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9th UHMWPE

INTERNATIONAL MEETING PROGRAM

OCTOBER 10-11, 2019

THURSDAY & FRIDAY

UNION LEAGUE OF PHILADELPHIA
DREXEL UNIVERSITY AND UNIVERSITY OF TORINO
PHILADELPHIA, PA, USA

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THE PURPOSE OF THE MEETING is to bring together engineers, scientists, clinicians, and regulators from academia, industry, and FDA and present leading-edge research on advancements in medical grade UHMWPE technology and clinical applications.

The focus of the 9th meeting is:

- advances in processing, crosslinking, and sterilization of UHMWPE
- new methods of processing clinical and retrieval studies of highly crosslinked UHMWPE (HXLPE), with a special emphasis on the performance of thin acetabular liners and knee arthroplasty
- novel UHMWPE articulations with ceramic and PEEK bearing surfaces
- advances in Vitamin E and new antioxidant technologies for UHMWPE
- advances in drug delivery from HXLPE

SCIENTIFIC AND ORGANIZING COMMITTEE AND INVITED SPEAKERS:

President: Steven Kurtz, Ph.D.
Honorary President: Pierangiola Bracco, Ph.D.
Ebru Oral, Ph.D.
Orhun Muratoglu, Ph.D.
Gwo-Chin Lee, M.D.
Rainer Walkenhorst, Ph.D.
Mark Allen
Peter Allen

Organizer: Hannah Spece, M.S.

Sponsorship: We are pleased to announce that Celanese will be supporting the 9th International Meeting as a Platinum Sponsor. We also welcome the involvement of Orthoplastics, Mitsubishi Chemical Advanced Materials MediTECH and Stryker Orthopaedics as Bronze Sponsors. We would also like to acknowledge Lima Corporate and Zzyzx as Copper Sponsors.

Venue: The meeting will be convened at the historic Union League of Philadelphia (https://www.unionleague.org), which is easily accessible by public transportation and the train station. Note that the Union League has a dress code policy (https://www.unionleague.org/dress-code.php) which is strictly enforced.

DAY ONE

8:00 AM
On Site Registration Opens

9:00 AM
Opening Remarks
Steven Kurtz, Ph.D.

9:15 AM
Welcome: "Celanese Stewardship of Medical Grade Materials and Technologies: Past, Present, and Future"
Stephanie Barden, Rainer Walkenhorst, Celanese

9:20 AM
Invited Talk 1: Celanese Stewardship of Medical Grade UHMWPE: Past, Present, and Future
Presenter: Rainer Walkenhorst, Ph.D.

9:40 AM
Invited Talk 2: UHMWPE in Orthopaedics in 2019: A Surgeon's Perspective
Presenter: Gwo-Chin Li, M.D.

SESSION I: Clinical Topics in UHMWPE

Session Co-Moderators: Steve Kurtz, Ph.D. and Orhun Muratoglu, Ph.D.

10:00 AM
Podium Talk 1: Choosing Antioxidant Polyethylene — Are They All the Same?
Presenter: Barbara Currier

10:15 AM
Podium Talk 2: Wear Rates of XLPE are Nearly 50% Lower than First Thought Once the Initial Creep has been Eliminated: an RCT to Compare 4 Bearing Combinations
Presenter: James Wu

10:30 AM
Morning Coffee Break

11:15 AM
Podium Talk 3: Retrieval Analysis of Sequentially Annealed HXLPE in THA and TKA: Minimum 5 Year Follow-up
Presenter: Dan MacDonald, M.S.

11:30 AM
Podium Talk 4: Reasons for Revision, Wear, and Osteolysis in First-Generation HXLPEs
Presenter: Dan MacDonald, M.S.

11:45 AM
Buffet Lunch and POSTER SESSION

SESSION II: Processing, Crosslinking, and Additives

Session Co-Moderators: Ebru Oral, Ph.D., and Rainer Walkenhorst, Ph.D.

1:30 PM
Invited Talk 3: UHMWPE in Orthopaedics in 2019: Advances in Polymer Chemistry
Presenter: Pierangiola Bracco, Ph.D.

2:00 PM
Podium Talk 5: Quantitation and Comparative Assessment of Antioxidant-UHMWPE Formulations
Presenter: Venkat Narayan, Ph.D.

2:15 PM
Podium Talk 6: Comparison of Macro-, Micro- and Nanomechanical Properties of Clinically Relevant UHMWPE Formulations
Presenter: Miroslav Slouf, Ph.D.

2:30 PM
Invited Talk 4: 2019 UHMWPE Guidance from FDA
Presenter: Peter Allen, CDRH Office of Orthopedic Devices, Office of Product Evaluation and Quality

3:00 PM
Podium Talk 7: On the Need for New NIST Standard Reference Material
Presenter: Ryan Siskey, M.S.

3:15 PM
Afternoon Coffee Break

3:45 PM
Invited Talk 5: Update on Gamma vs. X-Ray Sterilization of UHMWPE
Presenter: Mark Allen

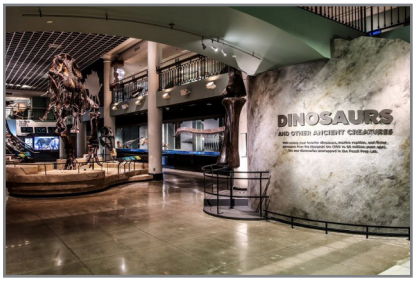
4:15 PM
Podium Talk 8: Equivalent Mechanical Properties of X-Ray and E-Beam Crosslinked Vitamin E Blended Polyethylene
Presenter: Marie Anne Mulliez

4:30 PM
Invited Talk 6: Radiation and Peroxide Crosslinking
Presenter: Orhun Muratoglu, Ph.D.

