ARTiC-L™ 3D Ti SPINAL SYSTEM

TOPOGRAPHY AND CHEMISTRY OF IMPLANTS ON BONE RESPONSE

EVIDENCE MATRIX

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ARTiC-L™ Evidence Matrix

EVIDENCE		SYNOPSIS
Implant Texture & Bone Response	Schwartz (2008)	Rough Ti6Al4V pedicle screws promoted bone-implant contact and required more torque strength to displace in sheep spine model.
	Deng (2015)	Rough PEEK threaded implants promoted bone growth in dog model.
	Pelletier (2016)	Plasma-treated Ti interbody implants promoted bone-implant contact in sheep spine model.
Osteolysis	Takenaka (2014)	Identification of foreign particles resulting in vertebral osteolytic defects in a case report.
Topography on Osteogenic Cellular Activity	Olivares-Navarrete (2013)	Topography (Ti/PEEK) impacts production of angiogenic and bone growth factors of osteoblasts.
	Olivares-Navarrete (2012)	Topography (Ti/PEEK) impacts production of bone growth factors and maturation of osteoblasts.
	Yoon (2016)	Topography regulates cell adhesion of hMSCs.

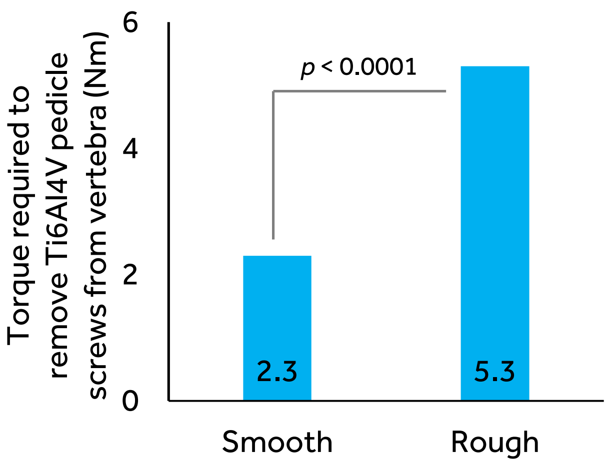
Implant Texture & Bone Response

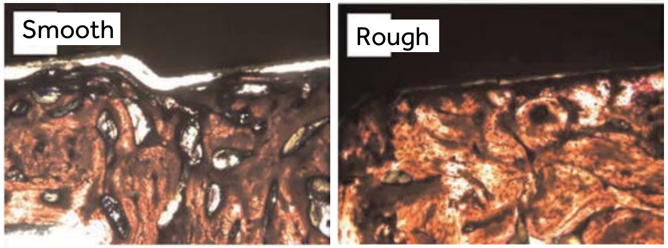
Schwartz et al

OBJECTIVES: To evaluate bone-implant stability of smooth and rough Ti6Al4V implants in a cellular and sheep spine model.

RESULTS:

- Rough compared to smooth Ti6Al4V surfaces:
  - *In vitro*: promoted osteoblast differentiation[1] and bone growth factors production[1].
  - *In vivo*: more bone-implant contact[1], less fibrous tissues, and more torque strength required to remove pedicle screws[1].





Histology section of smooth and rough Ti6Al4V pedicle screws in sheep spine. Smooth Ti6Al4V were covered by fibrous tissues whereas rough Ti6Al4V showed more direct bone contact and produced mineralized matrix.

INSIGHT: Surface roughness of Ti6Al4V promotes differentiation of osteoblasts and production of bone growth factors *in vitro* and stable bone-implant contact *in vivo* which can lead to increased bone-implant contact and stability.

