Advances in Surface Engineering of Spine Implants to Stimulate *Biologic* Responses

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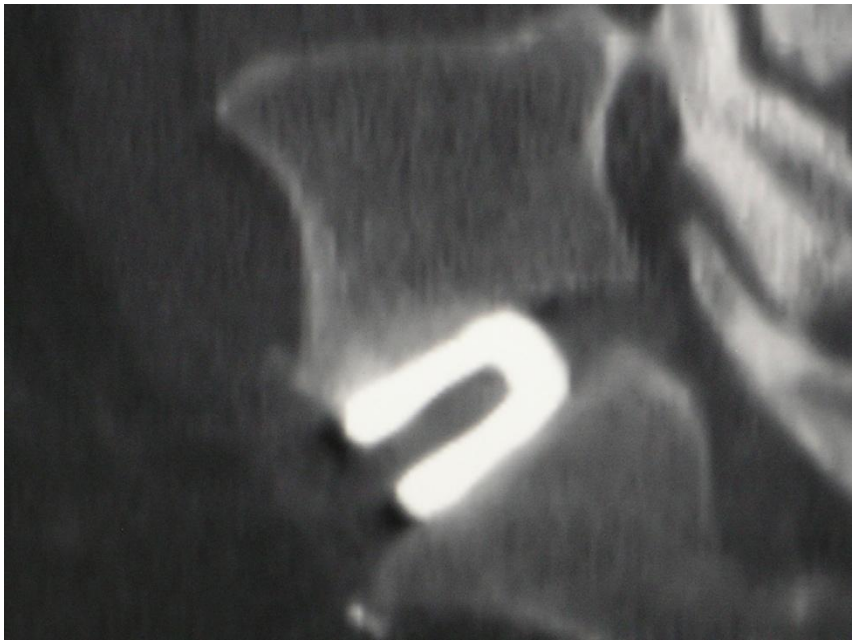
San Francisco Spine Institute

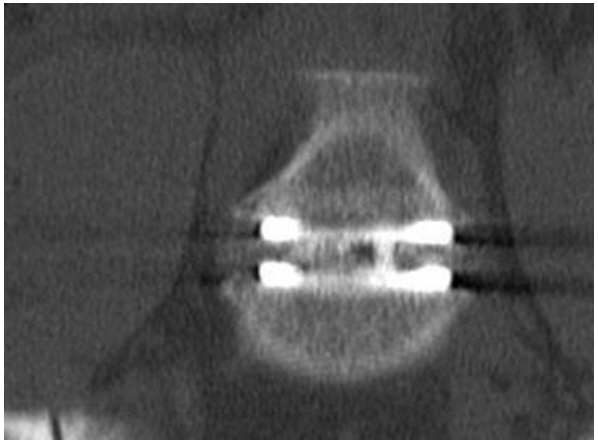
Disclosures

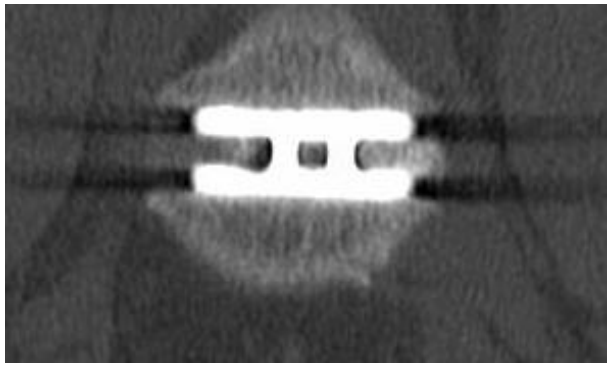
- Titan Spine, LLC: Consulting fees, royalties

Implant Surface Osseous Integration

Emerging area of interest in spine







Surface Matters

- “Surface technology is a complete blind spot to most spine surgeons. It’s because spine surgeons have been brainwashed to think the implant doesn’t matter, or else we wouldn’t be putting plastic in between two bones and hoping it will fuse.”
  - Paul Slosar, MD

Surface Matters

- “Our research shows that a small change in implant surface structure at the sub-micron level has a large impact on the bone formation response that is created. The osteogenic environment created by a nano-scale titanium surface may enhance implant stability and fusion.”
  - Barbara Boyan, Ph.D.

WHY TITANIUM?

Bone has a natural affinity for titanium

"Nature allows bone cells to attach to the titanium surface and the result is a firm and permanent anchorage for a prosthetic reconstruction."

-Branemark (father of dental osseointegration)

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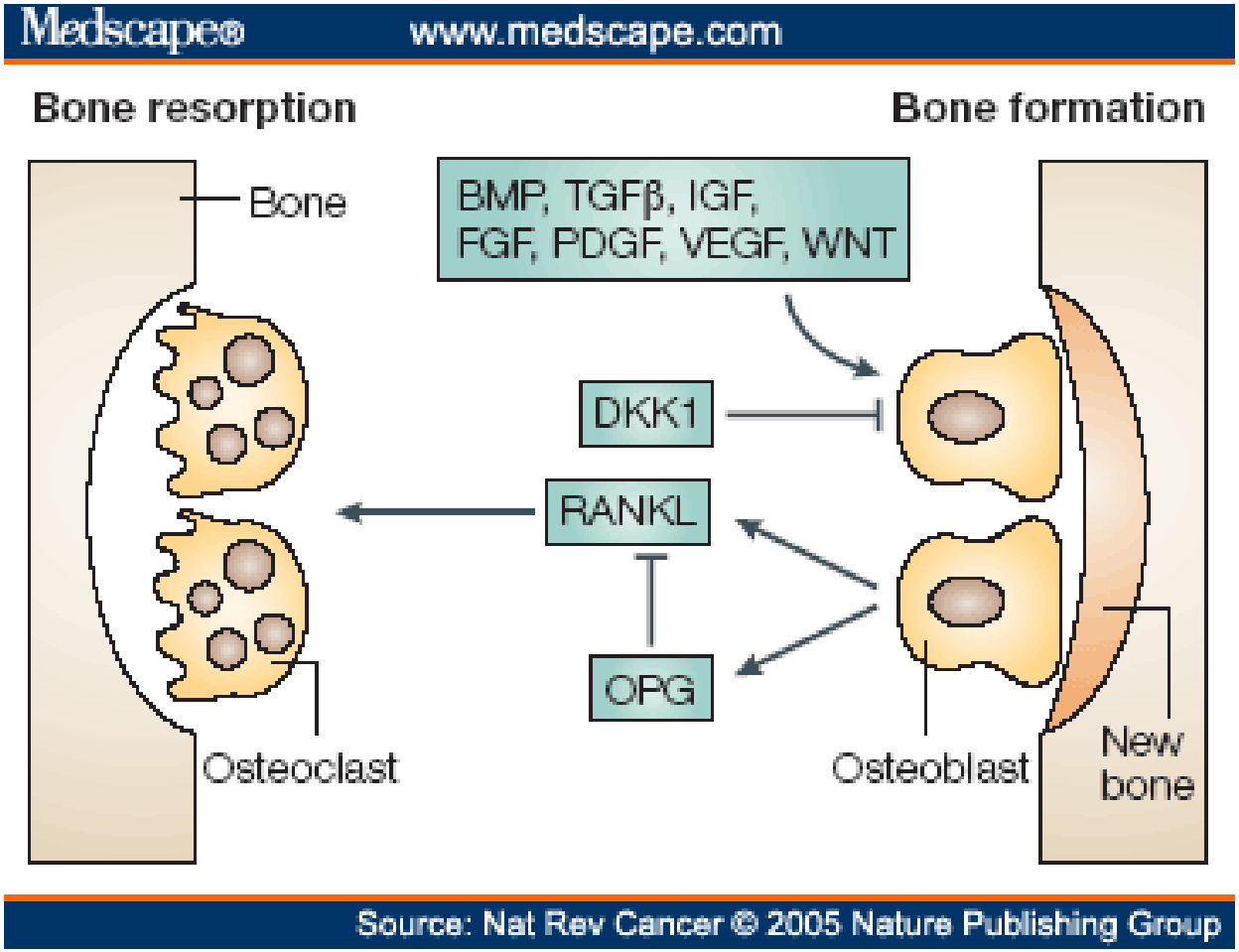
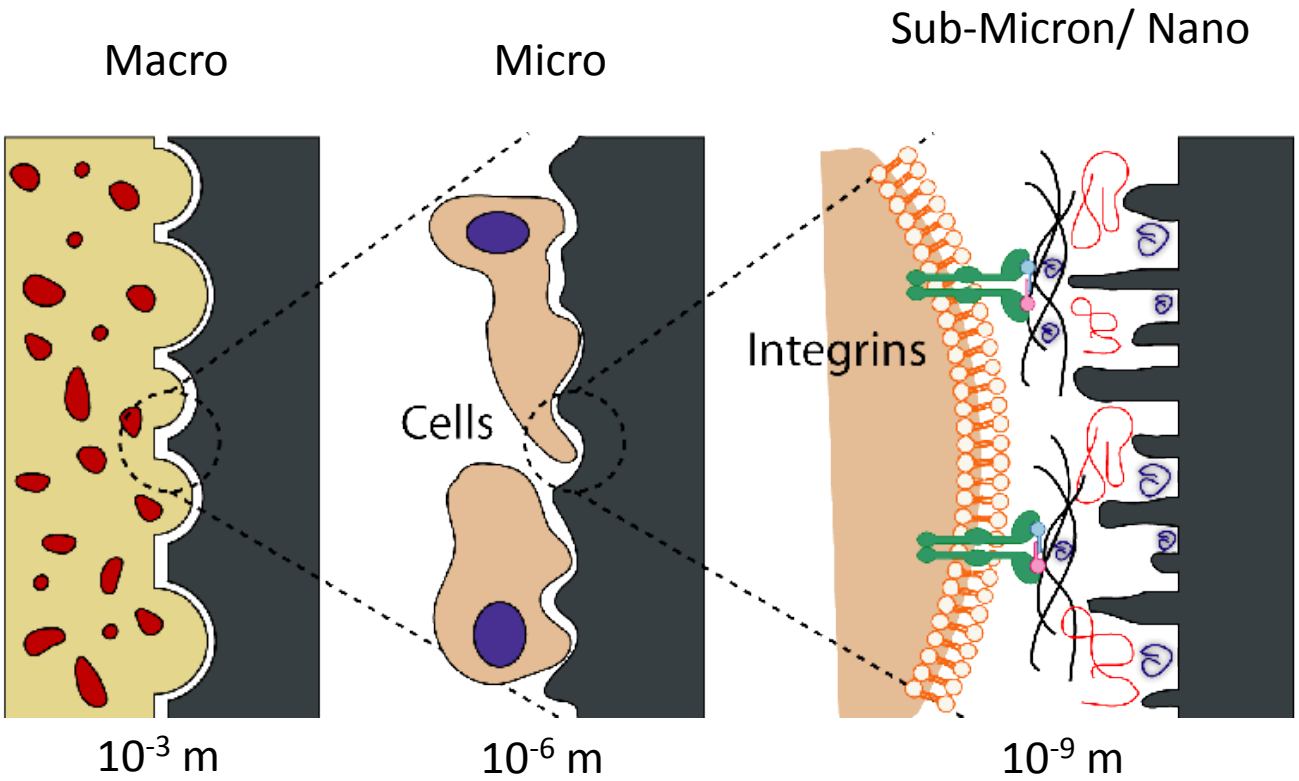
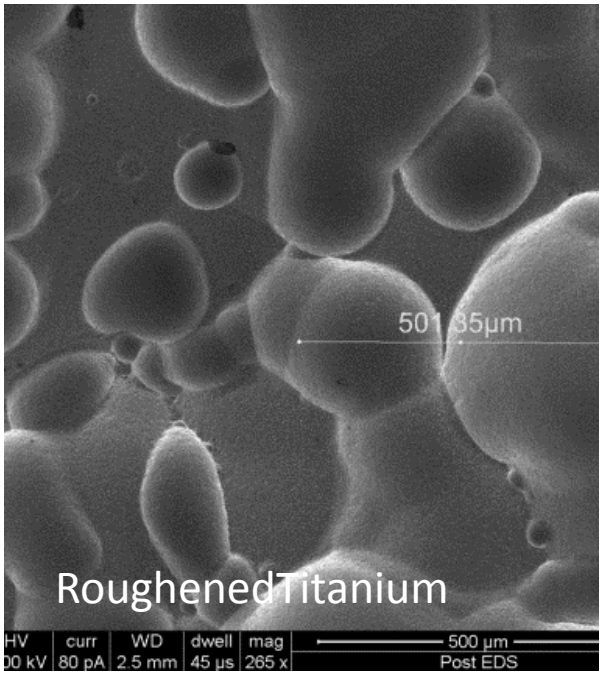
Bone Physiology