5:00 PM
Podium Talk 9: A Characterization Technique for Implant Retrievals: Nanomechanical Characterization of two Prolong® Highly Crosslinked Tibial Inserts
Presenter: Sofia Arevalo

5:15 PM
Day 1 Meeting Adjourns
Everyone makes their own way to the Academy of Natural Sciences (walking distance)

6:00 PM
Networking Dinner and Reception at the Academy of Natural Sciences:
https://ansp.org/ : Dinner with the Dinosaurs!
1900 Benjamin Franklin Pkwy
Philadelphia, PA 19103



DAY TWO

8:30AM
On Site Registration Opens

SESSION III: New Frontiers in UHMWPE

Session Co-Moderators: Pierangiola Bracco, Ph.D., Steve Kurtz, Ph.D.

9:00 AM
Invited Talk 7: Antibacterial properties of dual-analgesic loaded UHMWPE
Presenter: Ebru Oral, Ph.D.

9:30 AM
Podium Talk 10: Influence of Artificial Aging on the Delamination Risk of Different TKA Polyethylene Materials Under a High Demanding Activities Knee Wear Simulation
Presenter: Ana Laura Puente Reyna

9:45 AM
Podium Talk 11: Bupivacaine-eluting Polyethylene as an Alternative to Systemic Opioid After Total Knee Arthroplasty
Presenter: Ebru Oral, Ph.D.

10:00 AM
Morning Coffee Break and POSTER SESSION

10:30 AM
Podium Talk 12: Local Delivery of Pain Medication in an Infected Joint Replacement Model
Presenter: Ebru Oral, Ph.D.

10:45 AM
Podium Talk 13: Graphene/UHMWPE composites. Are they potential artificial joint replacement materials?
Presenter: María J. Martínez-Morlanes

11:00 AM
Podium Talk 14: Crosslinking Increased the Biological Reactivity of UHMWPE Particles
Presenter: Shen Weiqi

DAY TWO

11:15 AM
Invited Talk 8: Update on the PEEK-on-UHMWPE Knee
Presenter: Steve Kurtz, Ph.D.

11:45 AM
Closing Remarks
Presenter: Steve Kurtz, Ph.D.

12:00 PM
Meeting Adjourn

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Choosing Antioxidant Polyethylene—Are They All the Same?

+Barbara H. Currier; +John H. Currier; Douglas W. Van Citters
+Dartmouth College, Hanover, NH
Barbara.h.currier@Dartmouth.edu

Introduction: In the effort to increase wear resistance of UHMWPE orthopedic bearing surfaces, irradiation cross-linking at doses above the level used for sterilization have been employed. This irradiation produces free radicals which can crosslink, improving wear resistance [1,2], or initiate an oxidation cascade [3] that leads ultimately to loss of mechanical strength and ductility [4]. Addition of antioxidant to UHMWPE is the most recent method employed to provide oxidation-resistance to irradiated UHMWPE. Two methods of adding the antioxidant are currently marketed (1) blending with the UHMWPE resin before consolidation followed by irradiation cross-linking [5,6] and (2) diffusion of Vitamin E into consolidated and irradiation cross-linked UHMWPE [7]. Additionally, two antioxidants are currently marketed in blended antioxidant UHMWPE: Vitamin E and PBHP (pentaerythritol tetrakis [3-(3,5-di-tert-butyl-4-hydroxyphenyl) [6].
The purpose of this study was to compare the types of antioxidants and methods of delivery to determine their effectiveness at preventing oxidation while maintaining necessary wear- and fatigue-resistance.

Methods and Materials: An IRB-approved laboratory received 133 antioxidant tibial inserts at retrieval from 2010-2019. Retrievals with incomplete data (patient characteristics, reason for revision, time in vivo) were excluded from this analysis, producing a dataset of 89 antioxidant tibial inserts: 29 Vitamin E; 60 PBHP. The inserts were analyzed for oxidation and trans-vinylene index (TVI) using a Thermo Scientific iN-10 FTIR microscope. Oxidation was reported as the ketone oxidation index (KOI) [8]. Trans-vinylene index was determined for each retrieval as a measure of total irradiation dose [8]. Cross-link density was measured for 79 of the retrieved tibial inserts using a previously published gravimetric gel swell technique [8]. For tibial inserts of sufficient size and thickness (n=18), ASTM Type V uniaxial tensile testing was performed using a previously published technique [8]. Retrieval properties were compared to never-implanted samples of the same materials (Vitamin E, n=8, PBHP, n=6). Results were compared using SPSS v.25.

Results: Vitamin E retrievals had longer mean time in vivo than PBHP retrievals; however, the difference did not reach significance (Vitamin E, 2.1+/-1.39 years versus PBHP 1.9+/-1.03 years, $p=0.317$). Patient BMI and age at implant were similar between the groups ($p>0.367$). More Vitamin E retrievals were from female patients (18 F, 11 M); PBHP retrievals were more evenly divided (28 F, 32 M). The top three reasons for revision were the same in both groups- Vitamin E retrievals: instability (9) infection (7), and loosening (6); PBHP retrievals: loosening (20), infection (16), and instability (13). Oxidation increased with time in vivo ($p<0.001$, Figure 1), but no antioxidant retrieval exhibited subsurface oxidation (Figure 2). Cross-link density increased with TVI (Figure 3). Tensile toughness decreased with TVI (Figure 4). Comparing delivery methods of antioxidant (blending versus diffusion) for Vitamin E inserts showed statistically similar cross-link density ($p=0.127$) but statistically significant differences in TVI ($p<0.001$) resulting in statistically significant differences in tensile toughness ($p=0.004$, Table 1).

