Review Silicon nitride, a close to ideal ceramic material for medical application

Robert B. Heimann 1,*

¹ Am Stadtpark 2A, D-02826 Görlitz, Germany.

* Correspondence: robert.heimann@ocean-gate.de; Tel.: 0049 3581 667851

Abstract: This topical review describes the results of recent research into and development of silicon nitride, a ceramic material with unique properties. The outcome of this ongoing research strongly encourages the use of monolithic silicon nitride and coatings as contemporary and future biomaterial for a variety of medical applications. Crystallographic structure, synthesis and processing of monolithic structures and coatings, and examples of their medical applications are covered that relate to spinal, orthopedic and dental implants, bone grafts and scaffolds, platforms for intelligent synthetic neural circuits, antibacterial and antiviral particles and coatings, optical biosensors, and nano-photonic waveguides for sophisticated medical diagnostic devices. The examples provided show convincingly that silicon nitride is destined to become a leader to replace titanium and other entrenched biomaterials in many fields of medicine.

Keywords: Silicon nitride; structure; properties; processing; coatings; spinal implants; arthroplastic implants; bone scaffolds; dental implants; neural circuits; biosensors; medical diagnostics.

1. Introduction

Research and development of metallic, ceramic, polymeric and composite biomaterials have progressed to a level of involvement and sophistication comparable only to modern electronic and photonic materials. The reason for this is obvious: a large proportion of an aging world population relies on repair or replacement of body parts ranging from artificial dental roots and teeth, alveolar ridge augmentation, intraocular lenses, heart pacemakers and cochlear implants to hip and knee endoprostheses [1]. As these biomaterials are generally designed to interact with biological systems to replace a part or a function of the human body, they have to be biologically safe, mechanically reliable, economic, and physiologically and esthetically acceptable. Biomaterials are poised for continuing to make a large economic impact on modern medicine as parts of prosthetic devices in orthopedic, dental, cardiovascular, ophthalmological, and reconstructive surgery, including tissue engineering scaffolds, surgical sutures, bioadhesives, and drug and gene delivery vehicles. These developments comprise an ongoing process as new materials, devices, and applications are emerging at an ever increasing rate as witnessed by an avalanche of research papers on biomaterials emerging worldwide. Development of novel and improvement of existing biomaterials constitute a substantial economic driving force in our modern society [1].

Bioceramics come in two flavors: bioinert and bioactive. Typical bioinert ceramics in clinical use today are alumina, partially stabilized zirconia and carbon, bioactive ceramics are predominantly based on calcium phosphates and bioglasses. On the one hand, *bioinert ceramics* are used in applications that require mechanically strong and resilient wear- and corrosion-resistant materials with excellent tribological properties and high structural reliability, used, for example as femoral heads and acetabular cups of hip endoprosthetic devices but also as spacers in revision surgery, in knee arthroplasty, and in polycrystalline and single crystal form in dental applications such as dental root implants. These properties have earned alumina, zirconia, titanium dioxide, silicon nitride, graphite and diamond-like carbon important roles in designing, manufacturing and deployment of various load-bearing implants [3]. However, the inherent brittleness of ceramics and their limited ability to integrate with soft and hard tissues *in vivo* are restricting factors affecting clinical performance.

On the other hand, *bioactive ceramics* such as hydroxylapatite, resorbable tri- and tetracalcium phosphates as well as surface-active bioglasses are used predominantly for their osseoconductive and, in combination with bone growth-supporting non-collagenous proteins, osseoinductive properties. Hydroxylapatite is mainly used as osseoconductive coating [2] for endoprosthetic hip and dental root implants, bioresorbable tricalcium phosphates find use as bone cavity filler and bone restoration material, and tetracalcium phosphate is applied in bone and dental cements. Increasingly, bioactive ceramics are used in conjunction with polymers as hybrid biological-inorganic nanocomposites that mimic salient properties of natural biological materials.

Recently, increasing interest has been devoted to *silicon nitride*, an advanced ceramic material with high strength, high fracture toughness, low friction coefficient, high corrosion resistance, improved medical imaging ability based on radiolucency in the visible and near-infrared region, enhanced biocompatibility and osseoconductivity, and antimicrobial activity that is now emerging as novel and promising bioceramic material for a multitude of medical applications. These applications include wear-resistant bearings for hip- and knee endoprosthetic implants, novel dental implants, spinal intervertebral spacers, tissue engineering scaffolds, antibacterial and antiviral coatings, wave guides for medical diagnostics, microtubes for intelligent neural circuits, micro-spectroscopic imaging devices, photonic ICs, optical biosensors, and others. As an additional bonus, most recently silicon nitride has been found to be a powerful solid-state bioceramic deactivator of single-stranded RNA (ssRNA) viruses including the SARS-CoV-2 virus [4]. Developments are underway to commercialize antimicrobial 'catch-and-kill' face masks comprising silicon nitride-coated polypropylene fibers to protect against the COVID-19 pandemic [5]. In the light of all these beneficial properties, silicon nitride may be correctly considered a close to ideal bioceramics.

