integrity of the surface layers should be investigated.

4. *In vitro* and *in vivo* biological studies

The design of NiTi implant materials focused originally on minimizing the host tissue response in order to create "bio-inert" implants. The second stage of implant technology attempted to create "bioactive" implants that would elicit a desired response from the host tissue. This approach may involve coating surfaces with apatite mineral in order to promote bone bonding or apposition on the implant surface. Recently, progress has been made towards a "third generation" of NiTi implants with surfaces that are molecularly designed to induce bone regeneration on implant surfaces.

In vitro cell culture tests have been performed on various NiTi foams. Prymak et al. [69] showed immediate adherence of peripheral blood leukocytes to porous NiTi surfaces, and rapid viability within 24 h. Short-term *in vitro* tests (8 days) showed no immediate cytotoxicity from porous NiTi produced by CF-HIP, as well as surface deposition of mice osteoblast cells regardless of the type of surface treatment (PIII or oxidation) [62,64]. Porous NiTi made by other processes (e.g., MIM with space holder) also showed strong proliferation and attachment of cultured cells [55]. However, nickel release levels seem to affect how well osteoblast cells adhere and proliferate on porous NiTi surfaces. This is in agreement with the findings of Gu et al. [31], where no cell attachment was observed on porous NiTi surfaces containing unreacted, elemental Ni left from an incomplete SHS process, while fast proliferation and differentiation was found after surface treatment.

In 2002, Assad et al. systematically confirmed a low adverse potential at the *in vitro* cellular level, using cytocompatibility elution testing and three standard genotoxicity assays. The short-term biocompatibility of porous NiTi was determined to be comparable to that of dense NiTi [70]. Moreover, *in vivo* standard allergy potential evaluation showed that porous NiTi has no potential to produce irritation, systemic toxicity reactions, or sensitization in animal models [71].

In vivo study of bone ingrowth and bone apposition in porous NiTi has been the subject of much recent literature. No apparent adverse reaction was seen on or around the implant area in proximal tibia of rabbit after 6 weeks, and the in-grown bone has similar properties to the surrounding bone [32]. Porous NiTi also showed excellent bone implant contact and a high level of bone ingrowth in rabbits and rats [24,28] (up to 78% in 6 weeks in rabbits [32]) without signs of loosening. Although it has long been known that osseointegration and fraction of bony tissue ingrowth increase with post-surgery time in rabbits [25], porous structures can be a key factor in accommodating and/or accelerating such processes. Thus far, the effects of pore size and the porosity of NiTi foams on bone apposition and ingrowth are not obvious; however, after 12–30 weeks, some effect of porosity (ranging from 47% to 66%) and pore size (from 260–510 μm) on bone implant contact and incidence of fibrosis has been documented [24].

The porous NiTi used in the above studies was made by the SHS process, which guarantees a high amount of porosity and a desirable range of pore size, but is unlikely to allow simultaneous control over both features. For example, the three groups of porous NiTi used by Kujala et al. [24] have porosity and mean pore size as follows: (a) 66% and 259 ± 30 μm, (b) 59% and 272 ± 17 μm, and (c) 47% and 505 ± 136 μm. It is desirable to test biocompatibility on samples where pore size and fraction can be controlled independently, so as to determine the effect of each of these two variables. Such flexibility and control could be achieved using one of the space-holder processes [54–56], since the space-holder size and fraction determine pore size and fraction in the foam, and they can be modified independently.

Finally, biocompatibility studies will need to be performed on next-generation NiTi foams, where the alloy composition and the pore fenestrae, shape, aspect ratio and surface roughness (with or without gradients) are systematically varied with the goal of finding an optimal combination of mechanical and biological performance. Furthermore, it will be interesting to develop the optimal bioactive systems that promote bone regeneration. Work along these lines has been recently reported by Sargeant et al. [72] describing the modification of Ti foams with self assembling peptide amphiphiles in order to promote regeneration of bone. A similar idea for tissue engineering was introduced in 1995 by Endo et al. [73,74] who used chemical modification with biofunctional proteins to improve bioactivity and corrosion resistance of solid NiTi surface.