Discussion: All antioxidant polyethylenes evaluated in this study successfully prevented oxidation of the polyethylene over the time in vivo represented by these retrievals, confirming results of an earlier study [8]. None of the antioxidant retrievals exhibited subsurface oxidation that has resulted in degradation of mechanical properties in both gamma-sterilized [4] and annealed highly cross-linked polyethylene [9]. Method of antioxidant delivery (blending versus diffusion) resulted in higher irradiation doses needed to achieve similar levels of cross-linking in blended antioxidant polyethylenes. Antioxidants present in blended materials interacted with free radicals during irradiation and inhibited their ability to form the cross-links needed for wear-resistance. Comparing the Vitamin E containing materials showed almost double the TVI for the blended Vitamin E compared to the diffused Vitamin E. This higher irradiation dose needed to produce similar cross-link density resulted in lower tensile toughness for the higher dose blended Vitamin E, which could potentially reduce its fatigue-resistance. Blended PBHP (and lower irradiation dose blended Vitamin E) had higher toughness than the higher irradiation dose, blended Vitamin E in this study, due to the lower cross-linking irradiation dose. With the caveat that the longest duration device in this study was in vivo for less than 7 years, we conclude that all antioxidant polyethylenes tested in this work remain suitable for use in total joint arthroplasty, provided the manufacturer and surgeon appropriately match the mechanical properties to the device design and patient demands.

References

1. Gaudiani MA, et al. JoA 2018;33(2):586-9.
2. Hopper RH, Jr., et al. CORR 2018;476(2):279-90.
3. Costa L, et al. Biomaterials. 1998;19(7-9):659-68.
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8. Currier BH, et al. JBMR-B 2018:106B:353–359.
9. A.M. Kop et al. JoA 2015 30:1842–1846.

Table 1: Mean values of TVI, cross-link density, and tensile toughness by antioxidant and delivery method illustrate the different cross-linking doses used and their effects of measured properties.

Material	TVI	Cross-link Density (mol/dm^3)	Tensile Toughness (MPa)
PBHP blended	0.032± 0.002	0.179± 0.010	118.0± 13.3
Vitamin E blended	0.086± 0.006	0.220± 0.020	75.7± 11.6
Vitamin E diffused	0.048± 0.005	0.232± 0.016	93.3± 10.6

Figure 1: The trend of oxidation versus time in vivo suggested that these materials could provide oxidation-resistance over the life time of the patient.

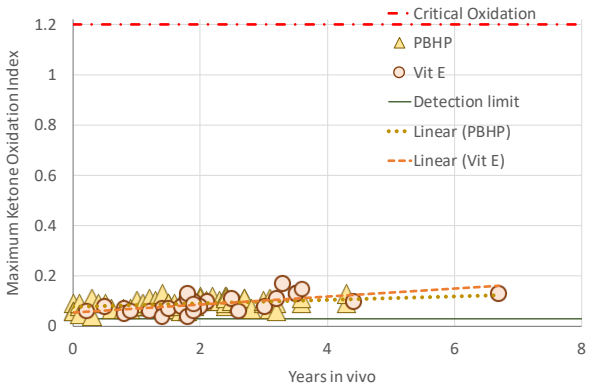


Figure 2: Antioxidant retrievals compared with never implanted bar stock showed oxidation only from absorbed materials from the in vivo environment, present in a diffusion profile from the surfaces of the inserts. No antioxidant retrieval exhibited a subsurface oxidation peak.

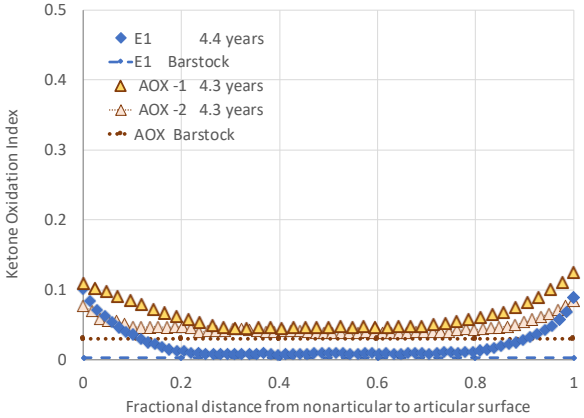


Figure 3: Cross-link density increased with increasing TVI, a proxy for absorbed irradiation dose. Variability in cross link density is attributed to inhibition of crosslinking by antioxidant present during irradiation.

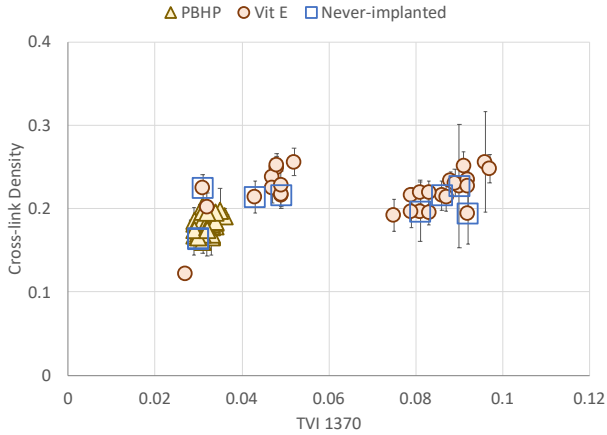
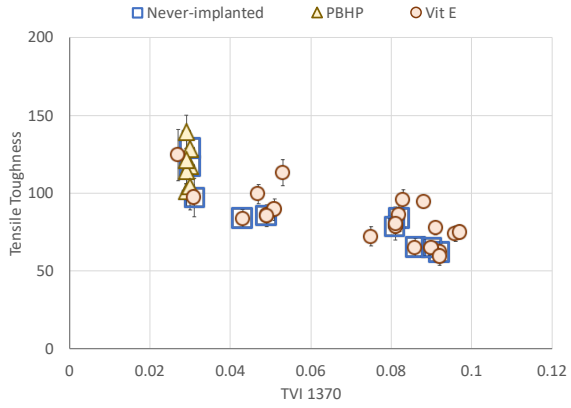


Figure 4: Tensile toughness decreased with increasing TVI.