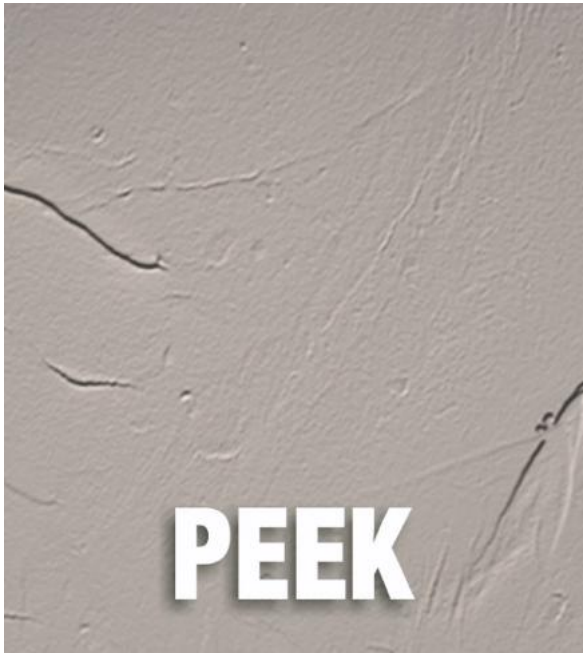


Cells interact at micron/ nano scale



Surface:
Material and Topography





Surface <u>chemistry</u> and <u>topography</u> affect:

- Surface energy
- Protein adsorption

Drive a favorable cellular response (fusion)

Terms

- **Macro** is texture you can **feel**
  - Primary benefit is mechanical; resistance to migration
  - Concerns about a Macro Rough surface damaging endplates (subsidence)
  - Too much “Macro” impedes device insertion
- **Micro** is scale visible with Electron Microscope
  - **Micron 10^{-6} / Nano 10^{-9}**
  - Primary benefit is <u>cellular</u> response
  - Stimulate interactions with Host bone
- **Porous/ Porosity**
  - Size/ Space for bone to grow
  - Just because there is space doesn’t mean bone will grow into it
  - Smooth Ti (Electron Microscopy)

Surface Hierarchy

- **Macro** level (10^{-3}m): anti-expulsion surface (not important to cells)
- **Micron** level (10^{-6}m): Osteoclastic-like pits that allow osteoblast insertion and circumvent the *resorptive* phase of bone remodeling
- **Nano** level (10^{-9}m): nano-scale features bind with stem cell membrane through proteins
  - up-regulation of osteoblasts, down-regulation of osteoclasts, and up-regulation of angiogenesis

PEEK vs. Titanium

- PEEK is a polymer
  - Spine market (almost exclusively)…no other significant use for other bone applications
  - New offerings: PEEK coated with Ti
  - Radiolucent
  - Modulus of Elasticity (Irrelevant)
  - Fibrous tissue at contact surface between PEEK and host bone

PEEK vs. Titanium

- Titanium
  - Widely used across all many Bone applications
  - Bio-compatible
  - Compatible with MRI and CT
  - Bone ingrowth directly onto surface of some Implants (surface dependent)
  - (Re-) Emerging as the material of choice for interbody fusion implants

Ti Plasma Spray Coatings (TPS)

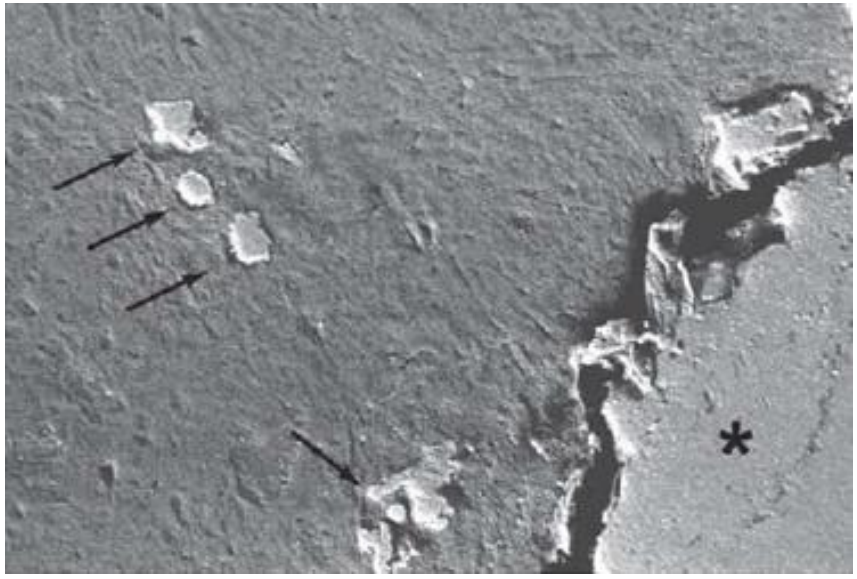
(plasma spray abandoned years ago in Dental industry)

- PEEK + Ti (plasma spray)
- Bone-implant interface
  - *smooth* Ti (micron-scale)
  - Rough> smooth> PEEK
- Plasma spray Ti
  - **Delamination risk**
  - Particulate debris
- MOE
  - **Not clinically relevant**
  - All spine implants have substantially higher MOE than host bone
- Radiolucent

!!!!

