SETTING THE RECORD STRAIGHT

Literature Review
Setting the record straight

Research and in-situ failures address the hidden dangers of titanium plasma sprayed PEEK interbody fusion devices

Introduction

The debilitating pain caused by degenerative spine disease drove the development in the 1950s of the first interbody devices for spinal fusion: dowel grafts harvested in many cases from the patient’s own iliac crest. Although autografts avoided issues related to graft-versus-host disease, complications often included harvest-related pain, poor wound drainage, infection, nerve injury and iliac crest fractures.1

Consequently, the focus shifted to cage implants; the first in 1988 was a cylinder of hollow stainless steel to allow bone ingrowth into an incompressible spacer.1 Fusion cages continued to evolve in the ensuing years to include different cage designs, some threaded and others non-threaded (box-shaped), made primarily of titanium and titanium alloys to improve osteointegration and cell adhesion.1

Polyetheretherketone (PEEK) implants emerged on the scene in the late 1990s and, by virtue of intensive marketing, gained traction as an alternative to titanium interbody devices. PEEK implant manufacturers argued that the plastic device’s elastic modulus was much closer to that of cortical bone and therefore less likely to subside than titanium devices. They also said that in contrast to titanium, PEEK’s radiolucency did not interfere with assessment of fusion and adjacent neural structures on CT and MRI.

In-vitro research on microtextured titanium implant surface characteristics began in earnest in the late 2000’s and continued at an accelerated rate, each new study confirming and elaborating on previous work that showed the remarkable pro-bone growth response that specific microscopic surface roughness triggered at the cellular level.2-8 The studies examined Titan Spine implants with proprietary macro, micro and nanoscale (MMN™) surface structures, features that were shown to drive osteogenesis and angiogenesis, particularly in comparison to PEEK implants. The smooth-surfaced, plastic PEEK devices were shown to promote fibrous tissue formation rather than bone. As a result, the market began to shift back toward surface-enhanced titanium implants in 2012.
Acknowledging the osteogenic superiority of microtextured titanium implants, many PEEK device manufacturers acquiesced to market demands by introducing implant lines with a titanium plasma spray (TPS) coating applied to their PEEK devices. TPS implants are marketed as “the best of both worlds” that combine the osteogenic benefits of titanium with the elastic modulus and radiolucency of PEEK.

Research now, however, disputes all major contentions regarding the supposed benefits of TPS implants. Investigations have set the record straight that:

- Titanium coatings are susceptible to creating particulate debris during insertion that could have a harmful long-term effect on the patient.
- It’s the design of the implant, not its elastic modulus that is the key factor in minimizing subsidence.
- Advances in implant design and imaging technology have eliminated the challenges with assessing fusion in the presence of titanium devices.

The danger of titanium plasma sprayed PEEK implants

It is self-evident that an interbody fusion device should not have the potential to be damaged during normal insertion techniques, especially in a way that poses a significant risk to the patient. A laboratory study on TPS PEEK implants and a clinical case study demonstrate the consequences – potential and real – of losing titanium particles from the surface of an implant.

Impaction debris generated by titanium-coated PEEK implants

In a 2016 laboratory study, Kienle, et. al set out to determine if simulated clinical impaction forces (i.e., shear loading) would cause titanium particles to be shed from the surface of TPS implants and/or cause delamination of the titanium-PEEK interface. The deposition of titanium particulate debris in the body has the potential to cause an insidious inflammatory reaction that inhibits osteogenesis, leading to implant failure and revision surgery.

The researchers compared Titan Spine ENDOSKELETON® titanium interbody fusion devices to TPS PEEK devices of similar geometry. The surface of all Titan Spine implants is created by proprietary acid etching processes that subtract (versus adding) surface material to generate its unique roughened architecture at the macro, micro, and cellular levels. As noted above, the surface of TPS implants is generated by the application of titanium particles to the PEEK substrate. Both groups of implants were subjected to real-life simulated impaction forces, which were calculated to be roughly 60,000 times faster than ASTM standard biomechanical shear testing requirements.

After impacting both groups of implants between polyurethane blocks used as vertebral body substitutes, the researchers focused on the implant surfaces and particles captured. While they found that the Titan Spine implants showed no signs of particulate debris or surface damage, the TPS PEEK implants showed a disturbing propensity to shed titanium particles:
- 20% of the PEEK implant teeth were affected by up to 25% of their surface area
- 6% of the PEEK implant teeth were affected by 25-50% of their surface area
- Captured particles in the PEEK group were 1-191 μm in size, with particles <10μm more frequently captured than particles >10μm
- >50% of the lost particles were <10μm in size

The researchers noted that previous studies of the effects of titanium wear debris in animal studies showed that such debris causes a cytokine-mediated pro-inflammatory response with increased osteoclastic activity and cellular apoptosis.\textsuperscript{10-12} They added:

“All, macrophages seem to mediate inflammatory reactions to titanium particles. However, titanium wear particles with a diameter larger than 5-10 μm are reported to be not phagocytosable. In the present study, over 50% of all captured particles were within the range of up to 10 μm. An inflammatory reaction of the human body is therefore possible.”

