

From Material to Medicine

THE STORY OF SILICON NITRIDE

A Brief Narrative - By SINTX Technologies Corporation

Introduction:

SINTX Technologies is a manufacturer of silicon nitride ceramics for medical implants. This summary will share our knowledge and experience with silicon nitride.

What is silicon nitride (Si_3N_4)?

Silicon nitride is an inorganic and non-metallic material made of silicon and nitrogen, two elements that are essential for life.¹⁻⁴ First synthesized in 1857, silicon nitride was commercialized in the 1950s.⁵ Research funded by the US, EU, and Japanese governments during the 1970s and 1980s helped optimize the material and reduce manufacturing costs. Because of its advantages, silicon nitride was adopted in many industries.⁶



In the 1990's, naturally-occurring silicon nitride was discovered in meteorite stardust, suggesting intergalactic origins of the material from the beginning of time.⁷

Properties:

Silicon nitride is made by mixing highly refined raw powders that are formed into desired shapes. The final product is finished in precision kilns or furnaces. This is similar to the making of pottery; the word "ceramic" derives from its Greek root "kéramos" which refers to pottery.⁸

Dense silicon nitride is a very hard, abrasion-resistant and corrosion-resistant solid. Unlike familiar ceramics such as porcelain or glass, silicon nitride has very high strength, with the highest fracture resistance of any advanced ceramic.⁹



Industrial Uses:

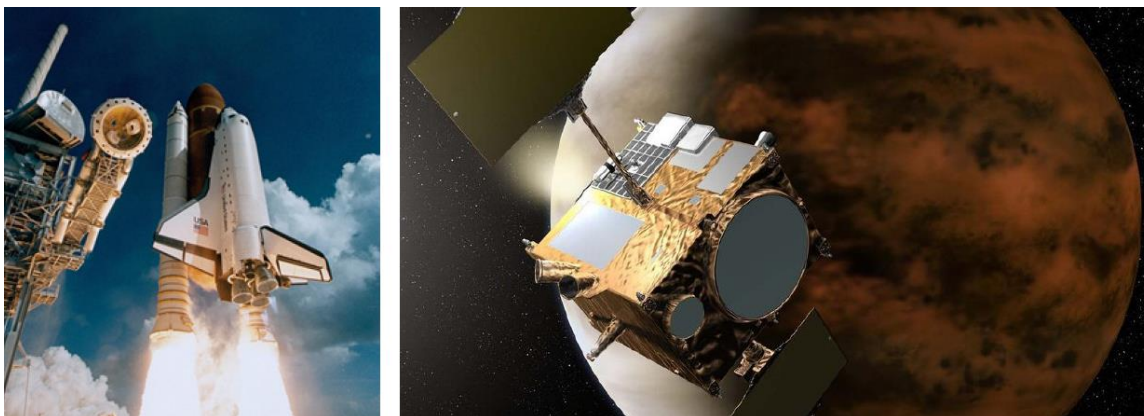
Silicon nitride is found in bearings for gas and diesel engines, wind turbines, motorsports equipment, bicycles, rollerblades, skateboards, computer disk drives, machine tools, dental hand-pieces, and flap-actuators in aircraft.¹⁰ Wherever corrosion, rapid wear, and electric or magnetic fields limit the use of metals, silicon nitride is used instead.^{7, 11, 12} Silicon nitride bearings are used in underwater ocean tidal flow meters, where severe seawater corrosion would damage other materials.¹³

Because of extreme strength, hardness, and resistance to chemical and thermal factors, silicon nitride is used in high-speed cutting tools,^{11, 12, 14-16} and to break up rocks during oil fracking.¹⁷ Its heat resistance has led to uses in the valve trains of gas¹⁸ and diesel engines,¹¹ rotors and stators in gas turbines,^{19, 20} as automotive turbochargers,²¹ and as rocket nozzles and thrusters.²² Other materials cannot survive these extreme conditions.