DESIGN

- *In Vitro*: Osteoblasts (MG63) grown on Ti6Al4V disks. Smooth (0.2 µm Ra) or rough (2.0, 3.0, 3.3 µm Ra). Evaluated differentiation markers (AP, Osteocalcin) and bone growth factor production (PGE_2, OPG, TGF-β1).
- *In Vivo*: Smooth (0.2 µm Ra) and rough (3.0 µm Ra) Ti6Al4V pedicle screws (Ti6Al4V) implanted bilaterally in L4/L5 of sheep spine (12 weeks). Evaluated bone-implant interface (Histology), torque displacement (Biomechanical Testing).
- [1]Statistically Significant ($p < 0.05$)

REFERENCE

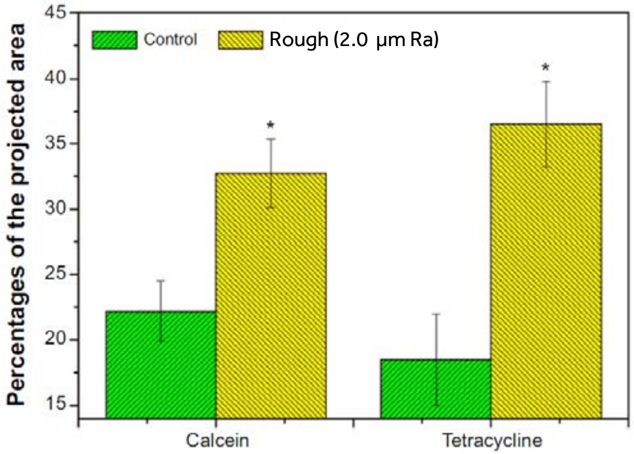
Schwartz et al, J Bone Joint Surg Am. 2008; 90(11):2485-98.

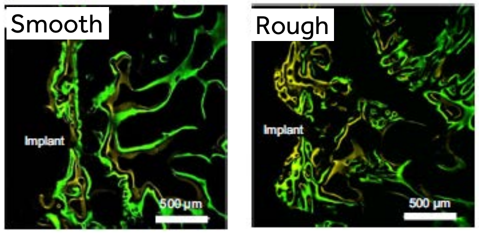
Implant Texture & Bone Response
Deng et al

OBJECTIVES: To evaluate bone-implant stability of smooth and rough PEEK implants in a cellular and dog model.

RESULTS:

- Rough compared to smooth PEEK surfaces:
  - *In vitro*: promoted osteoblast adhesion[1], proliferation[1], differentiation[1], ECM absorption[1], bone mineralization[1], and viability[1].
  - *In vivo*: more bone growth[1], bone mineral density[1], trabecular number/thickness[1] without fibrous layer.
- Surface roughness was optimal at 2.0 μm Ra.





Histology of Calcium binding Calcein and Tetracyline administered into dog mandible to assess osteogenic activity revealed that rough PEEK surface implants had greater osteogenic activity.

INSIGHT: Surface roughness of PEEK promotes differentiation of osteoblasts and bone mineralization *in vitro* and bone growth *in vivo* which can lead to increased bone-implant contact and stability.

DESIGN

- *In Vitro*: Osteoblasts (MG63) grown on smooth (0.1 μm Ra) or rough (0.9, 2.0, 3.0 μm Ra) PEEK/-HA/CF. Evaluated differentiation (AP), adhesion (F-Actin), mineralization (Calcium), ECM (Albumin), apoptosis (Flow Cytometry).
- *In Vivo*: Smooth (0.1 μm Ra) and rough (2.0 μm Ra) PEEK/-HA/CF threaded implants in dog mandible (8 weeks). Evaluated trabecular architecture (Micro-CT), osteogenic activity (Calcein, Tetracycline Histology).
- [1]Statistically Significant for 2.0 μm Ra ($p < 0.05$).

REFERENCE

Deng et al, Int J Nanomedicine. 2015; 17;10:1425-47.