They also concluded that, with standard impaction forces, there is a “certain risk of wear if titanium-coated PEEK cages are used even if the coating complies with the FDA requirements for mechanical testing.”
A Real-World Example

Clinical Case Study Courtesy of David Jackson, MD

A 34-year-old female patient underwent an L5-S1 microdiscectomy in January 2015 for right lower extremity radiculopathy and subsequently sustained a recurrent disc herniation eight months later. Her surgeon at the time prescribed minimally invasive (MIS) TLIF.

In December 2015, she underwent an L5-S1 right-side revision laminotomy with complete facetectomy and MIS TLIF using a TPS-coated PEEK cage (Aurora ECHO TiNano). No pedicle screws or other posterior fixation were applied and the patient was discharged the same day.

Pain returns

Her medical record shows she did well post-operatively, with nearly complete leg pain relief and minimal back pain. However, shortly thereafter, she reported that her leg and back pain had returned and had exceeded pre-operative levels. Despite her symptoms, no x-rays or other imaging studies were obtained and the patient was referred to pain management after her three-month follow up.

The patient presented to my office in November 2016 with progressive and moderate to severe low back/right lower extremity pain, despite daily narcotic pain medication. Her pain was worsened by standing, walking, bending and lifting.

Imaging shows subsidence and osteolysis

An x-ray showed evidence of severe subsidence around the TPS-coated PEEK cage, with a CT scan also demonstrating subsidence in addition to lysis surrounding the cage and clear pseudoarthrosis. An MRI scan revealed recurrent stenosis at L4-L5 on the right side.

The patient elected to proceed with revision interbody fusion via anterior approach (ALIF), with anterior and posterior instrumentation. The surgery was performed in November 2016 using a titanium implant with integrated screws (Titan Spine ENDOSKELETON® TAS) to maximize the likelihood of fusion.

Metallic debris

The TPS-coated PEEK implant was located from the anterior approach and easily removed. There was substantial metallic debris surrounding the cage in the disc space, as well as soft, fibrous material within the cage. There was no evidence of fusion. On inspection of the cage following explantation, it was apparent that the majority of the titanium coating had sloughed off.
After removal of the TPS implant, the remainder of the intervertebral disc and metallic debris were removed, and the Titan Spine TAS device was implanted following standard surgical techniques. Unilateral pedicle screws were then placed percutaneously on the left.

**The next 16 weeks**

At two weeks post-op, the patient had substantial improvement from her pre-operative leg and low back pain. At the six-week post-operative mark, the patient was doing well enough to start physical therapy, and at 16 weeks she was virtually pain-free and had resumed all normal activities and had begun a weight loss/exercise program.

**Other Real-World Examples**

Unfortunately, Dr. Jackson’s case study is not the only example of failed TPS implants. The following images are retrieved implants either following revision surgery or after explantation to reposition the implant.

At the time of this white paper’s publication, the US Food & Drug Administration had not yet amended its American Society for Testing and Materials (ASTM) standards to evaluate the degree to which a spinal interbody fusion device will shed debris under normal insertion forces. As previously noted, current ASTM standard biomechanical shear testing requirements involve impaction forces that are 60,000 times slower than the impaction forces these devices are subjected to in the operating room. Therefore, the health of spinal fusion patients who receive TPS implants is at risk until the ASTM standards are modified to address the potential of impaction-related debris.
Clearly, scientific research has revealed that merely coating a PEEK implant with a titanium spray – in the hopes of duplicating the osteogenic properties of acid-etched Ti implants – presents an untenable risk for the patient. Nevertheless, TPS manufacturers persist in their claim that their implant designs should be considered superior due to their bone-like elastic modulus and imaging-friendly radiolucenty. These supposed advantages, as explained below, have been thoroughly dismissed after further examination and study.

The misplaced focus on modulus of elasticity

When PEEK implant producers commercialized their solutions, they claimed that a fundamental advantage of PEEK cages over titanium implants was an elastic modulus* (modulus) much closer to that of cortical bone. The implication was that PEEK devices would exhibit better load sharing and stress distribution between the vertebrae, contributing to a reduced potential for implant subsidence and, in turn, a higher fusion rate.

Av Edidin, PhD, writing for Becker’s Spine Review in 2015 explained the basic errors in this supposition. In the article\textsuperscript{13}, he writes:

“While PEEK does possess a lower modulus than titanium, the net result is that more material must be used when building a PEEK cage to overcome its lower modulus property to ensure the PEEK device can withstand the overall loads in the spine. As such, the critical property to consider when determining the response to an applied load when comparing the two cages is not the modulus of elasticity, but rather the structural stiffness of the cage. Whereas modulus is one of the properties that factors into the overall structural response equation, \textit{the design of the structure} [emphasis added] plays a much greater role.”