5. Implant applications

Intervertebral fusion devices are one of the recently identified applications for porous NiTi in spine surgery, with one commercial product commercially available since 2002 under the trade-name Actipore™ (from Biorthex, Canada) for lumbar and cervical interbody devices. One additional advantage of porous NiTi as compared to other porous metals for implants (e.g., Co and stainless steel) is the excellent compatibility of NiTi for magnetic resonance imaging and computer tomography scanning [75]. Assad et al. [27] and Likibi et al. [76] proved that porous NiTi provides higher bone ingrowth stimulation (which further increases with time), due to its cellular, bone-like architecture, and a bone apposition rate two orders of magnitude higher, but still performs similarly to traditional Ti–6Al–4V fusion cages, without the need of bone grafting. After 12 month implantation, complete bone bridging across the full porous implant with inherent vascularization and intimate bone attachment, without inflammatory response, on porous surface was observed (Fig. 2).

The *in vitro* corrosion behavior of porous NiTi (made by SHS) was also evaluated by potentiodynamic polarization [77]. The results showed good resistance to localized and general corrosion (at an acceptable rate of <0.02 mm year^{-1}) within the potential range relevant to

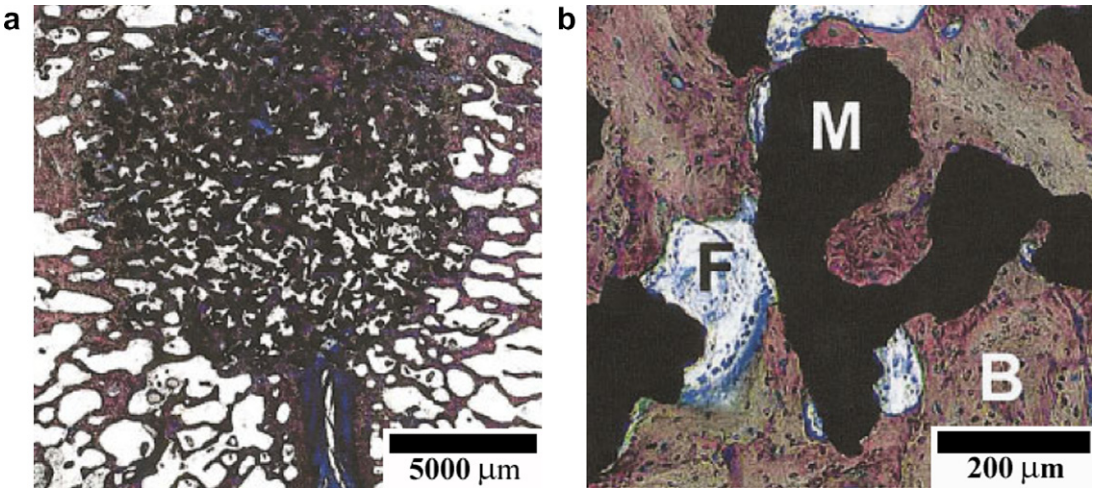

Fig. 2. Optical micrographs (transverse section) of porous NiTi (Actipore™; Biorthex, Canada, 55–75% porosity, 100–360 μm) implanted in sheep model after 12 month post-surgery time at: (a) low magnification (black, implant; white, bone matrix; blue, strained osteoblast; brown, mineralization surface), and (b) high magnification (B, bone tissue; F, fibrous tissue; M, metal implant) [27].

intervertebral fusion devices. Moreover, porous NiTi was stable against galvanic corrosion when directly coupled to Ti–6Al–4V, as shown in tests performed to simulate the presence of a Ti–6Al–4V supplemental fixation device in contact with the NiTi implant. The authors also suggest that surface treatment improves the corrosion resistance of the final NiTi product. Rhalmi et al. [78] simulated the event of fatigue debris release from porous NiTi, and evaluated the toxicity of alloyed NiTi particles in direct contact with surrounding tissue, particularly spinal cord dura mater. The implanted NiTi particles caused inflammation (acute at first, and reducing to mild chronic over time) only at the adjacent epidural space, while a normal response from the dura mater was maintained over one year of implantation. In summary, all investigations mentioned above support the potential use of porous NiTi as biologically safe in intervertebral fusion devices. Products under development by Biorthex (according to their 2007 website) include anterior lumbar fusion systems, vertebral body replacement devices and surface coating on total knee, total hip or any other titanium or cobalt–chrome permanent implants. Given the unique suite of mechanical, magnetic imaging and biological properties of porous NiTi, we can expect further biomedical applications to be developed in years to come. The use of the superelastic or shape-memory effects to add functionality to porous NiTi implants is still unexplored. For example, superelastic or shape-memory NiTi foams could be deployed at the implant site, similar to the widely used deployment of NiTi stents [79], guide wires [80] and the activation of hingeless NiTi medical instruments [16]. Furthermore, the very large recoverable strains that are achievable in superelastic NiTi foams (up to 4.7% [54]) at relatively low stresses (e.g., during physiological stresses associated with activities such as walking and running) could be used to encourage bone ingrowth in and near NiTi implants, unlike other metallic porous implants which tend to be stiffer and thus produce lower strains. Indeed, it is known that mechanotransduction plays a crucial role in bone resorption and formation *in vivo* [81] and tensile cyclic strain has been shown to affect the morphology, directionality, and proliferation of soft tissue cells [82,83], and the biological activity of bone cells *in vitro* [84,85]. *In vivo* experiments using a guinea-pig model have also demonstrated stimulated bone growth as a result of implant strain [86].