1. Structure of silicon nitride

Silicon nitride crystallizes in two hexagonal (α - and β -Si₃N₄) and a cubic γ -modification with spinel structure that is only stable at high pressure and temperature. The space groups of α -Si₃N₄ is *P31c* (159) with *a* = 774.8(1) pm and *c* = 561.7(1) pm. The space group of β -Si₃N₄ is *P6₃/m* (176) with *a* = 760.8 pm and *c* = 291.1 pm.



Figure 1. Structures of hexagonal β - and α -silicon nitride. Projection down the c-axis onto the AB plane. Black circles: silicon atoms, white circles: nitrogen atoms [6]. © With permission by Wiley-VCH.

As shown in Figs. 1 and 2, the structure consists of slightly distorted corner-sharing SiN₄ tetrahedra forming distorted hexagonal rings arranged in layers with ABCDABCD... stacking (α -Si₃N₄) and ABAB... stacking (β -Si₃N₄). In β -Si₃N₄, the bond lengths between Si and N1 are 173.0 and 173.9 pm, respectively, and between Si and N2 174.5 pm. In α -Si₃N₄, the bond lengths vary between 156.6 pm (N1-Si1) and 189.6 pm (N1-Si2).

Although the basic AB layer is identical in both α - and β - phases, in the α -phase the CD layer is related to the AB layer by a c-glide plane. Hence, the double layer in α -Si₃N₄ can be thought of as a superposition of a β -Si₃N₄ layer and its counterpart inverted by 180°. Consequently, there are twice as many atoms per unit cell in α -Si₃N₄ (Z = 4) than in β -Si₃N₄ (Z = 2) (Fig. 2). The SiN₄ tetrahedra in β -Si₃N₄ are interconnected

in such a way that wide channels form parallel to the c-axis of the unit cell. Owing to the c-glide plane, the α -structure contains two (isolated) and comparatively narrow interstitial sites per unit cell instead of channels. Since the channel structure of the β -phase supports easy diffusion of ions through the lattice thus greatly promoting the sinterability at high temperatures, fabrication of load-carrying biomedical devices with required high density should preferentially start from β -Si₃N₄ precursor powders [6].



Figure 2. Stick-and-ball models of the structure of α -Si₃N₄ and β -Si₃N₄. Si atoms are shown in yellow, N atoms in blue. © Creative Commons Attribution 4.0 International License.

2. Synthesis and Processing

3.1 Synthesis and properties of monolithic silicon nitride ceramics

There are several structural and textural variants of silicon nitride that differ remarkably in their mechanical, elastic, and thermal properties (Table 1), depending on their synthesis route (Fig. 3).



Figure 3. Flow chart of silicon nitride processing routes to manufacture monolithic compacts [6]. © With permission by Wiley-VCH.

Table 1. Selected mechanical and thermophysical properties of RBSN and SSN [7]

Property	RBSN	SSN
Density (Mg·m-3) (% of theoretical density)	70-88	95-100
Compressive strength (MPa)	600	2950
Flexural strength (4-point, 25°C) (MPa)	150-350	500-1,000
Fracture toughness (25°C) (MPa·√m)	1.5-3	5-8
Fracture energy (J·m ⁻²)	4-10	~60
Modulus of elasticity (25°C) (GPa)	120-220	300-330
Thermal conductivity (25°C) (W/m·K)	4-30	15-50

Thermal shock resistance R (K)	220-580	300-780
Thermal shock fracture toughness R' (W·m ⁻¹)	500-10,000	7,000-32,000
Coefficient of thermal expansion (10 ⁻⁶ K ⁻¹)	2.5	3.2
Specific heat capacity (J/kg·K)	720	800
Poisson ratio	0.24	0.27

In engineering applications, the most frequently used variants are porous *reaction-bonded silicon nitride* (RBSN) and dense *sintered silicon nitride* (SSN). To form RBSN, direct nitriding of fine compacted silicon powder leads to formation of a mixture of α - and β -Si₃N₄ during prolonged heating in nitrogen or ammonia atmospheres between 1000 and 1450°C. Since a volume increase of about 22% is completely accommodated by the inter-particle void space of the compacted silicon powder, no shrinkage during nitriding occurs. Hence, the original dimensions of the green compact will be faithfully retained. This is the underlying cause to utilize RBSN for complex shaped components that do not require costly post-sintering diamond grinding and machining. Thus, parts manufactured from RBSN are economically highly competitive. Although the porosity of RBSN is between 20 and 30%, its mechanical performance is remarkable as flexural strengths values up to 350 MPa can readily be attained (Table 1). In addition, this strength can be retained to about 1400°C so that designing with RBSN leads to monolithic ceramics with high Weibull moduli and hence, high reliability in service [6].