Cabraja, et. al retrospectively compared the long term results of stand-alone PEEK and titanium cages in a comparable patient cohort under identical operative settings.\textsuperscript{14} The researchers’ hypothesis was that the titanium cages would show a higher rate of cage subsidence after ACDF, leading to a higher loss of correction.

In a radiological comparison of 44 patients with titanium cages and 42 patients with PEEK cages, no statistical difference in subsidence rates was found after an average of 28.4 months. The investigators concluded that “elastic modulus of the interbody device material did not affect resistance to subsidence.”

Finally, Antonio Valdevit, PhD, et. al subjected PEEK and Titan Spine titanium interbody devices to cyclic physiologic loads (350N) for 600 cycles in porcine spines and measured for subsidence.\textsuperscript{15}

The researchers found that the titanium implants displayed the least amount of subsidence by a statistically significant margin. PEEK devices subsided 40% more than the Titan Spine implants despite having a modulus that is 32 times lower than titanium. Most significantly, the titanium implants subsided at a statistically significant \textit{410\% slower rate} (i.e., “soft landing”). Dr. Valdevit hypothesized that the PEEK implant’s “hard landing” may be the result of its anti-expulsion ridges, which distribute the overall compressive force over a significantly smaller contact area as compared to Titan’s roughened macro surface.
Elastic modulus is a measure of a material's inherent tendency to change elastically under applied force.

**Latest titanium implants enable CT assessment of fusion**

Producers of PEEK and TPS devices aggressively market the concept of enhanced radiographic imaging qualities due to PEEK's radiolucency compared to the opacity of titanium. They contend that imaging artifacts from titanium devices prevent radiographic assessment of fusion and surrounding neural structures on CT and MRI. However, with the development of enhanced artifact reduction software for imaging systems and Titan's open-aperture designs, which include significantly less titanium mass than threaded titanium interbody device predecessors, these challenges have been eliminated.

In a 2014 study that evaluated the ability to assess fusion with Titan Spine titanium implants, Slosar et. al stressed that previously observed metal artifact issues with titanium devices were due to dated technologies using dense, threaded designs. The researchers sought to test the Titan Spine ENDOSKELETON® implant, which features a large footprint and a wide central aperture for bone graft.

According to the investigators:

“Compared with earlier titanium implants, this design may allow for more accurate CT imaging and fusion assessment. We conducted a study to determine the interobserver reliability of using CT to evaluate bone formation and other radiographic variables with the new titanium interbody device.”
Thirty-three patients underwent ALIF with the same Titan Spine titanium interbody implant and reconstructed CT images were obtained randomly at six, nine, or 12 months. Two independent radiologists reviewed the scans. Fifty-six spinal fusion levels among the 33 patients were examined. Interobserver reliability was found to be high; the radiologists agreed on 345 of the 392 fusion data points reviewed and agreement for solid fusion was 0.77 for exactly the same fusion grade, and agreement to within one category grade was 0.95.¹⁶

The researchers added that the titanium interbody device exhibited nominal metal artifact and minimal subsidence, and that trabecular bone throughout the cage – indicating solid interbody fusion – was easily identified throughout the implant in the majority of cases reviewed.¹⁶

As a result of these findings, the authors concluded that:

“Although surgical exploration remains the gold standard for fusion assessment, surgeons should have confidence in using CT with this titanium implant.”

Ironically, the reduction of CT and MRI artifact associated with Titan Spine’s ENDOSKELETON® implants is due, in large part, to its elevated elastic modulus, which allows for the reduction of the amount of titanium required within the implant to withstand axial loads.

**Conclusion**

PEEK manufacturers have aggressively turned to TPS designs over the past few years in an effort to soften the blow from the market’s shift toward surface-enhanced titanium interbody fusion devices. However, any claims of TPS’ superiority over titanium fusion implants have been shown to be little more than marketing hype when subjected to scientific scrutiny.

For example, the benefit of PEEK’s plastic modulus is neutralized by the need to include considerably more material to make the PEEK device sufficiently stiff to withstand the applied load. Therefore, the lower modulus of PEEK is meaningless relative to subsidence; it is the structural stiffness of the implant and its design (e.g., ridges versus macro roughness) that truly matter. Valdevit et. al demonstrated that PEEK implants subsided significantly more and faster than similar titanium devices.

Secondly, the claims of PEEK manufacturers that titanium implants cause metal artifacts severe enough to prevent fusion assessment have been overtaken by improved implant design and advances in CT and MRI artifact reduction software.

Finally, TPS coatings have been found to be dangerous due to their propensity to shed microscopic debris during implantation. Coating the surface of an implant is not equivalent to creating a surface by subtracting material (i.e., as in Titan Spine’s subtractive, acid-etching process). Kienle, et al showed compellingly that a TPS coating is likely to shed particles under clinical impaction forces, many of which that can lead to phagocytosis. Conversely, native surface textures created by Titan Spine’s proprietary acid-etching process remain bound during the rigors of implantation and are not lost.
References