Wear rates of XLPE are nearly 50% lower than first thought once the initial creep has been eliminated: an RCT to compare 4 bearing combinations.

Wu James[1], Khoshbin A[1], Waddell JP[1], Schemitsch EH[1], Atrey A[1]
[1]University of Toronto, Canada
James.wu.tck@gmail.com

Introduction:

The ideal bearing combination for Total Hip Arthroplasty (THA) remains debatable. Highly Cross-Linked Polyethylene (XLPE) has largely replaced conventional polyethylene (UHMWPE) but long-term wear rates are unknown and how much the initial viscoelasticity/ creep/ bedding-in, if any, effects overall wear is also unknown. Creep is known to be a viscoelastic property that polyethylene demonstrates and it is important in decreasing contact forces. Once it is complete, it will not recur and is therefore a distinct entity from wear.

Additionally, use of oxidized Zirconium (OxZir) is purported to lower polyethylene wear rates but has not been proven.

In this RCT, we demonstrate the effect that the initial creep affects the overall wear.
We also attempt to discover whether OxZir affects the wear rates of polyethylene.

We present the ten-year data of a cohort of patients who underwent THA. Patients were prospectively randomized to one of four bearing combinations: UHMWPE or XLPE acetabular liner coupled with either a cobalt-chrome (CoCr) or OxZir femoral head. The aims were twofold; first to assess the extent to which creep affects overall wear rates and second if OxZir decreases wear rates when compared with CoCr.

Methods and Materials A total of 92 hips (92 patients) aged between 22 and 65 years (mean 52.2±9.3), were randomized into four groups. At ten years, 70 hips (76%) were available for analysis. Patients who had revisions, deaths or lost to follow-up were excluded from final analysis. Radiological analysis was performed using a validated digital assessment program to give linear, volumetric and directional wear of the polyethylene for all four bearing couples. This methodology (Polyware) is avalidated to be as successful as RSA.

Radiological assessments were taken immediately post-op, 6 and 12 weeks and then annually for a minimum of 10 years.

Results: There were significantly lower wear rates for XLPE than UHMWPE irrespective of the head coupling. Once creep (the initial three-month loss) was eliminated, annual and overall wear rates were 50% lower over the remaining time period. This was proportionally more important in the XPLE group than the UHMWPE group. While there was a trend toward a lower wear rate in the OxZir group, this was not statistically significant.

Discussion: Creep plays a significantly more important role than first thought. Once creep is eliminated the wear rate is even lower than first assumed. This has important implications for the overall survivorship of hip arthroplasties and may affect the bearing choices that surgeons use for their patients.

While there was a difference in the wear rates of polyethylene with the OxZir head, it was not statistically different, but we are performing a higher powered study based on this preliminary data.

Quantitation and Comparative Assessment of Antioxidant-UHMWPE Formulations

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[2] DePuy Synthes Joint Reconstruction, USA
v.narayan@antharatech.com

Introduction: Oxidation of irradiated Ultra High Molecular Weight Polyethylene (UHMWPE) for orthopaedic implants both, on the shelf in the packaging as well as *in vivo* has been extensively reported to cause adverse effects on the mechanical properties [1]. Irradiation of UHMWPE using ionizing radiation sources such as gamma or electron beam generates free radicals which can trigger oxidation if left unaddressed. Clinical and *in vitro* test results have verified oxidative stability by remelting the irradiated UHMWPE materials used in orthopaedic devices [2,3]. Another approach to stabilizing UHMWPE is with the use of antioxidants such as α-tocopherol (hereafter referred to as **αT**) [4] or a hindered phenol antioxidant, pentaerythritol tetrakis [3-(3,5-di-tert-butyl-4-hydroxy phenyl) propionate] hereafter referred to as **PBHP** [5]. The study reports the characterization and comparative assessment for various **PBHP**- and **αT**-stabilized GUR 1020 UHMWPE formulations as a function of antioxidant type and antioxidant loading before and after gamma irradiation of the consolidated materials generated to a nominal dose of 100 kGy.

Methods and Materials:

Oxidation Induction Time (OIT) by DSC: OIT measurements were done on the consolidated forms for both, non-irradiated and irradiated, at concentrations of 0.05, 0.075, 0.1, 0.15 & 0.3% (w/w) for both, **PBHP** using the method previously reported [6]. The intent here is to characterize the OIT change as a function of concentration for each respective series (**PBHP** and **αT**) as well as to quantify the OIT values at the same concentration due to gamma irradiation. Characterization of the formulations also included:

a. Antioxidant Index by FTIR
   i. The **PBHP** Index is determined from the ratio of the area in the range of 1125 – 1150 cm^{-1} to the peak height at 1888 cm^{-1} using the baseline between 1850 – 1985 cm^{-1} as basis for normalization
   ii. The **αT** Index is determined from the ratio of the area in the range of 1245 – 1275 cm^{-1} to the normalizing peak for thickness using the peak area between 1850 – 1980 cm^{-1}.
b. Crosslink density by Gravimetric Swell Ratio (ASTMD2765)
c. Double Notched Izod (DNI) toughness per ASTM F648

Results and Discussion: Comparative quantification of the antioxidant indices before and after gamma irradiation to the same dose (100 kGy) show that there is depletion of the antioxidant in both formulation types (**Figures 1a and 1b**). The negative values up to 0.15% αT would suggest that values are near zero and in the noise regime of measurement suggesting a very high degree of signal depletion. This was confirmed by the lower OIT values for the **αT** concentrations relative to the same corresponding **PBHP** concentrations (overlay shown in **Figure 2**). Thus, **αT** formulations at 0.3% (w/w) loading have the same oxidative stability as **PBHP** formulations at <0.15%, thereby demonstrating lower antioxidant efficiency.