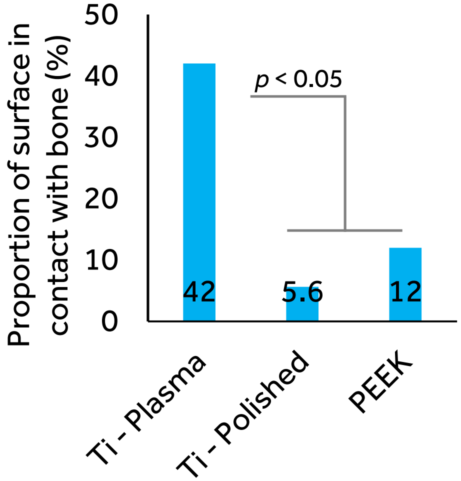
Implant Texture & Bone Response

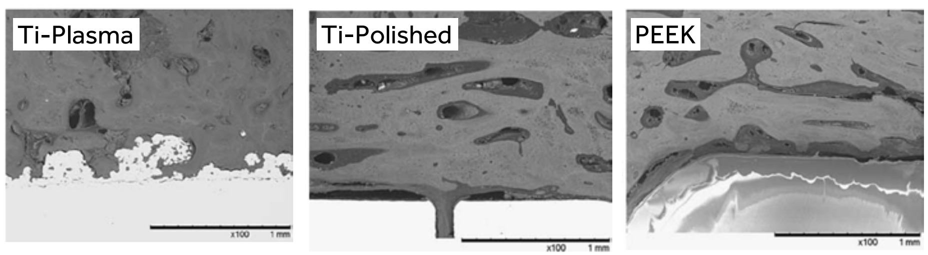
Pelletier et al

OBJECTIVES: To compare fusion rates between PEEK and Ti interbody fusion devices in sheep spine model.

RESULTS:

- Fusion rates did not differ between Ti and PEEK interbody implants.
- Plasma-treated Ti surfaces compared to polished Ti and PEEK surfaces:
    - More bone-implant contact[1] compared to polished Ti surfaces and PEEK surfaces.
    - Less direct fibrous tissue contact.





SEM of implants in sheep spine model. Ti-Plasma treated surfaces had greater proportion of surface in contact with bone with less direct fibrous tissue contact than Ti-Polished surfaces and PEEK.

INSIGHT: Surface roughness promotes bone-implant contact *in vivo* which can lead to increased bone-implant contact and stability.

DESIGN

- TI (with both plasma-treated and polished surfaces) and PEEK interbody implants in sheep spine model in a 2 adjacent level (L2-L4) ALIF procedure (26 weeks). Evaluated bone-implant interface (SEM).
- [1]Statistically Significant ($p < 0.05$).

REFERENCE

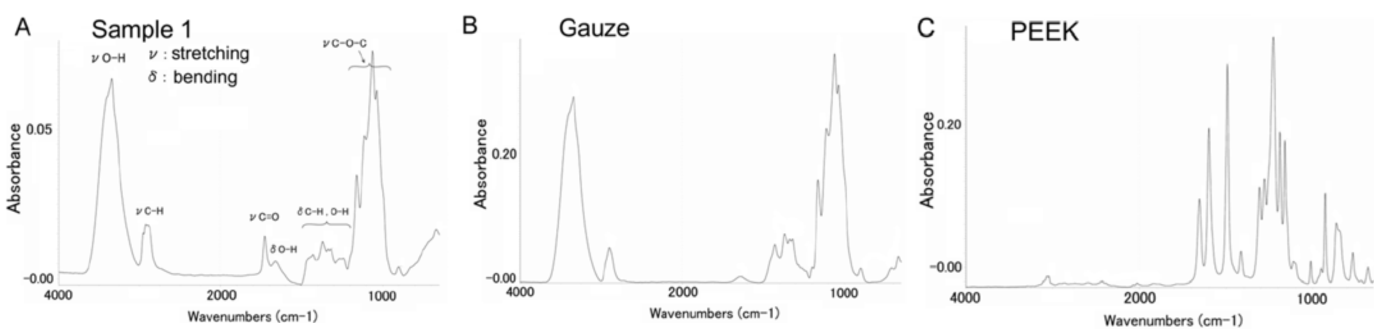
Pelletier et al, Clin Spine Surg. 2016; 29(4):E208-14.
Study Supported by SeaSpine.

Osteolytic Defects
Takenake et al

OBJECTIVES: Identification and evaluation of foreign body particles at a vertebral osteolytic defect.

RESULTS:

- Samples obtained from patient with vertebral osteolytic defect after PLIF surgery with two PEEK interbody cages contained collagenous connective tissue, bone fragments, consistent with noninfectious pseudarthrosis.
- Samples also included foreign body-type, multinucleated giant cells with 10 µm particles.
- FTIR spectroscopy suggests particles to be natural cellulose derived from cotton gauze.



FTIR Spectroscopy on foreign particles (sample 1) at vertebral osteolytic defect suggests it is derived from cotton gauze.