To achieve fully dense *sintered silicon nitride* (SSN) monolithic bodies, hot pressing (HP) or hot isostatic pressing (HIP) of silicon nitride powder with added metal oxides such as magnesia, alumina and yttria as binder materials is being employed. At temperatures above 1550°C, these additives form, with a contaminant silicon dioxide film around individual silicon nitride grains, a liquid siliceous phase in which the silicon nitride readily dissolves. This glassy binder phase leads to efficient densification of the sintered ceramic body. However, there is a catch. HP and HIP sintering techniques are very expensive and restricted to simple geometric shapes that rarely are required for biomedical devices and applications. Critical parameters are nano-sized powders in the range of 100 to 200 nm, the ability of the added oxides to form a film of liquid phase surrounding the silicon nitride grains, a high-pressure nitrogen atmosphere to prevent thermal dissociation, as well as sintering temperatures between 1700 and 1850°C. During processing in the presence of alumina and yttria particles, a significant proportion of Al and O ions enters the Si₃N₄ lattice to form various SiAlON alloy components. Cooling of the intergranular liquid grain boundary film results in glassy and/or crystalline (YAG) phases, depending on the cooling rate [6].

To manufacture strong and mechanically resilient silicon nitride monolithic shapes, an advanced texturing technique has been applied [8]. During high temperature densification of powder compacts, the α -Si₃N₄ phase stable at low temperature converts to β -Si₃N₄, and by so-called texturing a rod-like morphology is generated, forming a self-reinforcing microstructure that greatly enhances the mechanical and thermal properties of the final product. To speed up the conversion rate, seeds of β -Si₃N₄ are being added to the of α -Si₃N₄ precursor powder. The rod-like crystals will be aligned by either hot working techniques such as hot pressing, hot forging and sinter forging, or by template grain growth (TGG) involving alignment by cold pressing, slurry extrusion, tape casting, or static or rotating magnetic fields [6].

3.2 Synthesis and properties of silicon nitride thin films and coatings

In many industrial applications, it is required to strengthen, protect or functionalize the surfaces of materials by adding a suitable coating. Deposition of pure silicon nitride coatings by conventional deposition techniques including thermal spraying has been deemed impossible since Si₃N₄ dissociates in the hot plasma plume or combustion flame and, in turn, sublimates above 1800 °C. It is also subject to oxidation in the presence of an oxygen-containing atmosphere at elevated temperature. In contrast, thin amorphous silicon nitride films are routinely deposited by chemical vapour deposition (CVD) and applied as masking layers for semiconductor integrated circuits during profile etching, diffusion barriers in VLSI production lines to prevent cross penetration of dopants, for damage protection of optical fibers, as gate dielectrics

with low leakage and high resistance for specific metal-insulator semiconductor (MIS) memory devices, for antireflection coatings of solar cells, and as moisture barrier for OLED displays [9].

However, attempts to deposit mechanically stable, thick and well-adhering silicon nitride coatings for biomedical application by thermal spraying using metallic [10, 11] or silicate glass binders [12], conversion in the as-deposited state through a reactive spray process [13], or *in situ* nitridation in flight [14] were not met with resounding success as such coatings contained only little silicon nitride but instead, substantial amounts of embrittling metal silicides, binder ceramic materials, and unreacted precursor materials. More successful were endeavours to prepare high-Si₃N₄ coatings starting from β'-Si_{6-z}Al_zO_zN_{8-z} compositions of the SiAlON family with different degrees of substitution, z [15] or clad-type powder consolidation using alloy bond coats [16]. It was also recognised that high particle velocities generated by detonation spraying (DS), Top Gun technology, high-frequency pulse detonation (HFPD), and atmospheric plasma spraying (APS) with axial powder injection were conducive to deposit dense and reasonably well-adhering silicon nitride-based coatings [17-21]. In addition, optimization of heat transfer into the powder particles was found to be one of the most decisive factors to deposit well-adhering coatings [22]. This, however, necessitates special powder preparation procedures [23, 24].

All attempts to deposit silicon nitride coatings on metallic substrates are marred so far by the fact that addition of binder metal oxides such as Al₂O₃ + Y₂O₃ is required. Hence, no phase-pure homogeneous silicon nitride coatings could be produced. This problem was at least partially solved by applying extremely high-powder particle velocities up to 3 km/s, generated by an electromagnetically accelerated plasma (EMAP). Under these conditions, dense, homogeneous silicon nitride coatings with reduced amounts of binder oxides could be deposited with desirable mechanical properties that adhered well to polished steel surfaces [25, 26].