Comparative assessment of crosslinking was also done as shown with swell ratio calculations (**Figure 3**). At all concentrations, **αT** formulations show lower crosslinking relative to **PBHP** formulations by way of higher swell ratio values, thereby demonstrating lower crosslinking efficiency. This result is somewhat surprising as the higher depletion of **αT** was expected to provide higher crosslink densities. Clearly, the mechanism of crosslinking inhibition is different for the two antioxidant types.

Measurements of DNI toughness of the consolidated and irradiated formulations also show higher toughness for the **PBHP** formulations (**Table 1**), particularly at lower concentrations though there is convergence to similar values at higher concentrations. There is also much less sensitivity to concentration for the **PBHP** formulations relative to **αT** formulations.

Conclusion:

1. Successful characterization of the antioxidant formulations has been demonstrated for Oxidation Induction Time by DSC before and after consolidation and irradiation.
2. The depletion in concentration upon irradiation has been characterized by FTIR.
3. Good linearity of response has been demonstrated as a function of concentration for both antioxidant materials by OIT and FTIR, particularly for **PBHP** formulations.
4. The results confirm a more rapid depletion of the measurement signal for the **αT** formulations relative to that for the **PBHP** formulations upon irradiation by FTIR suggesting a higher level of stability of **PBHP** relative to **αT**.
5. This has been verified at each concentration by comparison of OIT measurements.
6. **PBHP** formulations demonstrate better crosslinking efficiency relative to the corresponding **αT** formulations at the same concentration.
7. Irradiated formulations based on **PBHP** show higher impact toughness than the corresponding **αT** formulations.

8. Confounding results suggest differences in mechanism of stabilization by the two antioxidants.

References

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[4] E. Oral *et al.*, Biomaterials, 25, pp 5515-22, (2004).

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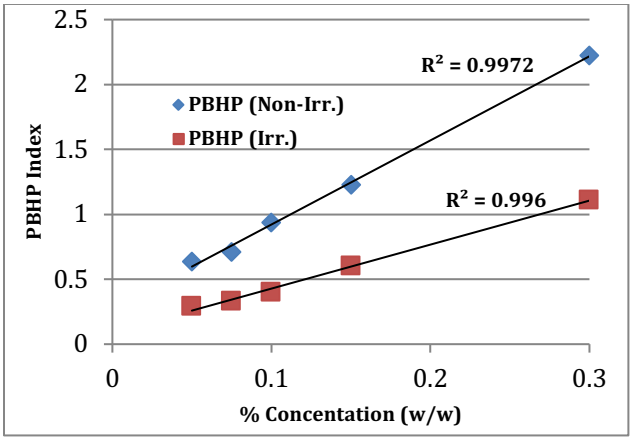

Figure 1a - Overlay of PBHP Index before and after 100 kGy Irradiation

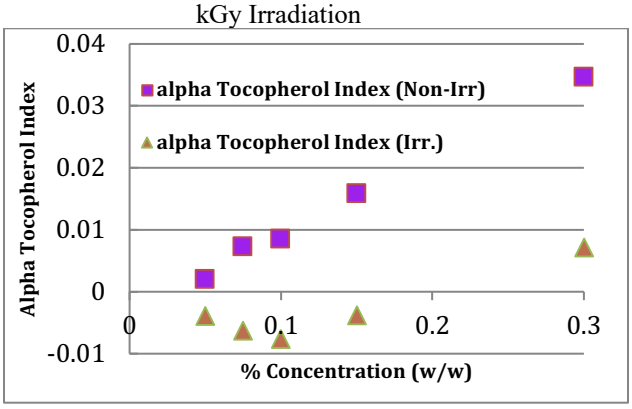

Figure 2b - Overlay of αT Index before and after 100 kGy Irradiation

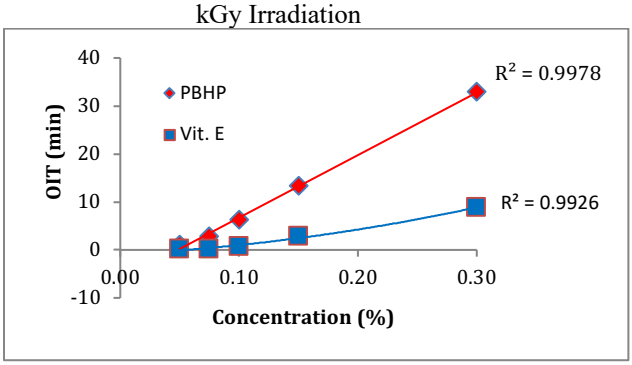

Figure 2. Overlay of the OIT values as a function of concentration for PBHP and αT Formulations after consolidation and irradiation

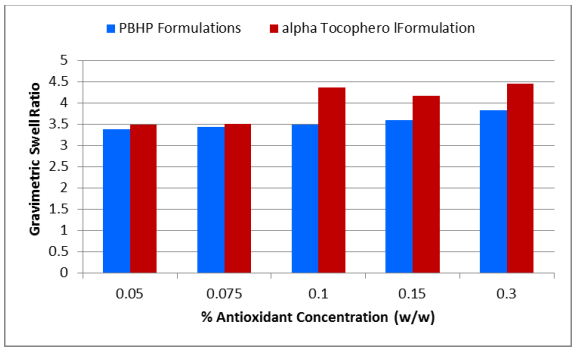

Figure 3. Comparative assessment of GSR values for PBHP and αT Formulations.