INSIGHT: Vertebral osteolytic defects in some instances may be aseptically induced by foreign particles, such as cotton gauzes.

DESIGN

- Case Report
- 69 year old, leg and low back pain, grade 1 isthmic spondylolisthesis at L5.
- Initial operation: PLIF at L5-S1 & 2 PEEK cages. Postoperatively, patient free from remarkable pain for 14 months where MRI revealed cystic lesions between L5-S1 endplates. CT at 16-19 months revealed vertebral osteolytic defect.
- Revision operation (21 months post first surgery): ALIF. Original PEEK removed. 3 samples removed for analysis (Histology, FTIR). Postoperative, reduced vertebral osteolytic defect at 6 months and without remarkable pain.

REFERENCE

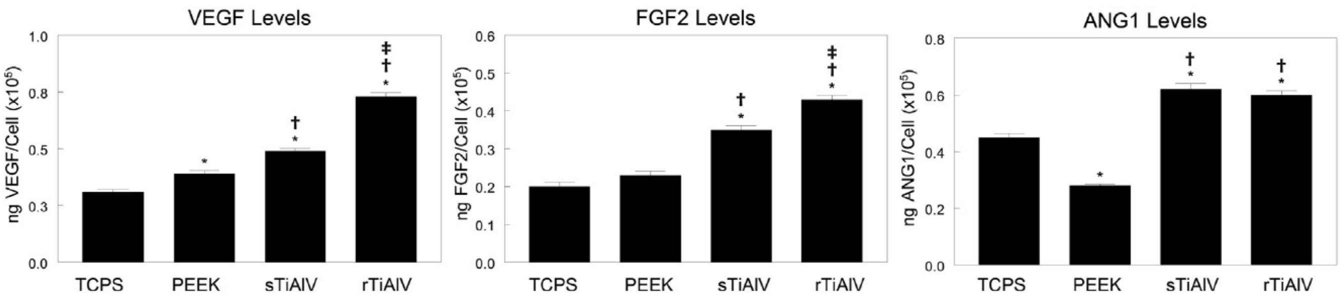
Takenaka et al, J Neurosurg Spine. 2014; 21(6):877-81.

Topography & Chemistry on Bone Biology
Olivares-Navarrete et al

OBJECTIVES: To evaluate the response of growth factors of osteoblasts to different topography (rough vs smooth Ti6Al4V) and chemistry (PEEK vs Ti6Al4V).

RESULTS:

- Rough Ti6Al4V promoted secretion of some bone growth factors[1] and some angiogenic factors[1], and expression of differentiated integrin markers[1] in osteoblasts compared to smooth Ti6Al4V.
- Ti6Al4V promoted secretion of some bone growth factors[1] and angiogenic factors[1], and differentiated integrin markers[1] in osteoblasts compared to PEEK.



Levels of secreted protein factors related to angiogenesis from osteoblasts when cultured on different substrates. * $p < 0.05$ vs TCPS (control), † $p < 0.05$ vs PEEK, ‡ $p < 0.05$ vs sTiAlV.

INSIGHT: Rough Ti6Al4V promotes the production of angiogenic and osteogenic growth factors of osteoblasts compared to smooth Ti6Al4V or PEEK.

DESIGN

- Osteoblasts (MG63) grown on PEEK, smooth or rough Ti6Al4V discs *in vitro*. Measured secreted protein bone growth factors (Osteoprotegerin, Active & Latent TGF-β1) and angiogenesis (VEGF, FGF2, ANG1) and RNA expression (Integrin A2/B1).
- [1]Statistically Significant ($p < 0.05$)

REFERENCE

Olivares-Navarrete et al, Spine J. 2013; 13(11):1563-70.
Study Supported by Titan Spine.