In the field of tissue engineering, Unger et al. [87] recently demonstrated the possibility of pre-seeding porous biomaterials, including porous NiTi, with human osteoblasts and endothelial cells. The cells grow on the materials and ultimately generate a prevascularized microcapillary-like network that may accelerate the vascularization rate after implantation. Research on how efficiently this network performs as a part of the circulatory system is still ongoing, however. It is likely that tissue engineering studies of porous NiTi will increase in the future.

6. Concluding remarks

Studies of porous NiTi for permanent bone implants have made great progress over the last ten years. Currently, many powder-metallurgy techniques can fabricate porous NiTi with pore sizes and fractions that fulfill the requirements of bone-replacement applications. As new processing methods arise and current processing methods are optimized, biological studies are being done on representative porous NiTi. Porous NiTi materials that appear in recent biological studies are typically made by SHS and CF-HIP processes using elemental Ni and Ti powder, and are characterized by pore sizes of 100–500 μm and porosity of 30–60%. Broadly speaking, the goals of these biological investigations into porous NiTi fall into three

categories: surface modification, biocompatibility analysis, and evaluation of specific applications. The goal of surface modification is to prepare porous NiTi surfaces with minimal or negligible Ni release and corrosion rates. Current surface treatments used on porous NiTi include thermal annealing, oxygen plasma immersion ion implantation, pre-soaking in SBF solution, TiN and TiO_2-PVD coatings, HA coatings, chemical treatment, and combinations thereof. In general, these surface modification methods help reduce Ni release rate by a factor of 3–24, to levels below the normal daily Ni intake. The biocompatibility of porous NiTi has been confirmed by evidence of good adherence and rapid cell growth observed in both *in vitro* and *in vivo* studies. Acceptable cytocompatibility, genotoxicity, irritation, toxicity reaction, and sensitization are reported, as well as high bone ingrowth with good fixation. Positive results have been shown in a few studies using porous NiTi in simulated operating situations using intervertebral fusion devices and tissue engineering.

Although the study of porous NiTi has developed rapidly over the past few years, biological studies are still at an early research stage compared to other porous Ti and Ti–6Al–4V alloys and to dense NiTi. More comprehensive studies are needed on biological performance in order to develop the biomedical applications of porous NiTi. For this purpose, optimization and long term *in vivo* studies on surface-modified systems is still needed. The purpose of this research should be to establish which surfaces are the best to rapidly induce ideal metal–tissue interfaces, including bone regeneration and bonding on the alloy surface. It is also important to understand what bulk and surface structures are best for the alloy's stability within the body environment without reduction or loss of shape-recovery effects. The design of bioactive surfaces using biomolecular structures on the metal surface that instruct cells is one of the most promising approaches to insure optimal biological performance of NiTi implants.

Manufacturing developments motivated by biological needs which may be expected in the near future include: (i) greater emphasis on final pore surface quality (i.e., NiTi surfaces with no potential Ni release sites) to minimize later surface treatments; (ii) synthesis of optimally bioactive surfaces leading to higher bone ingrowth and biocompatibility; (iii) introduction of ternary or higher alloys; (iv) creation of tailor-made microstructural features such as pore fraction, size, shape, fenestrations and orientation, which will permit control over test parameters in biological experiments, reveal precisely the relationships between microstructure and bone ingrowth, and perhaps allow manipulation of biological response through the large superelastic strains achievable in porous NiTi. With the simultaneous consideration of processing methods, mechanical properties, NiTi composition, microstructural features and biological performance, more rapid optimization of porous NiTi for biomedical applications is likely to occur in the near future.

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