Figure 4 shows such dense and well-adhering, mechanically stable silicon nitride-based coatings on austenitic stainless steel substrates deposited by conventionally detonation spraying (left) and ultrahigh-velocity pulsed plasma spraying, EMAPS (right). However, at the time of this writing, the novel technology has not progressed to a state where the pulsed mode could be replaced by a continuous delivery mode. Consequently, the deposition process is still economically untenable while tedious since after each 'shot' the detonation chamber must be refilled with powder to be ready for the next shot. Nevertheless, this advanced deposition method may be at the cutting edge of future medical coating technologies designed for silicon nitride coatings as protective bearing surface for novel arthroplastic devices or ceramic hip resurfacing (HR) prostheses (see below).



Figure 4. Silicon nitride-based coatings on austenitic stainless steel produced by detonation spraying (left) [18] and ultrahigh velocity pulsed plasma spraying (right) [25]. © With permission by Wiley-VCH.

In a similar development, a magneto-plasma-dynamic (MPD) arc jet generator was utilized to deposit silicon nitride coatings by reactively spraying material from a crystalline silicon rod in a nitrogen atmosphere [27]. After 200 shots at a frequency of 0.03 Hz with a discharge current of 9 kA, 30 μm thick, dense and homogeneous β-Si₃N₄ coatings could be deposited.

3. Biomedical applications

Although non-oxide ceramics such as silicon nitride are predominantly used in high-temperature applications including parts of advanced gas turbines [28], turbocharger rotors for high-performance automotive engines [29] and rocket thrusters [30], recent research results have strongly encouraged their use in a variety of biomedical applications [31, 32]. Silicon nitride exhibits a unique combination of bulk mechanical and surface chemical properties thus, making it a close to ideal biomaterial for orthopedic implants. It is already being used copiously for interbody spinal fusion cages and is being developed for total joint arthroplasty. Its surface texture and chemistry are both highly tunable, yielding physicochemical combinations of properties that may lead to enhanced osseointegration and bacterial and viral resistance.

Silicon nitride has demonstrated superior cell adhesion and enhanced osteoconductivity comparable only to Ca-deficient, non-stoichiometric biological hydroxylapatite. This is thought to be based on its zwitterionic-like behavior that is a function of the tradeoff between positively charged vacancies in the partial N lattice and negatively charged silanol groups at the surface [31].

3.1 Intervertebral spacers

Spinal implants are used to alleviate many forms of back pain and deformity including trauma-based injuries and disorders such as scoliosis, kyphosis, degenerative disc disease, and fracture. Their primary function is to help to fuse two vertebrae together and to replace natural disc material. The four types of surgery that utilize spinal implants are anterior, posterior, and transforaminal lumbar interbody (TLIF) and axial fusions.

Silicon nitride has been in use for porous intervertebral spacers for spinal fusion surgery for more than thirty years without showing any undesirable long-term effects [33-37]. Silicon nitride comprises a high strength, long-term resilient, mechanically reliable, and osseoconductive ceramic material, partly based on a high proportion of covalent bonds. To achieve interbody fusion, the ability of silicon nitride to achieve superior new bone growth and osseointegration, along with proven bacteriostatic properties and enhanced medical imaging, outperforms both conventional poly(ether ether ketone, PEEK) and titanium implants [38,39]. This is largely based on its hydrophilicity that attracts extracellular fluid rich in bone growth-mediating non-collagenous proteins, turning on osteoblasts and suppressing osteoclasts. Consequently, silicon nitride speeds up bone healing, bone fusion and thus, implant integration. The efficacy of silicon nitride for spinal reconstruction is supported by its strong bacterial resistance caused by the synergetic effects of surface chemistry, surface pH, texture and electric charge [36].

Anterior cervical discectomy with fusion is a common procedure to treat radicular arm pain. A study compared silicon nitride implants with PEEK cages filled with autograft harvested from osteophytes [40]. Patients treated with silicon nitride and PEEK reported comparable recovery rates during follow-up. No significant differences in clinical outcome were noticed at 24 months observation time. Fusion rates improved over time and were comparable between both groups. Figure 5 shows the Valeo C^{CsC®} silicon nitride cervical interbody fusion device used in the CASCADE trial with radiographic characteristics. The outer part of the device consists of dense silicon nitride whereas the inset comprises cancellous structured cervamic (CSC) of the same composition, providing a scaffold for easy bone ingrowth [41].



Figure 5. Silicon nitride cervical interbody fusion device (Valeo C^{CsC®}, left) with radiographic image of the implanted device (right) [40]. © Creative Commons Attribution 4.0 International License.

4.2 Knee- and hip endoprosthetic implants

Silicon nitride compacts can be polished to a high surface finish to provide an exceptionally smooth, wear resistant, and tribologically superior surface. This renders the material ideal for articulating applications including bearings for knee and hip endoprostheses [42-44] as well as acetabular cups. Salient materials properties conducive to supporting bearing applications are phase stability [45], wear resistance [45, 46], strength and fracture toughness [47], hydrophilicity [48], favorable medical imaging capability [36], and unsurpassed bacterial resistance [38, 49]. Figure 6 shows a selection of silicon nitride compacts produced by *Amedica Corporation* of Salt Lake City, Utah, USA, the only vertically integrated silicon nitride medical device manufacturer worldwide [50].