COATINGS ON TITANIUM

- Ti particulate debris/shedding has been observed following implantation in animal models
  - Franchi 2004, Martini 2003, Vercaigne 1997



Osteoblastic Differentiation
Bone Morphogenetic Proteins

ELSEVIER

The Spine Journal 12 (2012) 265–272

THE SPINE JOURNAL

Basic Science

Osteoblasts exhibit a more differentiated phenotype and increased bone morphogenetic protein production on titanium alloy substrates than on poly-ether-ether-ketone

Rene Olivares-Navarrete, DDS, PhD[a], Rolando A. Gittens, MS[b], Jennifer M. Schneider, MS[c], Sharon L. Hyzy, BS[a,d], David A. Haithcock, BS[a], Peter F. Ullrich, MD[e], Zvi Schwartz, DMD, PhD[a,f], Barbara D. Boyan, PhD[a,*]

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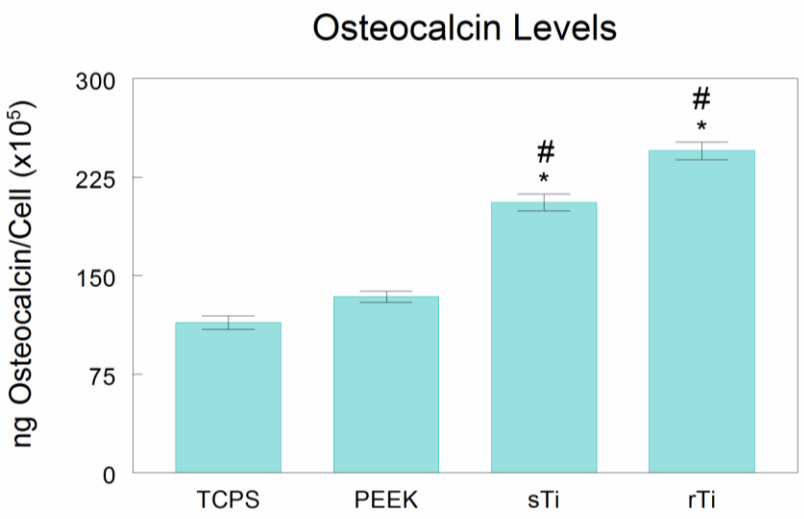
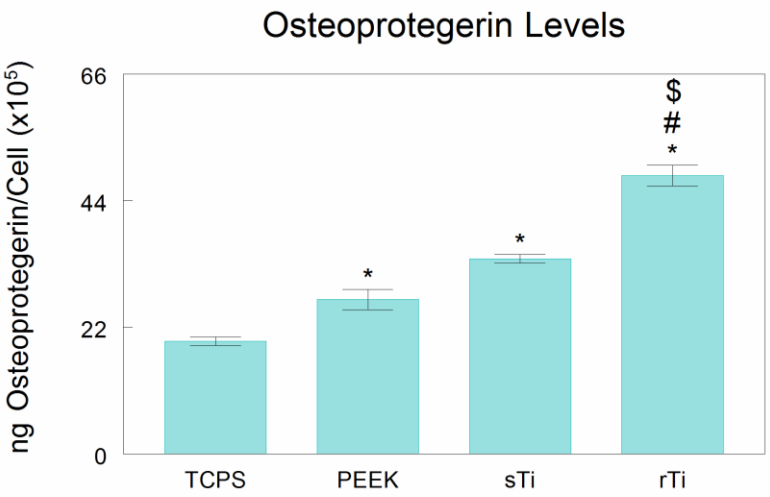
Received 1 February 2011; revised 3 October 2011; accepted 7 February 2012

Micron-rough Ti Surface Promotes Osteoblast Differentiation





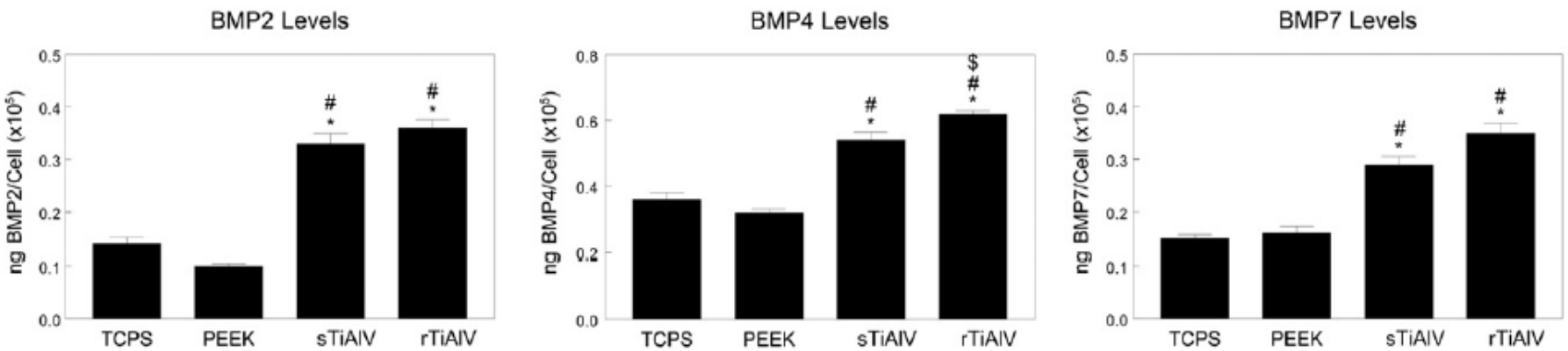
Biomarker for bone formation

"Turn off" osteoclast activity

TCPS = Tissue Culture Polystyrene
sTi = Smooth Titanium
rTi = Roughened Titanium (Micron scale)

Micron-scale Roughness > Smooth Ti> PEEK

Physiologic BMP production



Angiogenesis

ELSEVIER

The Spine Journal 13 (2013) 1563–1570

THE SPINE JOURNAL

Basic Science

Rough titanium alloys regulate osteoblast production of angiogenic factors

Rene Olivares-Navarrete, DDS, PhD[a], Sharon L. Hyzy, MS[a,b], Rolando A. Gittens, I, PhD[c], Jennifer M. Schneider, MS[d], David A. Haithcock, BS[a], Peter F. Ullrich, MD[e], Paul J. Slosar, MD[f], Zvi Schwartz, DMD, PhD[a,g], Barbara D. Boyan, PhD[a,*]

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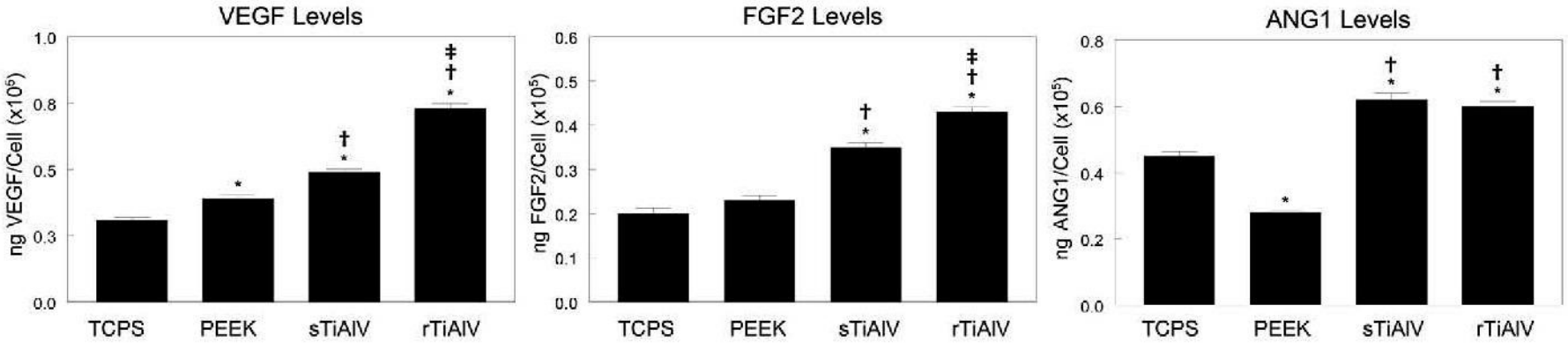
Received 3 March 2012; revised 28 November 2012; accepted 20 March 2013



IMAST 2014 PRESENTATION

Implant Materials Generate Different Peri-implant Inflammatory Factors: PEEK Promotes Fibrosis Micro-textured Titanium Promotes Osteogenic Factors*

Rene Olivares-Navarrete DDS, PhD[1]; Sharon Hyzy MS[1]; Paul J. Slosar MD[2]; Zvi Schwartz DMD, PhD[1]; Barbara D. Boyan, PhD[1]

[1]Dept. of Engineering Virginia Commonwealth University
[2]San Francisco Spine Institute

***Whitecloud Award Winner; Best Basic Science Paper; SRS/ IMAST 2014**

Scoliosis Research Society
IMAST 21ST INTERNATIONAL MEETING ON ADVANCED SPINE TECHNIQUES
VALENCIA spain JULY 16-19 2014

Introduction

- Osteoblastic differentiation of human mesenchymal stem cells (MSCs) is influenced by implant surface properties.

- PEEK
  - cells fail to exhibit increased alkaline phosphatase activity or osteocalcin production
- Titanium rough-textured (micron/ nano scale)
  - exhibit increased markers of osteoblastic differentiation

Clinical

- In-vitro studies are supported by in-vivo results examining peri-implant bone formation in sheep spine [1]

- Histologically, implants fabricated from PEEK
  - have a fibrous connective tissue surface interface
- Ti-alloy implants
  - demonstrate a close approximation with surrounding bone [1,2]

1. Schwartz et al., JBJS, 2008 2. Kurtz et al., PEEK biomaterials in trauma, orthopedic, and spinal implants. Biomaterials 2007