Sample ID	DNI Toughness (kJ/m²)
PBHP – 0.05%	71.2 ± 2.2
PBHP – 0.75%	72.5 ± 0.6
PBHP – 0.10%	72.9 ± 2.0
PBHP – 0.15%	76.0 ± 1.3
PBHP – 0.30%	79.7 ± 2.0
αT – 0.05%	58.2 ± 1.5
αT – 0.75%	60.4 ± 0.6
αT – 0.10%	62.9 ± 1.6
αT – 0.15%	65.3 ± 2.5
αT – 0.30%	75.4 ± 1.0

Table 1. Average DNI Impact Toughness Results per Formulation

Comparison of macro-, micro- and nanomechanical properties of clinically relevant UHMWPE formulations

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slouf@imc.cas.cz

Introduction: Ultra High Molecular Weight Polyethylene (UHMWPE) remains the primary polymeric material bearing for hip, knee and shoulder replacements [1]. The mechanical properties along with wear and oxidative resistance influence the lifespan of total joint replacements. In the late 1990's, manufacturers began crosslinking UHMWPE by means of ionizing radiation in order to increase its wear resistance. The radiation-induced crosslinking is usually followed by thermal treatment to eliminate residual radicals, and similarly antioxidants are used to mitigate oxidative degradation. However, these processing parameters and concomitant structural changes influence the mechanical performance of UHMWPE. This contribution aims at comparison of macro-, micro- and nanomechanical properties of eleven clinically relevant UHMWPE formulations.

Materials and methods: Table 1 summarizes the clinical formulations of UHMWPE (together with their manufacturers), which were used in this study.

Series	Sample ID	Full sample name	Manufacturer
S1	PE-1a	GUR 1050	Orthoplastic
	PE-1b	GUR 1050 75kGy RM	Quadrant
S2	PE-2a	GUR 1020	Orthoplastic
	PE-2b	GUR 1020 35kGy	Orthoplastic
	PE-2c	GUR 1020 75kGy RM	Orthoplastic
S3	PE-3a	GUR 1020 VE	Orthoplastic
	PE-3b	GUR 1020 VE 50kGy	Orthoplastic
	PE-3c	GUR 1020 VE 75kGy	Orthoplastic
	PE-3d	GUR 1020 VE 125kGy	Orthoplastic
S4	PE-4a	GUR 1020 AO	De Puy
	PE-4b	GUR 1020 AO 80kGy	De Puy

Table 1. List of samples used in current study. Full sample names consist of: material, radiation dose, thermal treatment (RM = remelting), and stabilizer (VE = vitamin E; AO = COVERNOX™ antioxidant).

Structural properties of UHMWPE were measured with Infrared (IR), Differential Scanning Calorimetry (DSC) and Small Angle X-ray Scattering (SAXS). The mechanical properties were measured in macroscale (elastic modulus, E, and yield stress, Y, from compressive tests), microscale (Vickers microhardness, H_V, from non-instrumented microindentation, MH, together with indentation modulus, E_{IT}, and hardness, H_{IT}, from instrumented microindentation, MHI) and nanoscale (instrumented nanoindentation, NHI, yielding analogous properties like MHI). All above methods have been described in detail in our previous studies [2, 3].

Results: All mechanical properties studied in this work, (i.e. elastic moduli, yield stress, and hardness at all length scales) depended mostly on the UHMWPE crystallinity (w_c). The correlation between w_c and the investigated properties was approximately linear. The strength and statistical significance of all correlations was quantified by Pearson correlation coefficients and p-values, respectively. The strength and significance of correlations between the properties and w_c decreased in the following order: microscale > macroscale ≫ nanoscale (Table 2).

	E	Y	MH/H_V	MHI/E_{IT}	MHI/H_{IT}	MHI/H_M	NHI/E_{IT}	NHI/H_{IT}	w_c
E	1.0000	0.0000	0.0012	0.0188	0.0039	0.0041	0.1208	0.2078	0.0048
Y	0.9488	1.0000	0.0008	0.0032	0.0002	0.0004	0.0636	0.3203	0.0038
MH/H_V	0.8402	0.8553	1.0000	0.0013	0.0001	0.0001	0.0202	0.2833	0.0002
MHI/E_{IT}	0.6899	0.7987	0.8366	1.0000	0.0000	0.0000	0.0160	0.2909	0.0020
MHI/H_{IT}	0.7887	0.8990	0.9119	0.9380	1.0000	0.0000	0.0115	0.2343	0.0010
MHI/H_M	0.7865	0.8799	0.9179	0.9483	0.9943	1.0000	0.0070	0.1630	0.0014
NHI/E_{IT}	0.4960	0.5761	0.6844	0.7020	0.7256	0.7571	1.0000	0.0640	0.1312
NHI/H_{IT}	0.4122	0.3309	0.3555	0.3503	0.3911	0.4518	0.5754	1.0000	0.3822
w_c	0.7779	0.7896	0.8906	0.8202	0.8469	0.8355	0.4843	0.2928	1.0000

Table 2. Correlation matrix table showing correlations between mechanical properties and crystallinity: Diagonal elements are equal to 1 (autocorrelations), lower left triangle contains Pearson correlation coefficients, r, and upper right triangle contains p-values. The colors denote strength of the correlations: the strongest correlations are blue, the weakest are red.

Discussion: Firstly, our contribution confirmed that various ways of crosslinking, thermal treatment and other modifications of UHMWPE result in different mechanical behavior of the final polymer at all length scales (macro-, micro- and nanoscale). Secondly, we showed that crystallinity is the decisive parameter influencing the stiffness of UHMWPE (i.e. its elastic moduli, yield stress and hardness at all scales). This was in good agreement with theoretical predictions, which apply to all semicrystalline polymers [3, 4]. Finally, we demonstrated that *micro-* and *macro*mechanical properties exhibited stronger correlations with UHMWPE structure (i.e. crystallinity) than *nano*mechanical properties. The advantage of micromechanical measurements was sufficiently high loading force (elimination of surface effects, which seemed to influence nanoindentation experiments) in combination with high number of measurements per sample (at least 30 indentations per sample, more than in common compressive tests).