In addition, silicon nitride possesses suitable biocompatibility as confirmed by cell culture tests with mouse fibroblasts (L-929) and human mesenchymal stem cells (hMSCs) [51]. These tests revealed excellent cytocompatibility as demonstrated by live/dead cell staining and pronounced differentiation towards osteoblasts. Biocompatibility was also confirmed by the tissue response around cylindrical silicon nitride implants installed in the tibiae of rabbits [52]. Histological analysis showed that bone growth occurred preferentially in the cortical area, and different types of tissue were identified on the implant surfaces such as lamellar bone tissue containing osteocytes and osteons, non-calcified matrix containing osteoblasts as well as collagen type III that might in time be converted to collagen type I.

In vitro tribological tests in a hip simulator showed an extremely low friction coefficient that was found to decrease to even lower values with increasing articulating time. This behavior has been attributed to hydrodynamic lubrication caused by a developing hydrogen-terminated silicon oxide boundary film separating the articulating components [53].



Figure 6. Various silicon nitride compacts produced by Amedica Corporation, including ball bearings (left), an acetabular cup (center), an intervertebral spacer with a CSC core (foreground, center), and spinal interbody fusion devices (right) [50]. © Creative Commons Attribution 4.0 International License.

The strength of silicon nitride with a high degree of covalent bonding was found to be significantly higher than that of oxide ceramics such as Al₂O₃ or ZrO₂ that possess largely ionic-type bonds. Finite element analysis (FEA) showed that the stress distribution within the femoral bone implanted with a silicon nitride prosthesis was comparable to that of a healthy, intact femoral bone [54]. In addition, lifetime predictions revealed that silicon nitride implants are mechanically reliable and, thus, suitable for hip prostheses. This indicates that high-strength non-oxide ceramics such as silicon nitride or even silicon carbide are future biomaterial candidates, in particular for highly loaded, thin-walled implants such as ceramic hip resurfacing (HR) prostheses. Hence, silicon nitride coatings are currently under investigation as bearing surfaces for joint implants, owing to their low wear rate, low friction coefficient, and excellent biocompatibility of both coating and its potential wear debris [55].

However, there is a drawback. Although the propitious mechanical properties of silicon nitride (Table 1), associated with high biocompatibility and promising tribological features including a low friction coefficient, high fracture toughness, and high wear resistance, render this ceramic material a possible candidate for replacing joint components, the high modulus of elasticity in excess of 300 GPa of both hot-pressed (HPSN) and pressureless sintered (SSN) silicon nitride are counter-indicative of their use for load-bearing hip implant stems. This is based on the risk of strong stress shielding, caused by the large gradient of the modulus of elasticity between implant material and cortical bone. As an alternative, reaction-bonded silicon nitride (RBSN) was suggested to be used with a considerably lower modulus around 150 GPa that, however, is still much higher than that of cortical bone (around 20 GPa). On the downside, as shown in Table 1 both flexural strength (150-350 MPa) and fracture toughness (1.5-3 MPa·√m) of RBSN are much lower than those of HPSN and SSN (500-1000 MPa and 5-8 MPa·√m, respectively), a consequence of the high porosity of the former [6].

In contrast, acetabular cups based on silicon nitride have already found their way into the orthopedic operation theater [56]. In the majority of hip endoprosthetic implants, the femoral head articulates against an acetabular cup liner composed of tough polymers such as ultra-high molecular weight polyethylene (UHMWPE) or X-linked polyethylene. These polymers degrade over time by chain scission and thus, strategies must be applied to slow done this deterioration, including radiative cross-linking [57] or doping with antioxidants such as vitamin E [58]. Owing to the unique surface chemistry of silicon nitride, this material is able to absorb oxygen released from degrading polyethylene [59], thus limiting acetabular liner degradation in hip endoprostheses. This also helps to avoid polymer wear debris that is known to cause the so-called 'particle disease' that may lead to aseptic loosening of the implant within the femur by periprosthetic osteolysis [60] and, when distributed by the lymphatic system throughout the body, may cause hepatic degeneration.