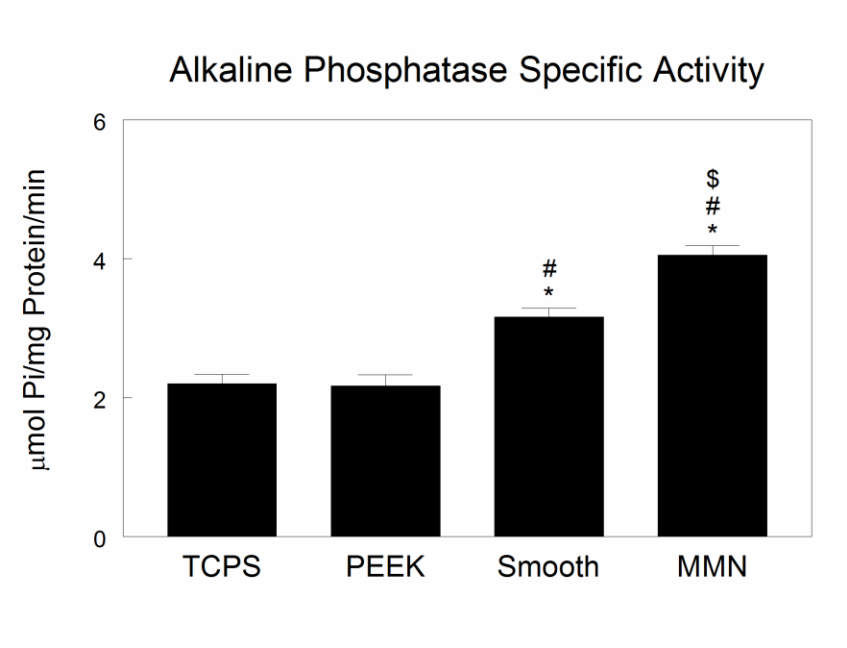
Methods

- Human MSCs cultured on
  - TCPS (tissue culture polystyrene) control
  - PEEK
  - smooth Ti-alloy (smooth Ti)
  - Micron / nano rough Ti-alloy (MMN) disks

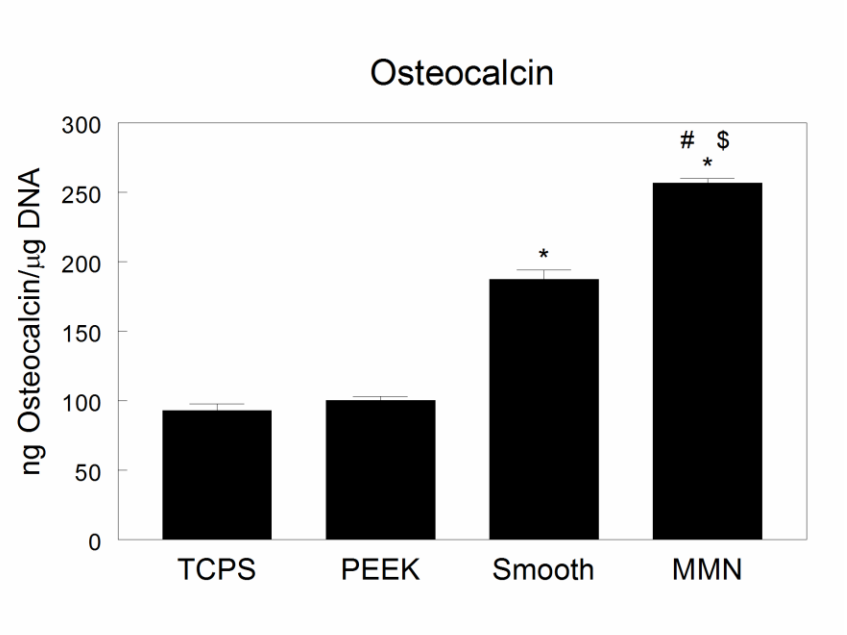
- Cell morphology and osteoblastic differentiation were assessed

- mRNAs for pro-inflammatory cytokines were measured and fold changes compared to control
  - 2x fold change considered significant