Outer Space:

Silicon nitride has been used in the cryogenic pump bearings on NASA space shuttles,²³ and in the thrust-ers of the Japanese space probe, Akatsuki.²⁴ When used in tungsten-etched memory chips for space-craft, silicon nitride enables a lifespan of >10,000,000 years of space travel.²⁵



Medical Implants:

SINTX Technologies is focused on medical-grade silicon nitride. When used to make spinal fusion implants, silicon nitride has the flexibility of a dense, porous, or a combined architecture that can mimic the cortical-cancellous structure of bone.^{26, 27} Silicon nitride is biocompatible, bioactive, and has shown bacterial resistance and superb bone affinity.²⁸ With >33,000 human spine implantations over 10 years, and less than 25 reported adverse events, silicon nitride has a good safety record.²⁹ Silicon nitride can be polished to a smooth and wear-resistant surface for articulating applications, such as bearings for hip and knee replacements.³⁰⁻³²

In summary, medical-grade silicon nitride has the following advantages:

- Material phase stability³³
- Strength and fracture toughness⁹
- Hydrophilicity³⁴
- Bacterial resistance^{33, 35}
- Favorable imaging³⁶
- Wear resistance^{33, 35}
- Osteoconductivity³⁷⁻³⁹
- Osteoinductivity^{40, 41}



History of Biomaterials:

Historically, materials such as wood, leather, pig bladders, glass, and ivory were used to treat hip fractures and hip arthritis.⁴² Today, metals, bone grafts, and polymers are the preferred biomaterials. In the warm saline environment of the human body, metals fret and corrode,⁴³ plastics oxidize,⁴⁴ and allograft procedures have a high rate of non-union.⁴⁵ Toxic metal wear has led to a recall of all-metal hip bearings;⁴⁶ while fretting and corrosion in total hip modular tapers are new concern.⁴⁷ Metal allergies to total knee implants remain an unsolved clinical problem.⁴⁸ Silicon nitride may be ideal for human implantation. Its wear rate is extremely low,⁴⁹ and the wear particles are soluble and can be cleared from the body.⁵⁰ Silicon nitride is chemically resistant, and it has a high dielectric constant that resists fretting and corrosion.⁵¹

Plastic (polyethylene) bearings in prosthetic hip and knee joints oxidize over time, leading to strategies such as cross-linking⁵² and vitamin E doping⁵³ to slow this degradation. In contrast, the surface chemistry of silicon nitride allows it to scavenge oxygen from the joint space,^{49, 54} thus potentially extending the durability of hip and knee replacements.



Image courtesy of W. M. Rambo, Jr., M.D.

Bone graft tissue is limited by donor-site morbidity, lack of bioactivity, and concerns about disease transmission.⁴⁵ Synthetic bone fillers are usually made of hydroxyapatite (HAp). Although HAp promotes bone healing, it is too brittle for load-bearing implants.⁵⁵⁻⁵⁷ Silicon nitride bone scaffolds and bone-fusion devices⁵⁸ provide excellent mechanical strength, with bone healing equivalent to hydroxyapatite.⁴¹

On X-ray images, plastic implants are invisible while metals obscure the visibility of bone. CT scans and MRI images are also distorted by metal implants. None of these limitations apply to silicon nitride, which is easily seen on X-rays. Furthermore, the dielectric and non-magnetic nature of silicon nitride eliminates distortion in CT and MRI scans.³⁶

In summary, silicon nitride has a fortuitous combination of strength, toughness, wear resistance, biocompatibility, bioactivity, bone integration, structural stability, corrosion resistance, and ease of imaging; all of which are desired properties in medical implants.⁵⁹

Other Bioceramics:

Alumina (Al_2O_3) and zirconia (ZrO_2) ceramics are used in the bearings of prosthetic hip and knee joints.^{61–63} Alumina is brittle; it can fail suddenly.⁶⁴ Zirconia is stronger, but it can degrade in the body, leading to failures.⁶⁵ Zirconia femoral heads are no longer favored because of unpredictable failures related to material transformation.⁶⁶

Zirconia-toughened alumina (ZTA) is made by mixing zirconia and alumina; it is used in prosthetic hip and knee joints.⁶⁷ ZTA is an engineering compromise between the limitations of alumina and zirconia.⁶⁸ While better than either material, ZTA can still degrade and lose its mechanical integrity.⁶⁹



Alumina and ZTA prosthetic hip joints⁶⁰

Since they are oxide ceramics, alumina and zirconia release oxygen ions, which can degrade polyethylene bearings.^{54, 70} In contrast, silicon nitride is a non-oxide ceramic. While it is stronger and tougher than alumina, and comparable to ZTA,⁹ silicon nitride also protects polyethylene by scavenging oxygen from the joint space.⁷¹ This remarkable property may help extend the useful life of prosthetic hips and knees.