Frequently, CoCrMo alloys such as ASTM F75-12 or ASTM F1537 are utilized as hip endoprosthetic stem materials [1], with high implant survival rates. However, certain risks including accelerated wear rates and release of cytotoxic Co and Cr ions limit their usefulness. In a recent study [61], 4 μ m thick silicon nitride (SiN_x) (N/Si = 1.10 to 1.25) coatings were deposited by reactive d.c. magnetron sputtering onto CoCrMo surfaces with an adhesion-promoting 0.5 to 0.8 μ m thick CrN bond coat. Coating wear tests performed against Si₃N₄ in a reciprocating ball-on-disc test revealed specific wear rates that were lower than, or comparable to CoCrMo. Similar results were obtained by Maria Petterson as reported in her Ph.D. thesis [62]. To address the question of cytotoxicity, the role of particle size, surface composition and donor variations of silicon nitride on its biological impact were investigated [63]. Cytotoxicity, inflammatory cytokine release, oxidative stress, and genotoxicity potential of silicon nitride and CoCr particles were tested and compared using human peripheral blood mononuclear cells (hPBMNCs). Minimum biological impact of silicon nitride on human PBMNCs was recorded as opposed to CoCr particles that showed significantly

higher levels of TNF- α cytokine release, oxidative stress, and DNA damage, confirming that silicon nitride, when properly engineered, is an attractive orthopedic biomaterial for joint replacement devices.

4.3 Bone grafts and scaffolds

Bone grafting is a surgical procedure that uses transplanted bone to repair and rebuild diseased or damaged bones. In the clinical practice, bone grafts present limitations that include harvesting morbidity, insufficient bioactivity, and concern about transmission of diseases [64]. Silicon nitride bone scaffolds and bone fusion devices [35] excel by high and reliable mechanical strength, biocompatibility, and antibiotic capability, resulting in a bone healing sequence comparable to hydroxylapatite [31]. MC3T3-E1 cells were used to study the osteoblastic differentiation and mineralization on sterile samples of silicon nitride, and compared them to samples of titanium and PEEK, standard materials for bone scaffolds [65]. The study reported more profound and faster ECM deposition and mineralization on Si₃N₄ surface as compared to titanium and PEEK. Results further indicated the upregulation of osteogenic transcription factors such as RUNX2 and osterix (SP7), as well as collagen type I and osteocalcin. Hence, silicon nitride rapidly conducts mineralized tissue formation via extracellular matrix deposition and biomarker expression in murine calvarial pre-osteoblast cells.

4.4 Dental implants

Silicon nitride is an emerging material for dental restoration and dental implant application. Besides excellent structural, mechanical, thermal, tribological and biocompatible properties, silicon nitride is a potent antibacterial material. Dental implants made from silicon nitride have been shown to exhibit mechanical properties including modulus of elasticity approaching those of bone tissue that promise to reduce stress shielding when compared to classic titanium alloy implants [66]. Hence, in view of available preclinical data, silicon nitride appears to have the essential characteristics to be a strong candidate for dental implants material. This novel ceramic has a surface with potentially antimicrobial properties, and if this is confirmed in future research, it could be of great interest for oral use [67, 68].

A recent study [69] investigated the potential use of porous silicon nitride for all-ceramic dental restorations as a core material and results were compared with those of a commercial ZrO₂ ceramic. The color of silicon nitride could be tailored by the porosity introduced and a color shade suitable for restorative applications was obtained. The flexural strength of Si₃N₄ was found to be 418 MPa despite an open porosity of nearly 10.5% (cp. Table 1). This rather high strength may be related to strong neck formation between β -Si₃N₄ grains, the intertwined distribution of these grains, and the crack deflection potential of rod-like β -Si₃N₄. The Vickers hardness of Si₃N₄ was found to be 10.9 MPa whereas ZrO₂ had 13.7 MPa, which reduces the risk for wear of opposing natural teeth. Shear bond strength to dentin was tested and indicated low values for silicon nitride without a coupling agent (2.24±1.15 MPa) that increased strongly by adding a silane coupling agent to 8.44±2.98 MPa, suggesting that the usage of coupling agents for Si₃N₄ is essential. The radiolucent behavior of Si₃N₄ will enable for both the restorations and the surrounding tissues to be imaged using plain radiography (Fig. 7). Hence, this study shows that with tailored manufacturing methods, silicon nitride can be considered an effective dental restorative material.



Figure 7. Silicon nitride as a material for dental core restoration, revealing radiolucency [70]. © Creative Commons Attribution 4.0 International License.

White silicon nitride can be prepared by pressureless sintering at 1650°C in a nitrogen atmosphere [68]. In a recent study [71], partially sintered Si₃N₄ ceramic blocks were prepared by heating to 1400°C in a N₂ gas environment. After full sintering at 1650°C for 2 h, the linear shrinkage value was recorded at $19.9\pm0.6\%$. The flexural strength and fracture toughness were measured, the results were 891.2±37.2 MPa and 6.3 ± 0.30 MPa· \sqrt{m} , respectively. In conclusion, white Si₃N₄ can be favorably used to fabricate multi-unit dental restorations conforming to ISO 6872 designation [72].

Although zirconia is still the most commonly used ceramic for dental implants, its intrinsic bioinert nature often results in a lack of biological integration. A silicon nitride-based laser-cladding process has been developed to improve the biological response to biomedical zirconia by forming a composite coating with Si₃N₄ particles dispersed in a nano-crystalline/amorphous silicon matrix. Raman spectroscopy revealed that the bone tissue quality parameters were comparable to healthy human bone tissue, suggesting that laser-cladding with silicon nitride might be able to improve the stability of zirconia dental implants [73].