Osteoblastic Phenotype



Early marker

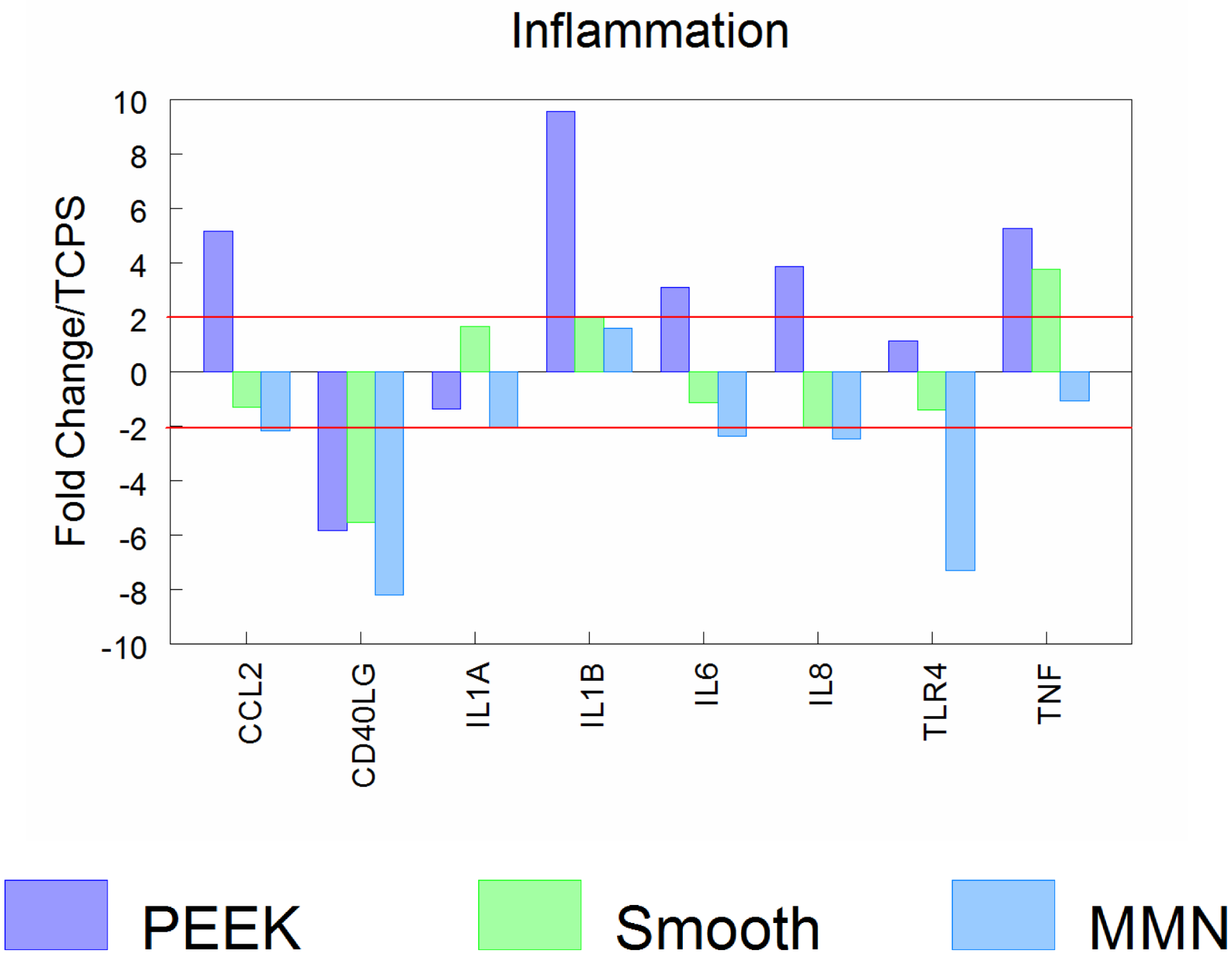


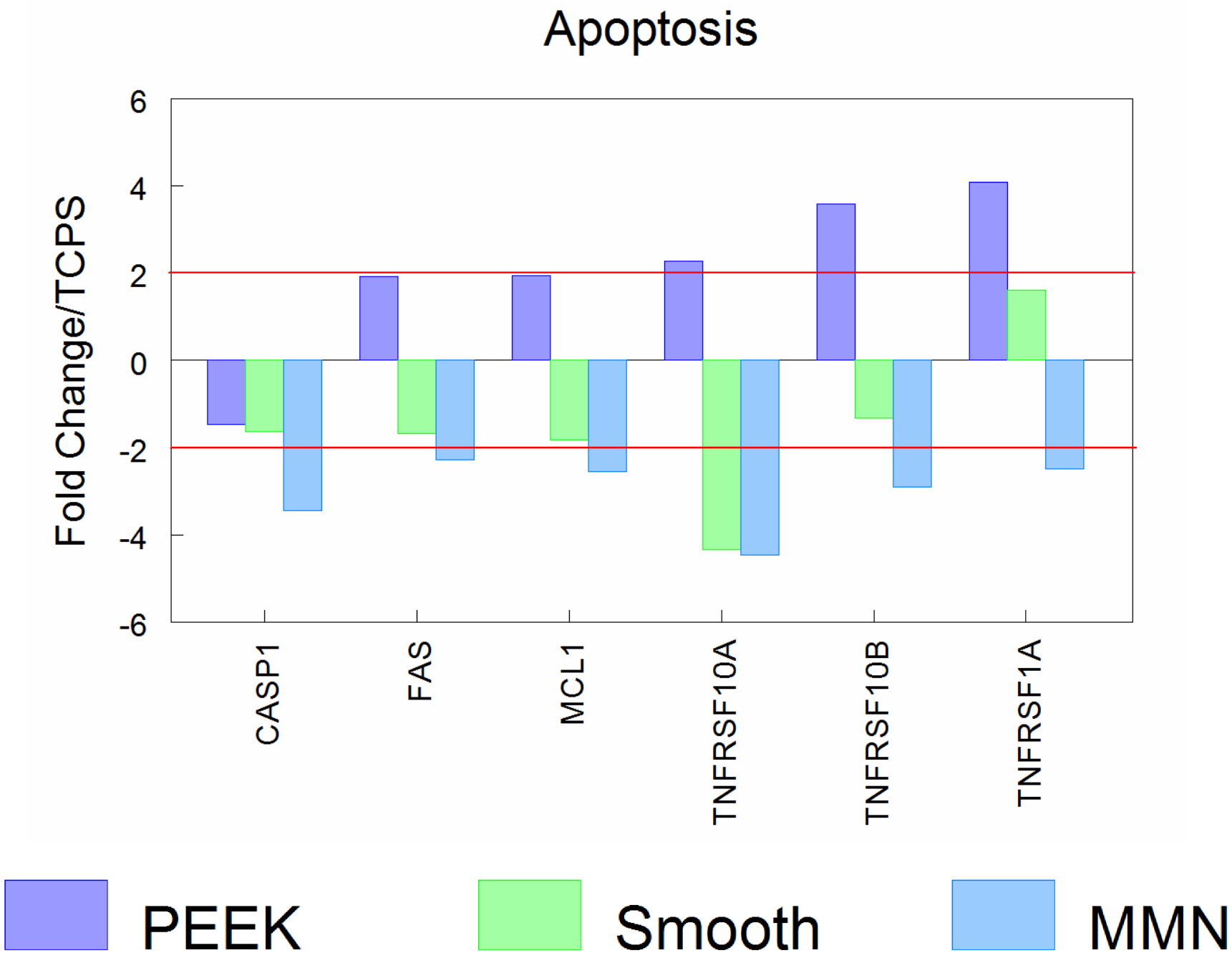
Later marker

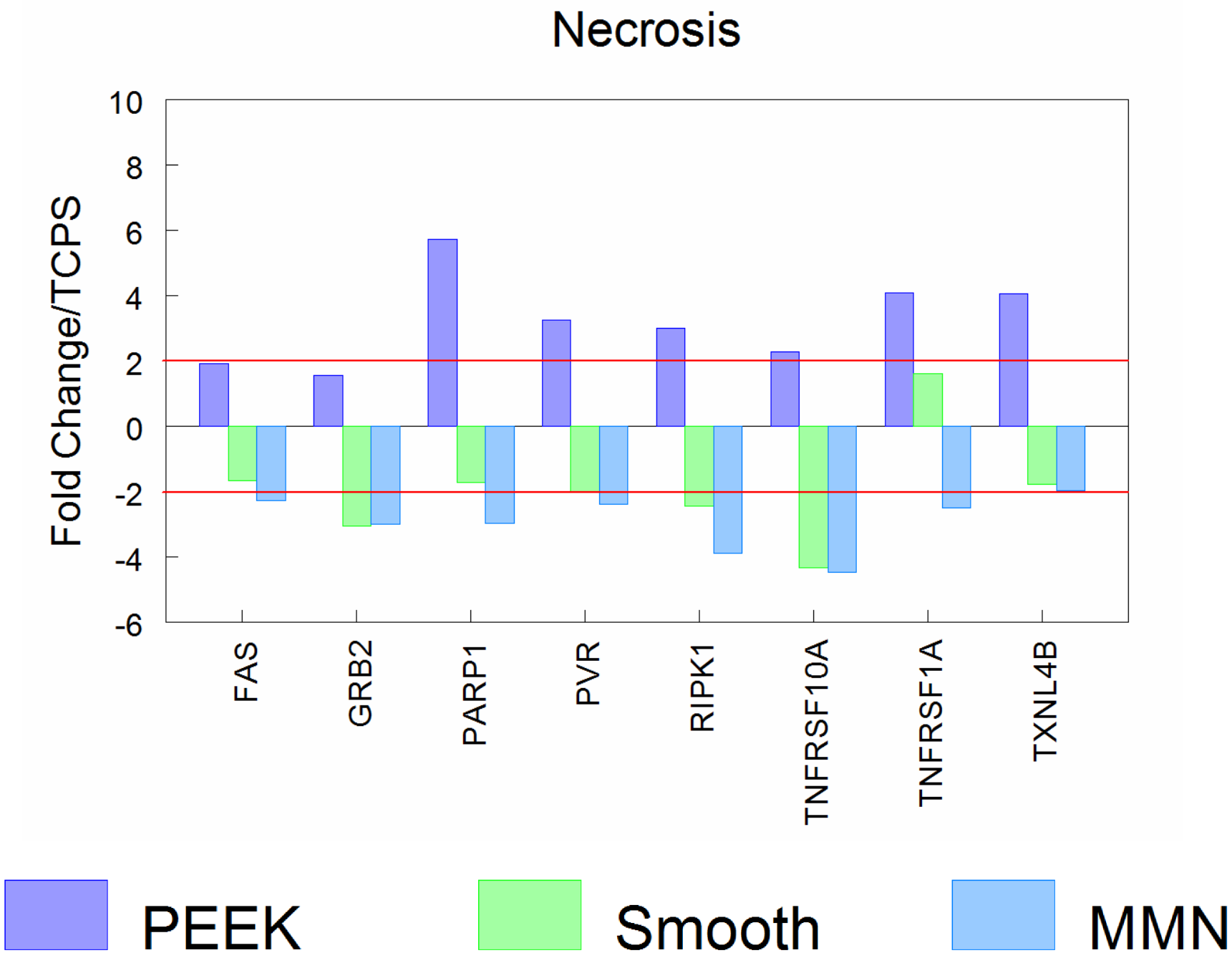
* vs TCPS

\# vs PEEK

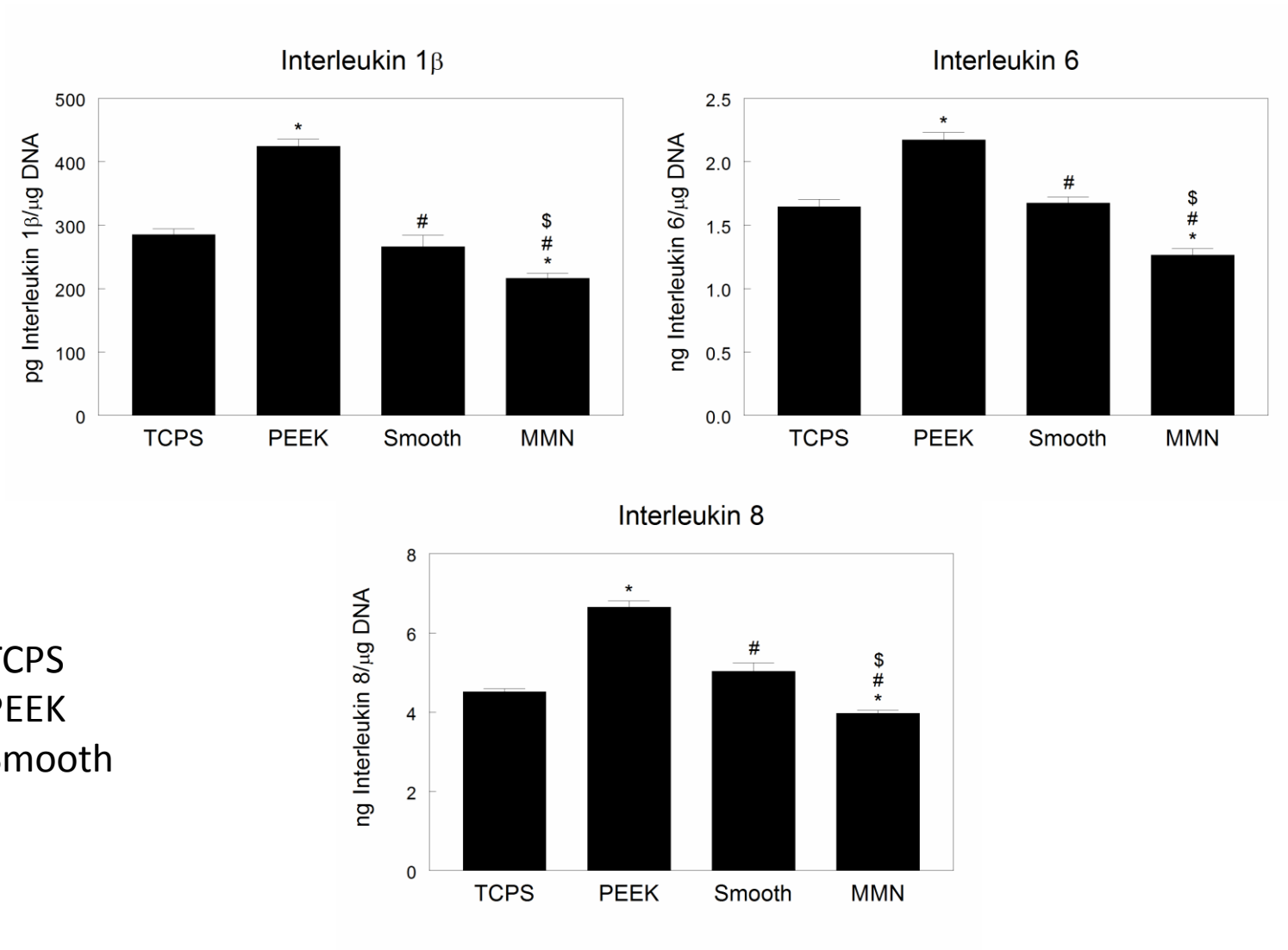
$ vs Smooth


Inflammation
Fold Change/TCPS
10
8
6
4
2
0
-2
-4
-6
-8
-10
CCL2
CD40LG
IL1A
IL1B
IL6
IL8
TLR4
TNF
PEEK
Smooth
MMN


Apoptosis
Fold Change/TCPS
6
4
2
0
-2
-4
-6
CASP1
FAS
MCL1
TNFRSF10A
TNFRSF10B
TNFRSF1A
PEEK
Smooth
MMN