Scientific and Clinical Data:

Although well-proven in industry,⁷ silicon nitride was first used in a spinal implant trial that began in 1986⁷² with follow-ups at 1, 5, and 10 years. Outcomes showed substantial pain reduction, as well as solid inter-body spine fusion, demonstrating the favorable properties of silicon nitride.

The biological response of living tissue to silicon nitride was described in a 1989 study.⁷³ By 12 weeks, up to 90% of the surface of porous silicon nitride contained woven trabecular bone and 75% of all pores were occupied by mature lamella bone. These results showed the favorable osteoconductive properties of silicon nitride.

Later studies with silicon nitride and bioglass composites demonstrated an osteoinductive effect on the proliferation and differentiation of human bone marrow cells and the formation of a mineralized matrix.^{74–76} The Si_3N_4 /bioglass composites were hydrophilic, with a negatively-charged surface at homeostatic pH; properties that contributed to rapid protein adsorption and bone formation.

Neumann *et al.* studied five compositionally similar industrial formulations of silicon nitride, none of which showed cytotoxicity.⁷⁷ In a small animal model, the authors showed lower bone-implant contact on alumina versus silicon nitride after eight weeks.⁷⁸ Separately, the same authors implanted silicon nitride plates and screws in the facial bones of another small animal model; results showed no implant loss, displacement, or fracture, with complete bone healing after 3 months of implantation.⁷⁹

Kue *et al.* examined MG-63 osteoblast cell adhesion and proliferation on reaction-bonded silicon nitride (RBSN) and sintered reaction bonded silicon nitride (SRBSN). Compared to polystyrene surfaces, cells grown on polished Si_3N_4 had higher levels of osteocalcin, a marker of bone formation.⁸⁰

Guedes e Silva *et al.* implanted silicon nitride in rabbits; results showed that osteoblasts and osteocytes directly contacted the Si_3N_4 implants along with a matrix of collagen I and III. Bone remodeling around

the Si₃N₄ implants was enhanced compared to titanium controls.^{81–83} To further aid osseointegration, these investigators showed that a biomimetic HAp coating could be effectively applied to Si₃N₄.⁸⁴

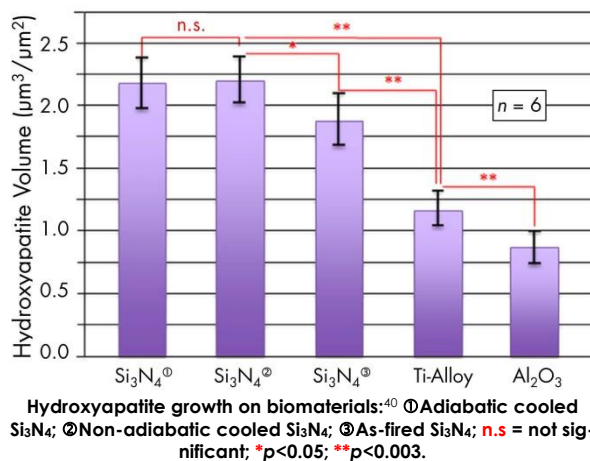
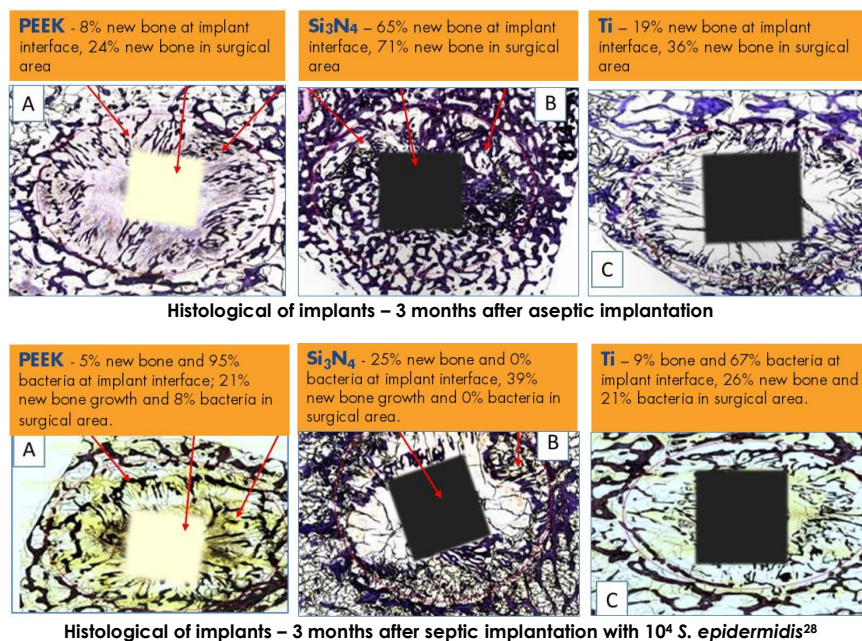
Webster *et al.* compared silicon nitride, titanium (Ti), and polyetheretherketone (PEEK);²⁸ three months after aseptic implantation into rats, Si₃N₄, Ti, and PEEK showed appositional healing of 65%, 19%, and 8%, respectively. While the addition of *Staphylococcus epidermidis* bacteria reduced bone formation; the Si₃N₄ implants still proved better, (i.e., 25% appositional healing for Si₃N₄, versus 9% for Ti, and 5% for PEEK.)