In conclusion, the metal-free nature of silicon nitride makes this material a promising candidate for dental implantology as release of cytotoxic metallic by-products able to invade any part of the body can be avoided. Higher esthetics, better osseointegration, biocompatibility, antibacterial property along with high wear resistance and metal-free corrosion products render silicon nitride a powerful contender for dental implant application.

4.5 Intelligent synthetic neural circuits

Synthetic regulatory circuits encoded in RNA rather than DNA could provide a means to control cell behavior while avoiding potentially harmful genomic integration in therapeutic applications. Post-transcriptional circuits have been developed using RNA-binding proteins that can be wired in a plug-and-play fashion to create networks of higher complexity [74]. Application of this research in the realm of future information technology include signal transmission platforms for artificial intelligence (AI) algorithms with unparalleled computing speed based on novel synthetic neural circuits.

A neuron cell culturing platform consisting of arrays of ordered silicon nitride microtubes (2.7–4.4 μ m in diameter) was formed by strain-induced self-rolled-up nano-membrane (s-RUM) technology using ultrathin (<40 nm) silicon nitride films deposited on transparent substrates such as glass [75]. These microtubes presented strong guidance for fast growing primary cortical neurons, with a coaxially confined configuration resembling that of myelin sheaths. Neurons revealed a dramatically enhanced growth rate inside the microtube compared to regions outside the microtubes. The acceleration and precise guidance provided

by the silicon nitride microtube array was attributed to 3D-adhesion and electrostatic interaction with the silicon nitride microtubes, respectively. The microtubes not only provide structure for the neural network and guiding connections, but also accelerate the growth of axons, an important feature as time is crucial for restoring severed connections in the case of spinal cord injury or limb reattachment. A time-lapse sequence of a cortical neuron rapidly growing from inside a microtube through neighboring microtubes can be watched on the Internet [76].

This research has important implications for designing and building of intelligent synthetic neural circuits for potential treatment of neurological disorders. In addition, the novel self-rolled-up silicon nitride microtubes could provide an ideal route to integrate electrodes into neural cultures, coupled with photonics, to directly monitor dynamic neural activities and record action potentials with enhanced resolution and fidelity [77].

In conclusion, self-rolled-up silicon nitride microtubes are attractive for photonic, electronic, and biological applications based on their transparency under visible light, tunable refractive index, non-toxicity, and compatibility with Si-integrated circuits [78]. Thus, they may become important additions to the tool box of 4th generation biomaterials that will be integrated with the human body to act as powerful diagnostic and therapeutic agents able to (i) manipulate cellular bioelectric signals required for tissue regeneration and (ii) monitor cellular responses to external cues and allow for communication with the host tissues [1, 79].

4.6 Antibacterial and antiviral particles and coatings

The efficacy of silicon nitride as a 'killer ceramics' for Gram-negative bacteria such as *Porphyromonas gingivalis* was found to be the result of chemically driven mechanisms, related to the peculiar pH-dependent surface chemistry of silicon nitride [49]. In an alkaline pH environment, a buffering effect controlled by the release of ammonium (NH₄⁺) ions causes lysis of bacterial proteins as confirmed by conventional fluorescence and *in situ* Raman microprobe spectroscopies. Formation of peroxinitrite within the bacteria leads to degradation of nuclei acid, and reduction in phenylalanine content and liquid concentration were observed. Experiments confirmed that modification of the surface chemistry of silicon nitride by chemical etching or thermal oxidation influenced the peroxinitrite formation and thus, affected bacteria metabolism.

Polyethylene coated by pulsed laser technique with silicon nitride powder in a nitrogen gas atmosphere showed antibacterial properties *in vitro* against *S. epidermidis*. The coating sensibly reduced the amount of living bacteria when compared to the uncoated polymer. Osteoconductivity was also tested *in vitro* using SaOS-2 osteosarcoma cells. The presence of the silicon nitride coating resulted in an increased amount of hydroxyapatite deposited from extracellular fluid (ECF). Hence, coating of polyethylene with silicon nitride may lead to improved performance of orthopedic endoprosthetic medical devices [80].

To confront the challenge of bacterial resistance to antibiotic treatment has become one of the most critical issues of present medical research. Methicillin-resistant strains of *S. aureus* (MRSA) are major killers of patients in hospitals or other health care settings, such as nursing homes and dialysis centers. In these settings, the harmful bacteria are known as health care-associated MRSA (ha-MRSA). A study has found that antimicrobial behavior of machined Si₃ N₄ surfaces was due to repulsion of the bacteria, a phenomenon that also limited osteogenesis, as host cells were also unable to adhere to the machined surface. This suggests that the *in vivo* biological behavior of Si₃N₄ orthopedic implants is driven by critical features of their surface nanotopography [81].