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Antibacterial properties of dual-analgesic loaded UHMWPE

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INTRODUCTION: Periprosthetic joint infections (PJI) remain a major challenge associated with total joint arthroplasty. Local delivery of therapeutics was shown to be an effective approach to address PJI, while minimizing adverse side-effects of antimicrobial therapies[1]. Previously we showed that ultra-high molecular weight polyethylene (UHMWPE) bearing surfaces can provide local delivery of various drugs, including antibiotics and analgesics[2,3]. Analgesic-loaded UHMWPE was shown to possess excellent antibacterial properties against *Staphylococci* – the most common pathogens causing PJI[2]. When used in combination, several analgesics yielded synergistic antibacterial effects. In the present study, we hypothesize that dual-analgesic loaded UHMWPE can provide efficient antimicrobial activity for possible use in post-arthroplasty prophylaxis.

METHODS: Bupivacaine (anesthetic) and tolfenamic acid (NSAID) were loaded into UHMWPE using phase-separated compression molding. Drug concentrations in an elution setup were obtained using high-performance liquid chromatography. Tensile tests were performed to evaluate mechanical properties using Type V specimens according to ASTM D638. Wear properties were characterized using multidirectional pin-on-disc testing[4]. Energy dispersive X-ray scans were obtained, and images were analyzed using a neural network to characterize morphology of drug domains (Fig 1). Anticolonizing activity was characterized using the "daughter cell" method[5]. Antibacterial studies were conducted against methicillin-sensitive *S. aureus* and *S. epidermidis*. Cytotoxicity was evaluated using the MG-63 osteoblast cell line. Effect of the tested samples on immune cell was assessed using the RAW 264.7 cell line.

RESULTS SECTION: Although bupivacaine and tolfenamic acid release rates generally increased along with the drug loading, dual-drug loaded UHMWPEs showed higher release rates when compared with the single-drug loaded UHMWPEs (Fig 2a). Tolfenamic acid and bupivacaine – loaded UHMWPEs were able to provide therapeutic doses for pain relief for both drugs. The increase of drug domain size and fractal dimension led to the increase of drug elution (Fig 2b). Bupivacaine and tolfenamic acid – loaded UHMWPEs possessed measurable antimicrobial properties against both strains of *Staphylococci*, and the activity was higher than that of the single-drug loaded UHMWPEs (Fig 2c-d). Pronounced anticolonizing properties of dual-drug loaded UHMWPEs were also observed – 4-log reduction of "daughter" cells was measured for the tested samples.

DISCUSSION: We showed for the first time that UHMWPE loaded with two drugs (anesthetic and NSAID) possessed antibacterial properties higher than those of the single-analgesic loaded UHMWPEs. These materials showed pronounced anticolonizing properties, effectively mitigating bacterial adhesion and proliferation. The results here suggest that dual-analgesic loaded UHMWPE, intended for use as a tool in a multimodal pain management after total joint arthroplasty, can also provide effective antibiotic prophylaxis.

SIGNIFICANCE/CLINICAL RELEVANCE: These results demonstrate that it is feasible to design dual analgesic-loaded implant surfaces that provide both post-arthroplasty pain relief and antibacterial effects with the potential to reduce morbidity and mortality and improve patients' quality of life.

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ACKNOWLEDGEMENTS: This work was supported by the Office of the Assistant Secretary of Defense for Health Affairs, through the Peer Reviewed Medical Research Program under Award No. W81XWH-17-1-0614. Neural network analysis was performed at the Center for Nanophase Materials Sciences, a US Department of Energy Office of Science User Facility managed by UT-Battelle, LLC, for the US Department of Energy

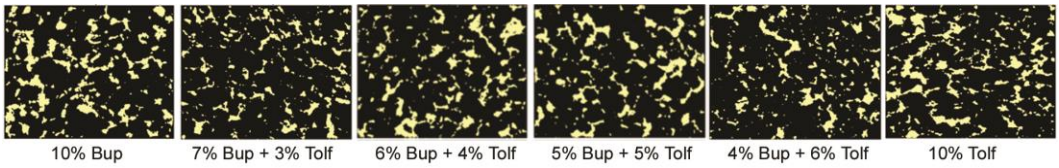

Figure 1. Tolfenamic acid and bupivacaine domains in UHMWPE identified using a neural network.

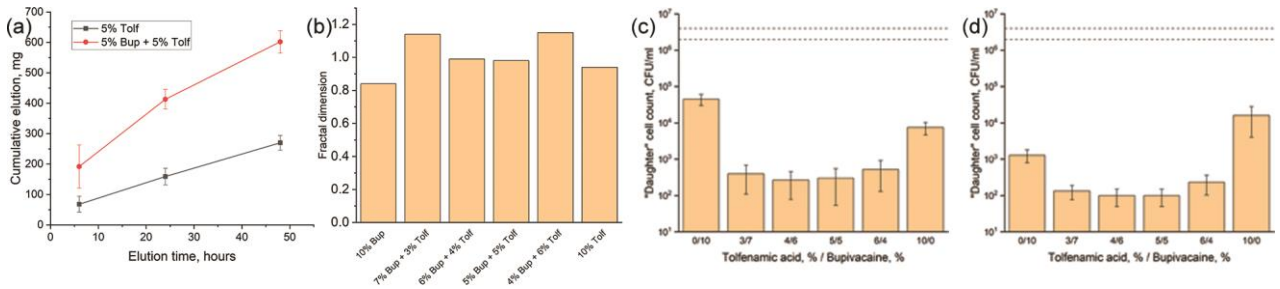

Figure 2. (a) – Cumulative elution profiles of tolfenamic acid from 5% tolfenamic acid-loaded UHMWPE and 5%+5% Tolfenamic acid+Bupivacaine loaded UHMWPE. (b) – Fractal dimension of drug domains in tolfenamic acid and bupivacaine-loaded UHMWPEs. (c-d) – Anticolonizing properties of tolfenamic acid and bupivacaine-loaded UHMWPEs against (a) MSSA and (b) *S. epidermidis*. Dash lines show the activity of virgin UHMWPE, which was used as a control material.