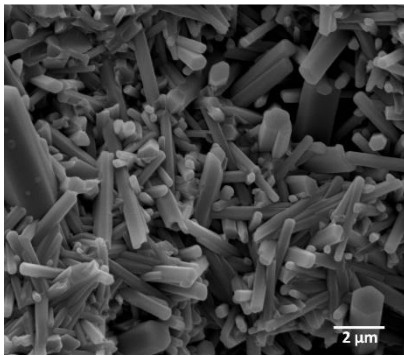
Several other reports have shown superior osseointegration of Si₃N₄.^{34, 37–41, 85–87} These studies report that enhanced osteogenesis and osteoconductivity is most likely related to the elutable surface chemistry of silicon nitride. Once implanted, silicon nitride's surface reacts with water to form silicic acid (H₄SiO₄) and ammonia (NH₃) in accordance with the following chemical reaction:



Bioavailable silicon in the form of silicic acid enhances osteogenic activity^{1–3, 88–93} while various nitrogen-based moieties can either be mild disinfectants or powerful oxidants that disrupt microbial cellular functions.^{86, 94–102} In addition, silicon nitride's surface charge, wettability, and phase chemistry also contribute to enhanced osteoconductivity.

Silicon nitride has a large negative surface charge compared to PEEK and Ti;⁸⁵ a phenomenon that is associated with higher serum protein adsorption and the upregulation of osteoblastic activity.^{103–105} Also, the hydrophilicity of Si₃N₄ is superior to that of PEEK and Ti, leading to earlier and more effective bone apposition than hydrophobic compounds.^{34, 106–110} Finally, the phase chemistry of silicon nitride affects osteoconductivity; bone forming cells adhere and proliferate differentially on various apatite, silicon-oxynitride, and SiYAlON phases.^{40, 87} Heat-treatments such as non-adiabatic cooling after hot-isostatic pressing, annealing in nitrogen (i.e., N₂-annealing), or thermal oxidation are manufacturing strategies to bring one phase or another to the surface of silicon nitride. A post-densification glaze coating using a SiYAlON composition also leads to enhanced osteoblastic activity.⁸⁷