Necrosis
Fold Change/TCPS
10
8
6
4
2
0
-2
-4
-6
FAS
GRB2
PARP1
PVR
RIPK1
TNFRSF10A
TNFRSF1A
TXNL4B
PEEK
Smooth
MMN

Pro-inflammatory Interleukins



* vs TCPS
\# vs PEEK
$ vs Smooth

Discussion

- We previously reported that cells on micro-textured Ti produce pro-angiogenic and pro-osteogenic factors whereas those on PEEK do not [1,3,4].
  - BMP 2, 4; VEGF
- Human MSC's respond to the surface characteristics of implants
  - Cytokine mediators drive osteoblastic vs. fibroblastic cell transformation
  - Micron/ Nano (10^{-9}) scale topography is what a MSC cell "sees"

3. Olivares-Navarrete et al., Spine J, 2012. 1. Schwartz et al., JBJS, 2008. 4. Slosar et al., ISASS, 2013.

Conclusion

- PEEK promotes Fibrosis Environment
  - Hypo-vascular
  - High Inflammatory cytokine micro-environment
  - Poor Cell Viability (spindle/ ↑apoptosis/ hypocellular)

- Micron Nano Ti promotes Osteogenic Environment
  - Angiogenesis / BMP
  - Low inflammation
  - Good Cellular viability (robust/ low apoptosis/ no necrosis)

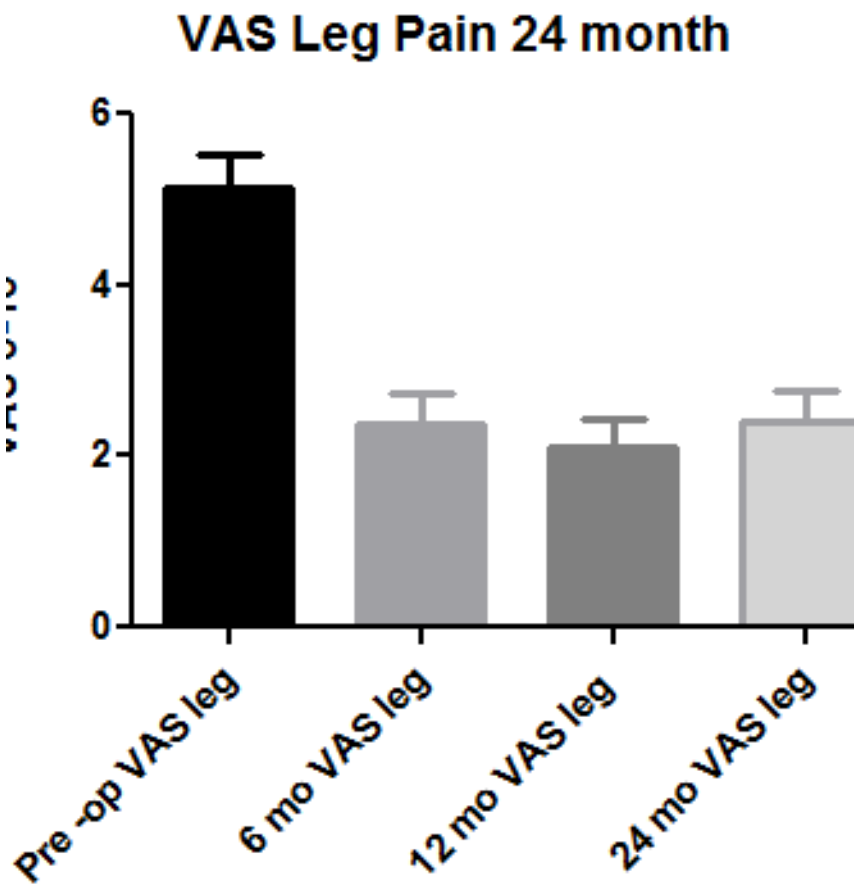
CLINICAL AND RADIOGRAPHIC OUTCOMES OF PAINFUL LUMBAR DISC DEGENERATION FOLLOWING INTERBODY FUSION

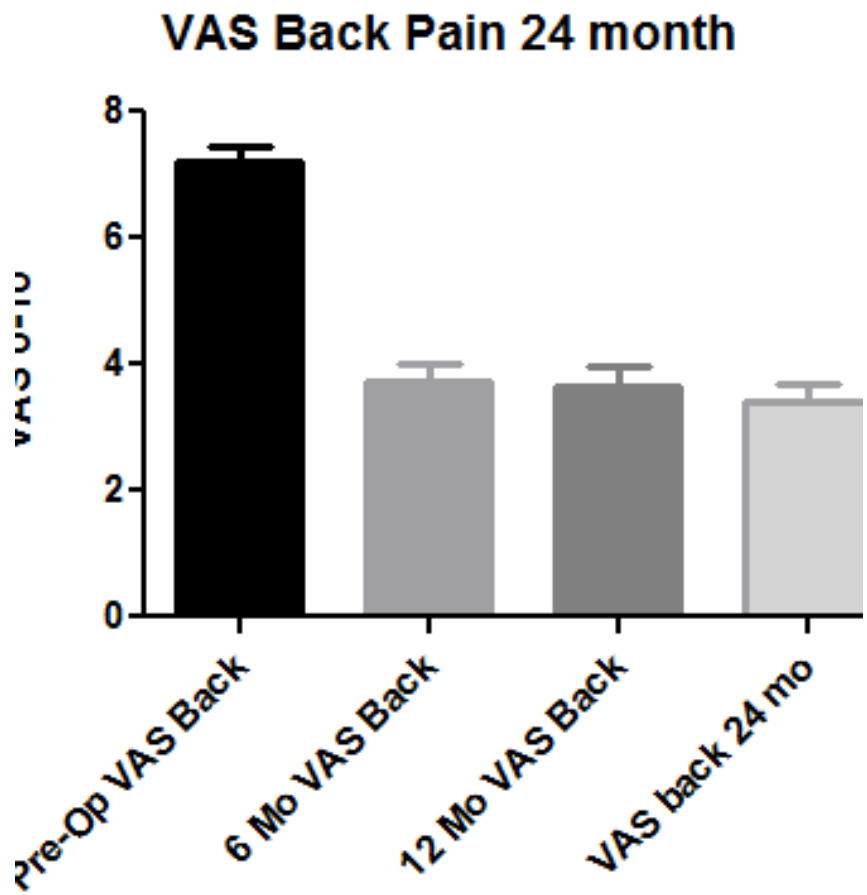
A Prospective Study of a Unique Lumbar Interbody Fusion Implant; Clinical and Radiographic Outcomes at 1 and 2 year follow up

Paul J. Slosar, Adam Cabalo, James B. Reynolds

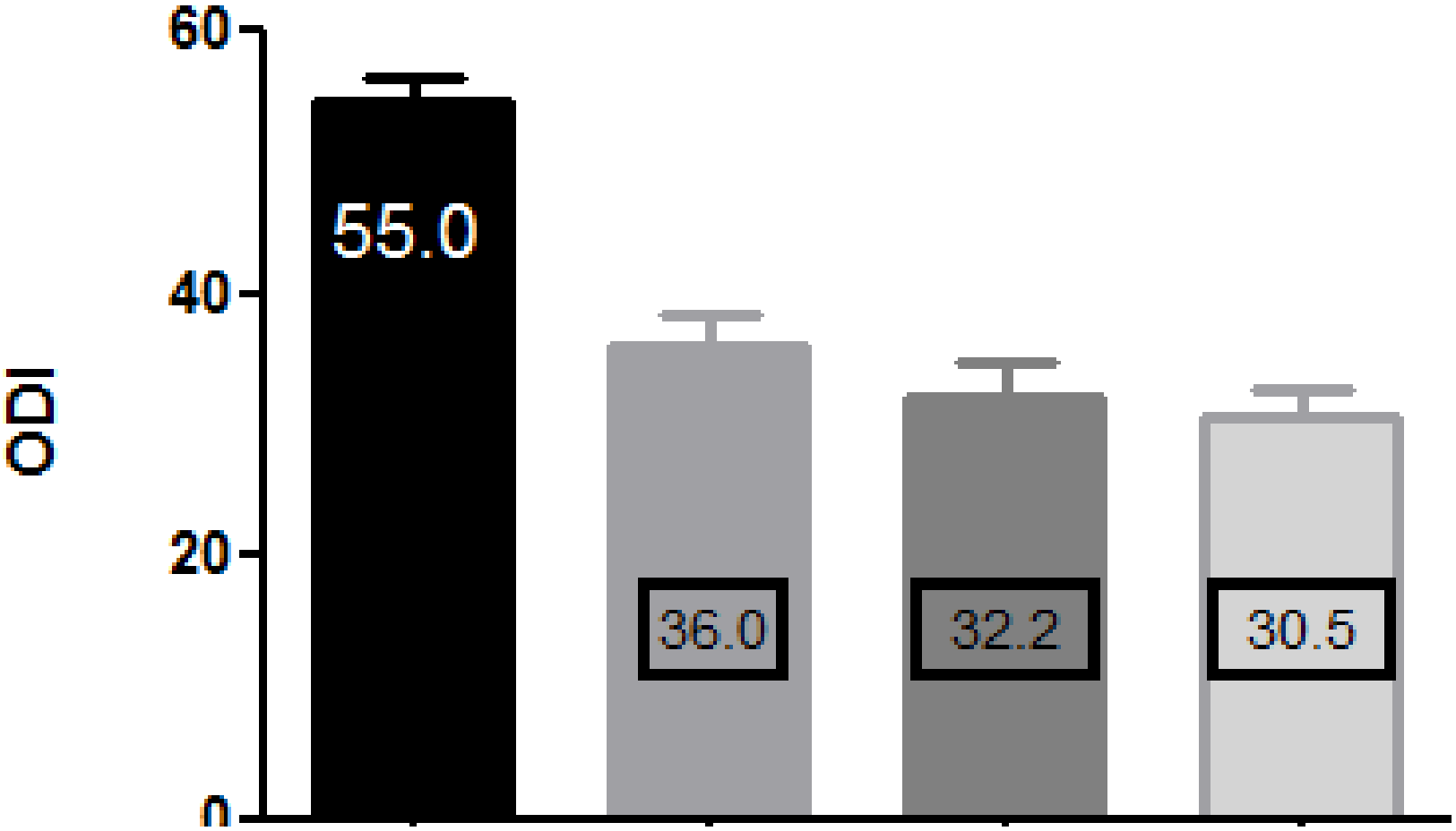
SpineCare Medical Group/ San Francisco Spine Institute

Clinical Outcomes





Clinical Outcomes



Clinical Results

- Meaningful Clinical Improvements
  - ODI >15 and VNS >3
  - Achieved in the majority of cases

- The clinical outcomes at 12 and 24 months were *not significantly different* than the results at **6 months**.