Silicon nitride has been shown to inactivate several bacterial species and viral strains including SARS-CoV-2, while mammalian cells would remain unaffected [82]. SARS-CoV-2 virions (2×10^4 PFU/mL diluted in growth media) were exposed to 5, 10, 15, and 20% (w/v) of an aqueous suspension of sintered Si₃N₄ particles for durations of 1, 5, and 10 minutes, respectively. Following each exposure to Si₃N₄, the remaining infectious virus was quantitated by plaque assay. It was found that the reduction in SARS-CoV-2 titers

were markedly reduced when exposed to all concentrations of Si₃N₄, showing reductions between 85% - 99.6%, depending on the dose and duration of exposure. In conclusion, surface treatment strategies based on silicon nitride particles or coatings may offer novel methods to discourage SARS-CoV-2 persistence and infectivity on surfaces and thus, control the spread of the COVID-19 pandemic. Additional research has provided insight into the mechanism of the antiviral properties of silicon nitride [4]. Conceivably, it derives from a hydrolytic reaction of the silicon nitride surface [49] and the related formation of reactive nitrogen species (RNS) that could be easily metabolized by mammalian cells but that are lethal to pathogenic bacteria and ssRNA viruses. It was confirmed by PCR (polymerase chain reaction) tests that RNS directly react with viral proteins and RNA. Consequently, silicon nitride may play an important role in controlling the spread of human epi- and pandemics caused by ssRNA mutant viruses and other pathogens.

4.7 Medical diagnostics

Cellular sampling and characterization include culture, differentiation and fixing of cell on silicon nitride substrates for imaging and mapping across the electromagnetic spectrum, from X-ray fluorescence (XRF) to X-ray absorption near edge spectroscopy (XANES) to visible and infrared microspectroscopies [83]. Cells were found to adhere strongly to silicon nitride surfaces, allowing for investigation of visually displayed proliferative and phenotypic growth.

Lasers for medical application operate in a wide range of the electromagnetic spectrum, from X-ray up to UV, continue in the visible and near-infrared (NIR) to mid-IR. These electromagnetic waves need to be transmitted from the laser source to the target tissue by a flexible device, called a waveguide that will enable easy manipulation of the laser beam in a medical diagnostic setting [84]. Novel integrated nanophotonic sensing devices operating in the visible and near-infrared regions with drastically reduced propagation losses were developed based on silicon nitride waveguides [85]. Silicon nitride is frequently chosen as the passive waveguide material due to its several advantages compared to silicon, including higher transparency at wavelengths below $1.1 \mu m$, ultra-low two-photon absorption effect at telecommunication wavelengths, and ultimately, smaller propagation losses. These properties have made silicon nitride a widely used platform in silicon-integrated photonic applications [86].

In addition, silicon nitride waveguide-based nano-photonic integration platforms have potential for the miniaturization of optical coherence tomography (OCT) systems [87, 88]. Novel silicon nitride-based nano-photonic waveguides find increasingly application in Raman spectroscopy to enhance signal strength [89] and to miniaturize chips for SERS (surface-enhanced Raman spectroscopy) [90].

Chemical activation of silicon nitride surfaces with either aqueous or organic solutions of 3-aminopropyl triethoxysilane (APTES) led to the development of an optical biosensor allowing for immobilization of biomolecules such as proteins by covalent bonding [91]. Protein immobilization was followed by incubation with murine γ -globulin and reaction with fluorescently labelled goat antimouse IgG antibody. Recording the surface fluorescence revealed improved signal intensity and reproducibility compared to other protocols.

4. Conclusion

Research and development effort on silicon nitride has impressively shown that this unique ceramic biomaterial provides a host of advantageous properties conducive to application in modern medicine as part of prosthetic devices in orthopedic, dental, cardiovascular, ophthalmological, and reconstructive surgery. These applications are based on high compressive and flexural strengths, high fracture toughness, low friction coefficient, high wear and corrosion resistance, improved medical imaging ability as a radio-lucent material, and enhanced biocompatibility, osseointegration and antimicrobial activity against bacteria and viruses. These unique properties suggest that silicon nitride is destined to become a leader to replace titanium and other entrenched biomaterials in many contemporary and future medical applications.

However, as advantageous the mechanical, tribological, chemical and biological properties of silicon nitride are, its comparatively high modulus of elasticity poses a challenge for application for load-bearing stems for arthroplastic implants. Even though modulus reduction can be achieved by using porous reaction-bonded silicon nitride (RBSN) instead of dense pressureless sintered silicon nitride (SSN), the modulus gradient between implant and cortical bone is still too large to suppress effectively stress shielding of hip endoprosthetic implants, in contrast to intervertebral spacers that have enjoyed lasting success for more than thirty years.

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