Surface microstructure of bioactive Si_3N_4

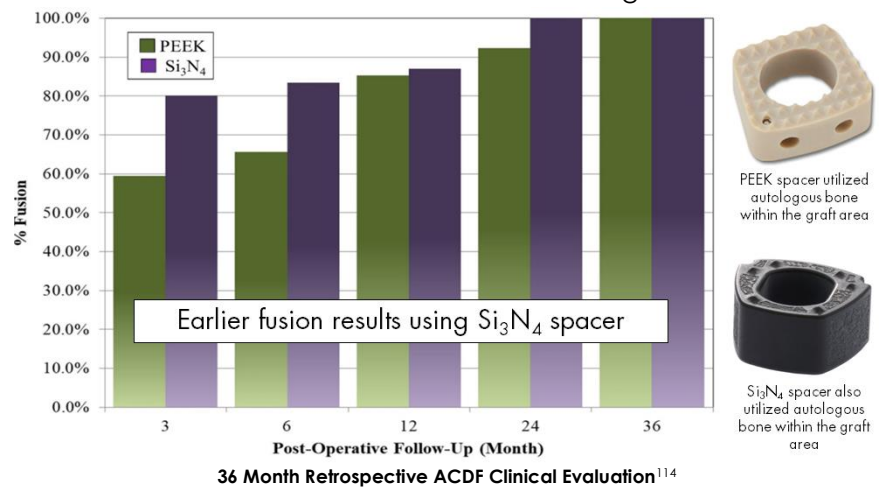
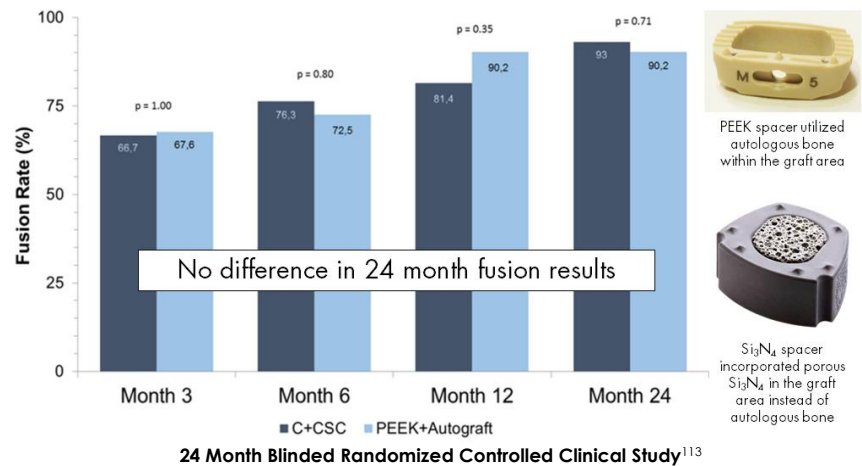
and proliferation.¹¹²

Several human studies agree with the above data concerning silicon nitride. A 24-month clinical trial¹¹³ compared PEEK cages with autograft bone to porous Si_3N_4 without added bone graft in cervical fusion. Results showed that porous Si_3N_4 spacers achieved spinal fusion exclusive of autograft bone. Two other clinical trials comparing cervical fusion rates for non-porous silicon nitride and PEEK cages or allograft spacers showed earlier and more effective fusion with silicon nitride.^{114, 115} Case studies have shown the effectiveness of silicon nitride in abating *in vivo* infections¹¹⁶ and in achieving solid arthrodesis in the lumbar spine.¹¹⁷

Aside from the properties that make silicon nitride attractive in industry, (*i.e.*, superior strength, wear resistance, corrosion resistance, and fracture toughness¹¹⁸) there is a related set of attributes that make silicon nitride attractive as a biomaterial. To summarize:

Bone Healing: Silicon nitride turns on osteoblasts (bone-forming cells) and suppresses osteoclasts (bone resorbing cells). A manufacturing change called “nitrogen-annealing” results in a near-200% increase in bone formation by cells exposed to silicon nitride.⁴¹ This finding has excellent implications for speeding up bone healing, bone fusion, and implant integration into the skeleton. Living cells adhere preferentially to silicon nitride over polymer or metal.¹¹⁹ Cell adhesion promotes tissue development and enhances the bioactivity of materials. Cell adhesion to silicon nitride is a function of pH, chemical, and ionic changes at the material's surface.

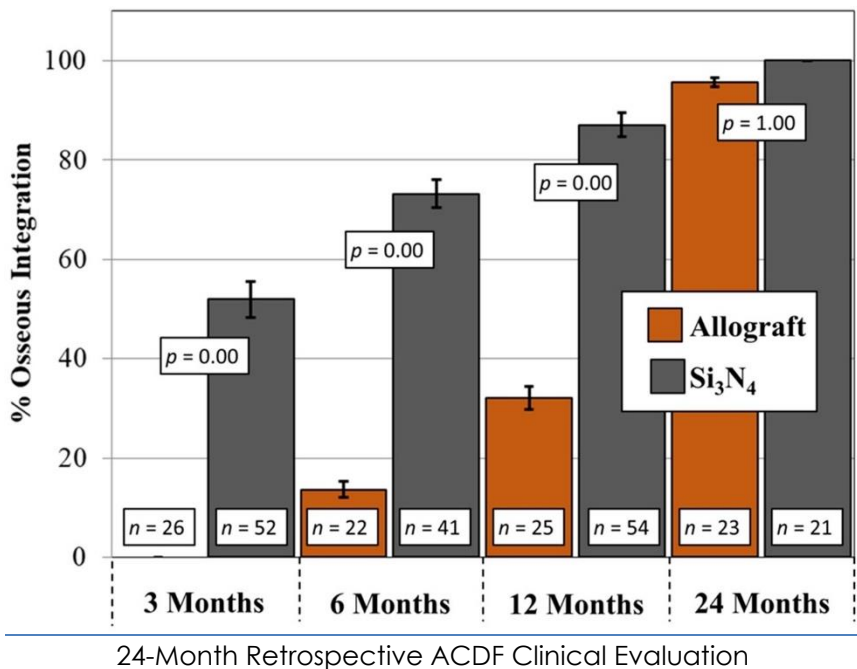
The surface topography of Ti-alloys and PEEK may aid in appositional bone healing;¹¹¹ recent work has addressed this phenomenology for silicon nitride.¹¹² Silicon nitride's topography is apparent at the micron and sub-micron scales. The surface of as-fired silicon nitride consists of anisotropic grains that are typically $\leq 1 \mu\text{m}$ x up to $10 \mu\text{m}$ with individual features (*i.e.*, asperities, sharp corners, points, pits, pockets, and grain intersections) that can range in size from $< 100 \text{ nm}$ to $1 \mu\text{m}$. While this structure is morphologically different from surface-functionalized titanium, it has some common features (*e.g.*, sharp corners, points, and pockets). Ishikawa *et al.* recently demonstrated that this type of surface microstructure is important in resisting bacterial attachment while concurrently promoting mammalian cell adhesion