Interobserver Agreement Using Computed Tomography to Assess Radiographic Fusion Criteria With a Unique Titanium Interbody Device

Paul J. Slosar, MD, Jay Kaiser, MD, Luis Marrero, MD, and Damon Sacco, MD

Abstract

The accuracy of using computed tomography (CT) to assess interbody fusion in patients with titanium implants has been questioned in the past. Radiologists have reported difficulty assessing fusion bone quality because of metal artifact and small graft windows. A new titanium interbody implant with a large footprint and a wide graft aperture has been developed.

We conducted a study to determine the interobserver reliability of using CT to assess radiographic fusion variables with the new titanium interbody device. Patients underwent anterior lumbar interbody fusion with the same titanium interbody implant. Reconstructed CT images were obtained randomly at 6, 9, or 12 months. Two independent radiologists reviewed the scans. Interobserver reliability was calculated using the κ statistic.

Fifty-six spinal fusion levels (33 patients) were analyzed. The radiologists agreed on 345 of the 392 fusion data points reviewed ($\kappa = .88$). Agreement for solid fusion formation was 0.77.

This interbody device demonstrated minimal artifact and minimal subsidence, and trabecular bone was easily identified throughout the implant in the vast majority of cases reviewed. High interobserver agreement was noted across all radiographic variables assessed.

The American Journal of Orthopedics®
February 2015

Results

- 33 patients
- 56 spinal fusion segments
  - 17 males / 16 females
  - Average age 46 years (range 23-66 yrs)
  - 6 patients (18%) were nicotine users.

Results
Artifact/ Subsidence

Reviewer	Artifact			Subsidence	
	Grade 0	Grade 1	Grade 2	Yes	No
A	43 (77%)	12 (21%)	1 (25)	0 (0%)	56 (100%)
B	54 (96%)	2 (4%)	0 (0%)	3 (5%)	53 (95%)
Agreement	**0.80**			**0.95**	

Artifact : Grade 0: Mild; Grade 1: Moderate; Grade 2: Non-diagnostic

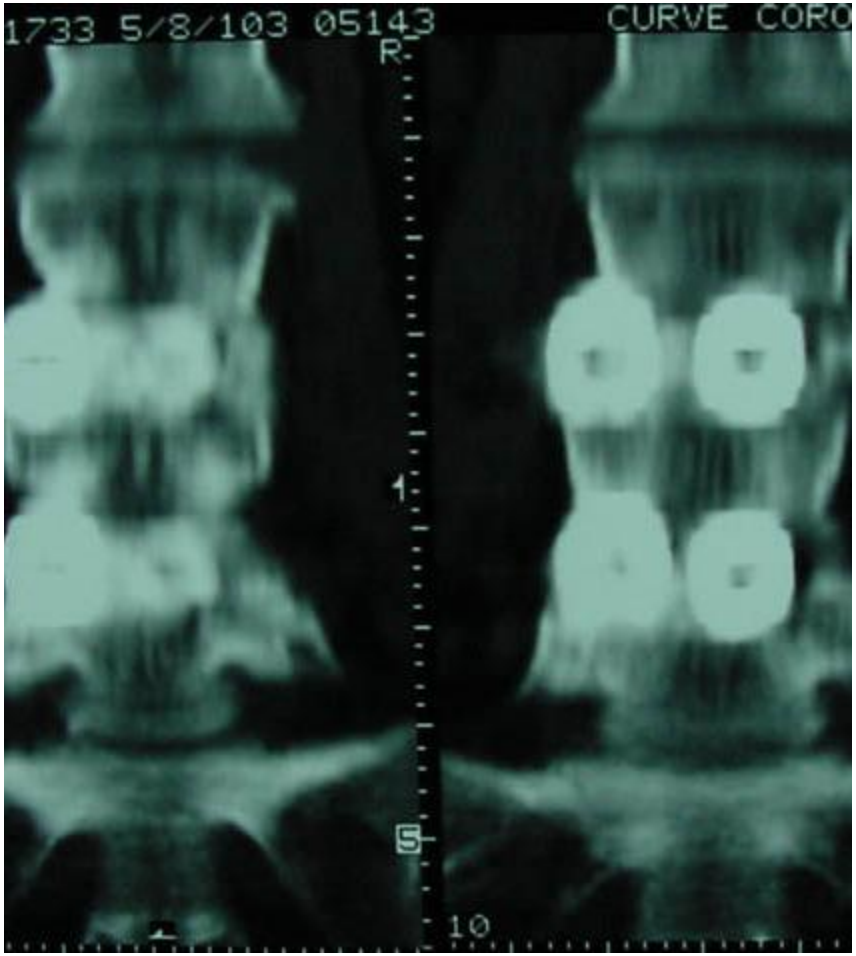
Subsidence: >3 mm

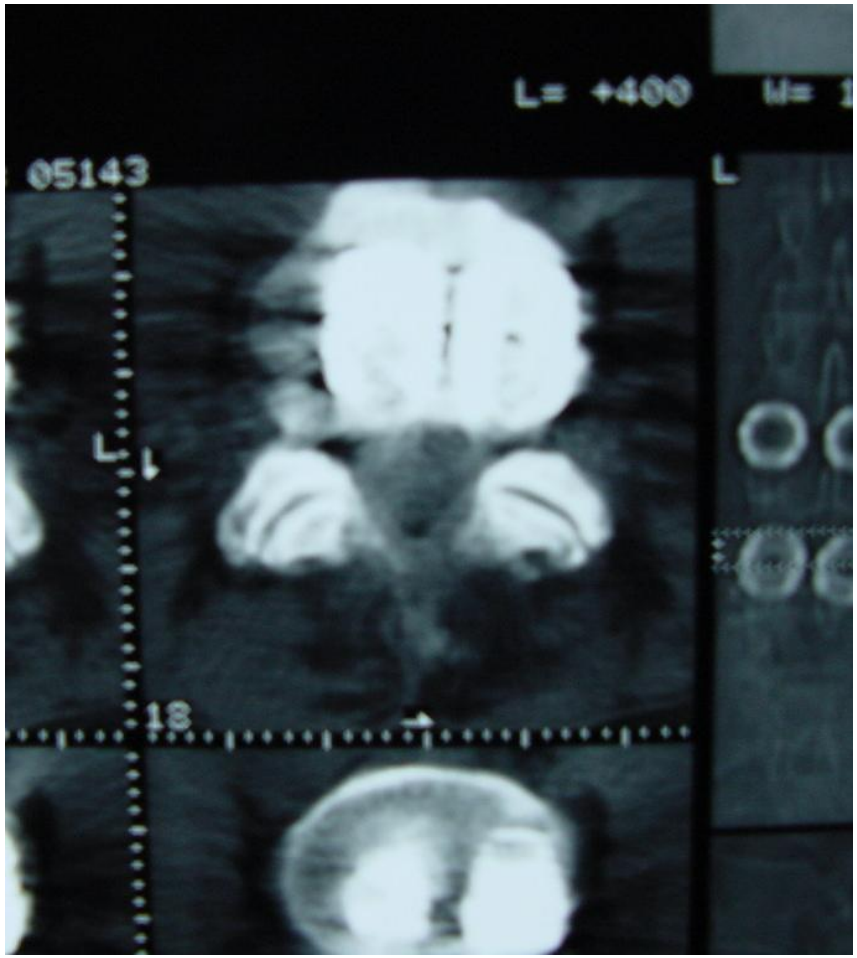
Results
Overall Fusion Grade

Reviewer	Grade 5	Grade 4	Grade 3	Grade 2	Grade 1
A	45 (80%)	8 (14%)	2 (4%)	1 (2%)	0 (0%)
B	51 (91%)	5 (9%)	0 (0%)	0 (0%)	0 (0%)
Agreement					
Same Grade	**0.77**				
Within 1 Grade	**0.95**				

Grade 5: Definitely Fused; Grade 4: Probably Fused;
Grade 3: Indeterminate; Grade 2: Probably Not Fused;
Grade 1: Definitely Not Fused