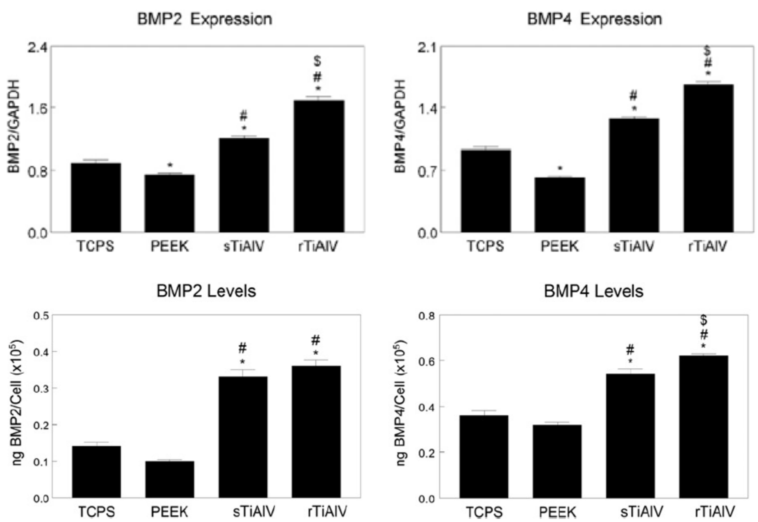
Topography & Chemistry on Bone Biology

Olivares-Navarrete et al

OBJECTIVES: To evaluate the phenotype of osteoblasts on different topography (rough vs smooth Ti6Al4V) and chemistry (PEEK vs Ti6Al4V).

RESULTS:

- Rough Ti6Al4V promoted expression and secretion of some bone growth factors[1] with a more differentiated phenotype[1] compared to smooth Ti6Al4V.
- Ti6Al4V promoted expression and secretion bone growth factors[1] with a more differentiated phenotype[1] compared to PEEK.



Expression (top) and level secreted (bottom) of protein factors related to osteogenesis from osteoblasts when cultured on different substrates. * $p < 0.05$ vs TCPS (control), # $p < 0.05$ vs PEEK, \$ $p < 0.05$ vs sTiAlV.

INSIGHT: Rough Ti6Al4V promotes the production of osteogenic growth factors and maturation of osteoblasts compared to smooth Ti6Al4V or PEEK.

DESIGN

- Osteoblasts (MG63) grown on PEEK, smooth or rough Ti6Al4V *in vitro*. Measured secreted protein and RNA expression on bone growth factors (BMP2, BMP4, BMP7). Differentiation markers (AP, Osteocalcin).
- [1]Statistically Significant ($p < 0.05$)

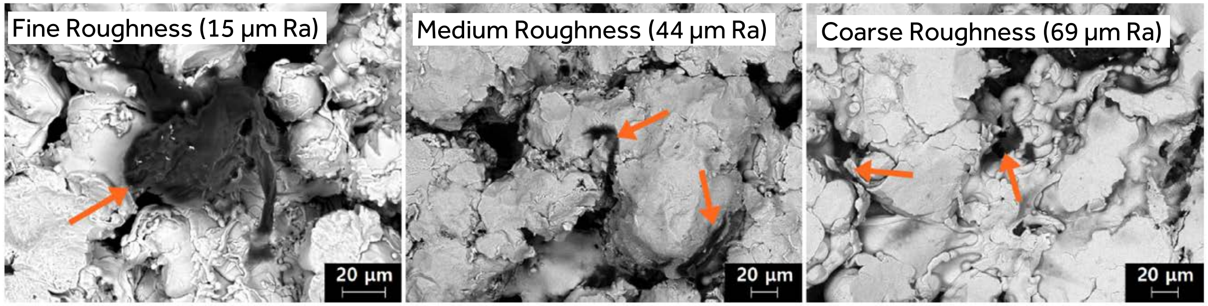
REFERENCE

Olivares-Navarrete et al, Spine J. 2012; 12(3):265-72.
Study Supported by Titan Spine.

OBJECTIVES: To evaluate the response of hMSCs to different surface roughness and polishing methods of CPTi.

RESULTS:

- Finer roughness surfaces of CPTi allowed hMSCs to form stronger adhesion and greater pseudopodia extensions.
- Polishing method did not affect these phenotypes.



Environmental SEM of hMSCs cultured on different roughness CPTi-coated PEEK. Fine roughness resulted in stronger adhesion and greater pseudopodia extensions (arrows).

INSIGHT: Surface roughness regulates cell adhesion and pseudopodia extensions in hMSCs.