Composite Devices: In a human clinical trial, a composite spine interbody device made of solid and porous silicon nitride fused the cervical spine without any autograft bone filler.¹¹³ Bioactive silicon nitride powder has also been incorporated into polyetheretherketone to form a polymer-ceramic composite. This new composite resists bacterial adhesion while promoting bone formation in a similar fashion as monolithic silicon nitride.¹²⁰ Composite devices based on silicon nitride herald a new class of reconstructive implants.^{27, 121}

Bacterial Resistance: Bacterial infection of any biomaterial implant is a serious clinical problem.

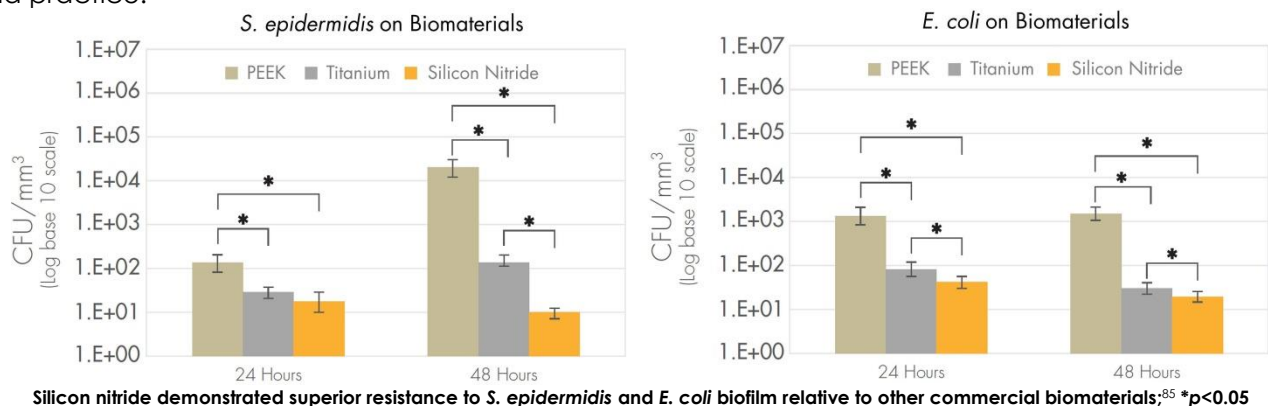
Silicon nitride offers a potential easy solution; it is inherently resistant to bacteria and biofilm formation.^{119, 122} In addition, a recent study has shown a direct bactericidal effect against an oral pathogen.⁸⁶ The antibacterial behavior of silicon nitride is probably multifactorial, and relates to surface chemistry, surface pH, texture, and electrical charge.³⁴ Optimizing these surface properties for specific implants is a clear advantage of the material.³⁴



The Future:

With an expanding, ageing and more active population, biomaterial innovations will lead to improved biomedical implant safety, high-performance, and lifetime durability. Already well-proven in diverse industrial applications and currently utilized as intervertebral spinal fusion cages, silicon nitride has the foundational evidence to be applied likewise across a range of biomedical applications.

We invite you to contact SINTX Technologies to see how silicon nitride might be beneficial to your patients and practice.



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