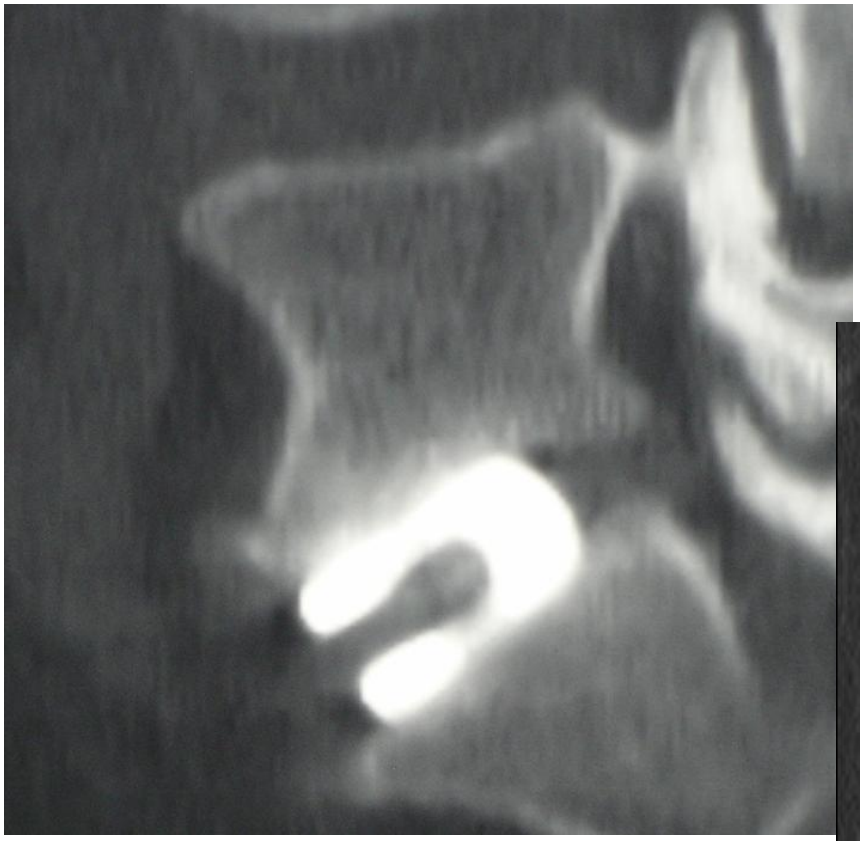
Old Titanium Technology

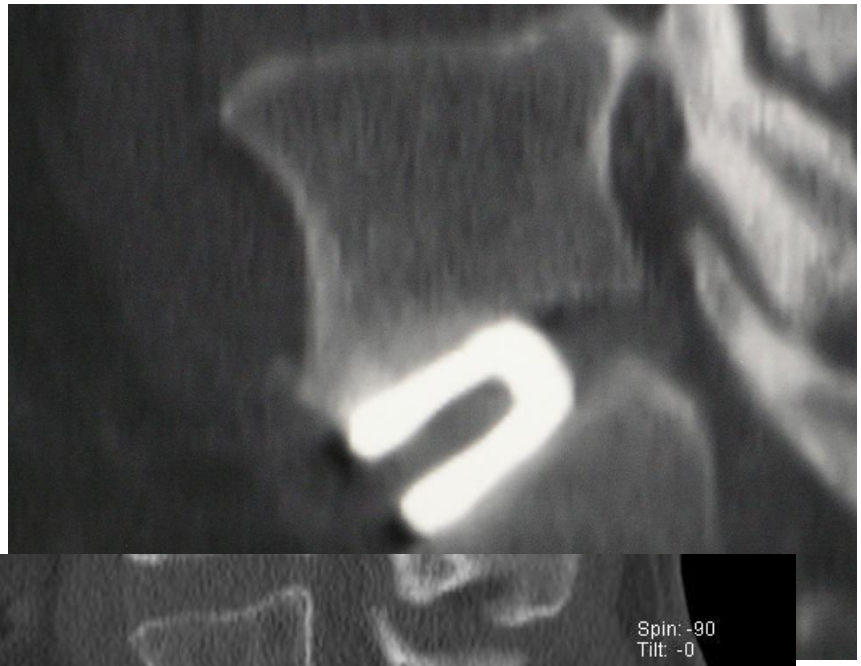




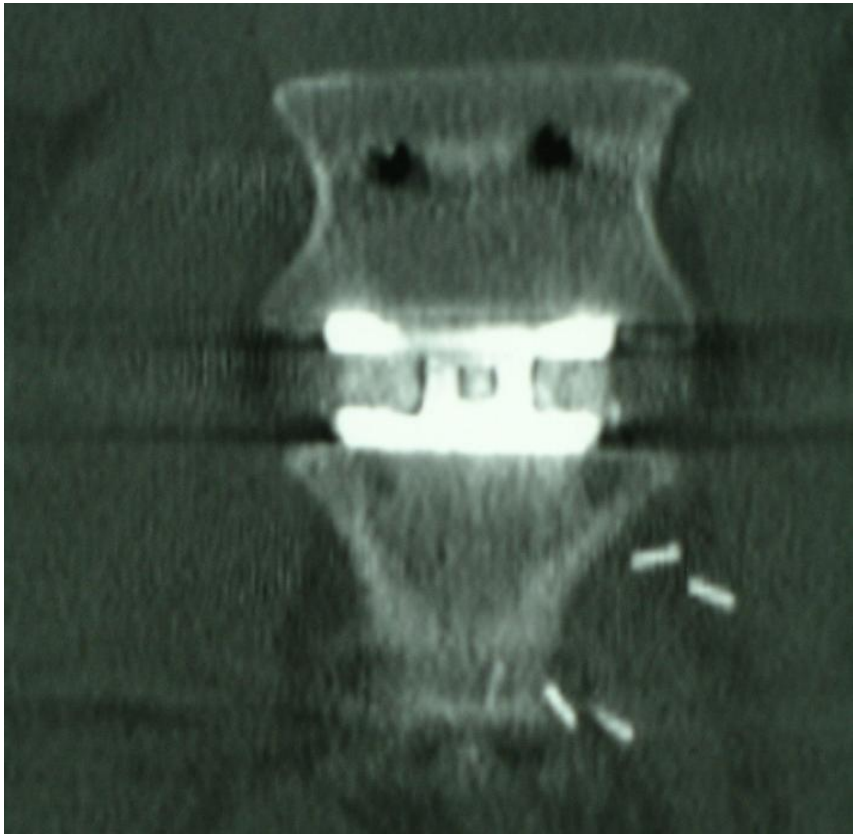
Minimal Artifact

Edge of implant

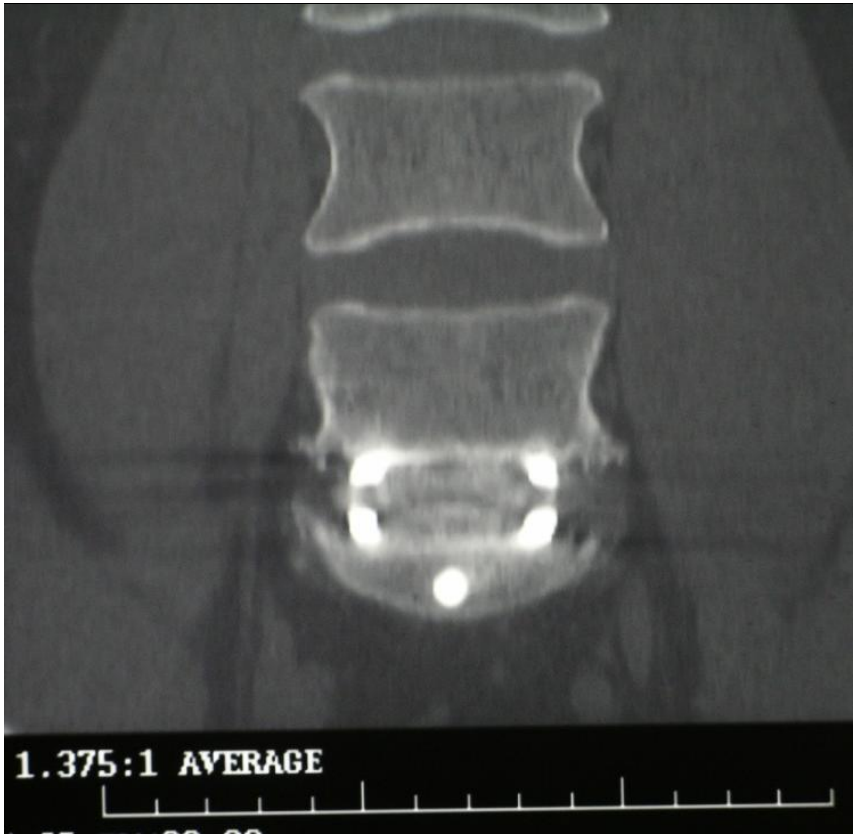




Surface integration



Linear lucency/ no subsidence



Radiographic Conclusions

- The titanium implant studied demonstrated minimal artifact, minimal subsidence, and trabecular bone was easily visualized.

- Radiographic fusion criteria <u>can be reliably assessed</u> using CT scans with a high degree of interobserver agreement.

Biological Conclusions

- PEEK
  - promotes Fibrosis Environment
- Smooth Ti
  - Better than PEEK
  - Not as effective as Micron/ Nano scale Ti
- Micron Nano Ti
  - promotes Osteogenic Environment
- PEEK with External Coatings
  - Concerning mechanical issues

Summary

- Welcome focus on the science of spine implant materials and their impact on bone physiology
  - Neutral/ Negative/ Positive
  - Implant is NOT simply a carrier for your biologic

- Evolution of the science of spine implant materials
  - Goal: Improved outcomes for patients

Thank you