DESIGN

- hMSCs grown on PEEK coated with CPTi that were different in roughness (15, 44, 69 µm Ra) and polishing methods (Ti powder, Zirconium Bead) *in vitro*.

REFERENCE

Yoon et al, 2016; 16(10):1238-1243.

Acronyms

ALIF – Anterior Lumbar Interbody Fusion
ANG1 – Angiopoietin-1
AP – Alkaline Phosphatase
CPTi – Commercially Pure Titanium
CT – Computed Tomography
FGF2 – Fibroblast Growth Factor 2
FTIR – Micro-Fourier Transform-Infrared
hMSCs – Human Mesenchymal Stem Cells
MRI – Magnetic Resonance Imaging
OPG – Osteoprotegerin
PEEK – polyether-ether-ketone
PEEK/-HA/CF – carbon fiber-reinforced polyetheretherketone-nanhydroxyapatite ternary composites
PGE_2 – Prostaglandin E_2
PLIF – Posterior Lumbar Interbody Fusion
TCPS – Tissue Culture Polystyrene
TGF-β1 – Transforming Growth Factor Beta-1
Ti - Titanium
Ti6Al4V – Titanium-Aluminum-Vanadium
Ra – Average Roughness
5TiAlV – Rough Titanium-Aluminum-Vanadium
SEM – Scanning Electron Microscope
sTiAlV – Smooth Titanium-Aluminum-Vanadium
VEGF – Vascular Endothelial Growth Factor

References

Deng et al, Effect of surface roughness on osteogenesis in vitro and osseointegration in vivo of carbon fiber-reinforced polyetheretherketone–nanohydroxyapatite composite. Int J Nanomedicine. 2015; 17;10:1425-47.

Olivares-Navarrete et al, Rough titanium alloys regulate osteoblast production of angiogenic factors. Spine J. 2013; 13(11):1563-70.

Olivares-Navarrete et al, Osteoblasts exhibit a more differentiated phenotype and increased bone morphogenetic protein production on titanium alloy substrates than on poly-ether-ether-ketone. Spine J. 2012; 12(3):265-72.

Pelletier et al, PEEK Versus Ti Interbody Fusion Devices: Resultant Fusion, Bone Apposition, Initial and 26-Week Biomechanics. Clin Spine Surg. 2016; 29(4):E208-14.

Schwartz et al, Effect of micrometer-scale roughness of the surface of Ti6Al4V pedicle screws in vitro and in vivo. J Bone Joint Surg Am. 2008; 90(11):2485-98.

Takenaka et al, Vertebral osteolytic defect due to cellulose particles derived from gauze fibers after posterior lumbar interbody fusion. J Neurosurg Spine. 2014; 21(6):877-81.

Yoon et al, Optimizing surface characteristics for cell adhesion and proliferation on titanium plasma spray coatings on polyetheretherketone. Spine J. 2016; 16(10):1238-1243.

Disclaimers

Intended use of document: The Evidence Matrix is an interactive PDF that highlights key literature on the impact of topography (surface roughness) and chemistry of spinal implants on bone and its integration through *in vitro* and *in vivo* studies. This document is intended for educational purposes only. Spinal implants from all manufacturers and study sponsors are included in an attempt to provide an objective discussion.

Indications: The ARTiC-L™ 3D Ti Spinal System with TiONIC™ technology is indicated for use as an intervertebral body fusion device in skeletally mature patients with degenerative disc disease (DDD - defined by discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies) at one or two contiguous levels of the lumbar spine (L2-S1). Additionally, the ARTiC-L™ 3D Ti Spinal System with TiONIC™ technology can be used in patients diagnosed with spinal deformities as an adjunct to fusion. These patients should be skeletally mature and have undergone 6 months of non-operative treatment prior to surgery. These implants are used to facilitate fusion in the lumbar spine using autogenous bone and/or allogenic bone graft comprised of cancellous and/or corticocancellous bone graft. When used as an interbody fusion device, these implants are intended for use with supplemental internal fixation systems.

Disclaimer: See the device manual for detailed information regarding the instructions for use, the implant procedure, indications, contraindications, warnings, precautions, and potential adverse events. For further information, contact your local Medtronic representative and/or consult the Medtronic website at www.medtronic.ca.

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