Equivalent Mechanical Properties of X-Ray and E-Beam Crosslinked Vitamin E Blended Polyethylene

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Introduction:

The most current crosslinking methods to improve thermal, chemical and ageing properties of polyethylene are high-energy electromagnetic ionizing gamma-rays and beta-rays or electron-beam (e-beam). Due to economic reasons and other technological drawbacks such as low dose rate for gamma-rays and low penetration depth for e-beam respectively, the need for a technology which overcomes these limitations is noticeable. X-rays which provide a homogeneous crosslinking in a relatively short time seem to offer an alternative solution. While only limited dimensions up to 40 mm can be irradiated by means of e-beam because of the limited penetration depth, whole rods could be crosslinked by x-rays. This would provide real manufacturing and economic advantages.

Only little is reported in the literature about x-ray crosslinking of polyethylene as a joint replacement material. This study was dedicated to examine the particular influence of x-ray crosslinking in comparison with e-beam crosslinking on UHMWPE mixed with vitamin E. More specifically the purpose was the investigation of the mechanical and thermal properties of a Vitamin E blended polyethylene after processing by x-rays versus e-beam. Two different irradiation doses and processing temperatures were considered.

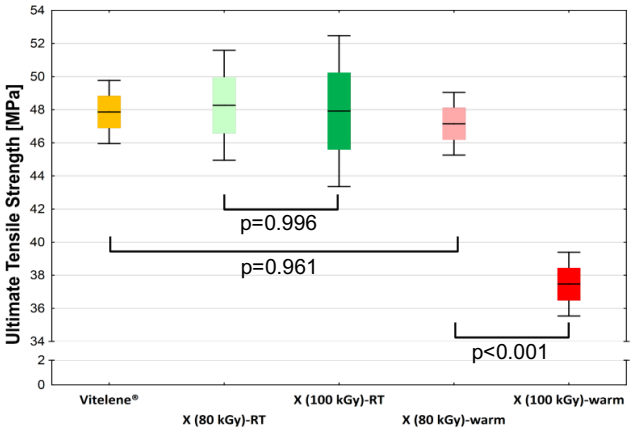
The hypothesis was that by same irradiation dose and process temperature both crosslinking technologies will lead to similar mechanical and thermal properties.

Methods and Materials:

The specimens were made of GUR® 1020 blended with 0.1 weight percent vitamin E. After consolidation and annealing, bars were cut from the sheet and submitted to x-ray radiation crosslinking. The material was split into four groups distinguished by absorbed dose and processing temperature respectively as follows: 80 kGy, room temperature (RT) “X (80 kGy)-RT”; 100 kGy, room temperature “X (100 kGy)-RT”; 80kGy, 100°C “X (80 kGy)-warm”; 100 kGy, 100°C “X (100 kGy)-warm”. Vitelene® (Aesculap AG, Tuttlingen, Germany), highly crosslinked (electron beam, 80 kGy), vitamin E (0.1%) blended polyethylene was taken as reference. No further post irradiation thermal treatment was performed. Crystallinity and melting temperature were measured according to ASTM F2625 (n=3). Uniaxial tensile testing was carried out according to ASTM D638. Yield stress, ultimate tensile stress (UTS) and elongation at break were calculated for each material. Izod impact strength according to ASTM D256 and bi-dimensional tensile resistance by so-called small punch testing (SPT) according to ASTM F2183 were ascertained ($n \geq 4$). Peak load, ultimate load, ultimate strain and work to failure were assessed.

Results:

The yield, ultimate tensile strength and elongation were 21.7 MPa, 48 MPa and 393% for Vitelene® and 21.7 MPa, 47 MPa and 402% for X (80 kGy)-warm respectively.



The peak load, ultimate displacement and work to failure accounted for 63 N, 5.7 mm and 331 mJ for Vitelene® and 65 N, 5.6 mm and 322 mJ for X (80 kGy)-warm respectively.

The Izod impact strength of Vitelene® accounted to 81 kJ/m², that of X (80 kGy)-warm to 82 kJ/m².

Crystallinity of both was 52%. Melt temperature of Vitelene® was 140°C, that of X (80 kGy)-warm 139°C.

Discussion:

In this study, increasing the temperature had more impact on the material properties than augmenting the dose. The temperature changed the thermal history and affected the crystal perfection and crystallinity. This confirmed the crucial influence of the processing temperature on the material properties.

Both, the dose influencing the crosslink density and the thermal processing influencing the crystallinity, are key predictors of the mechanical properties of UHMWPE. UHMWPE is a complex material and its properties are possibly transitory and dependent on functional loading and environmental conditions.

In conclusion, the hypothesis was verified: using the same processing temperature (100°C) and dose (80 kGy), the different radiation sources e-beam and x-rays resulted in equivalent thermal and mechanical properties.

A characterization technique for implant retrievals: nanomechanical characterization of two Prolong® Highly Crosslinked Tibial Inserts

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Introduction: Ultra High Molecular Weight Polyethylene (UHMWPE) remains the gold standard for total joint arthroplasty due to its biocompatibility, desirable mechanical properties and tailoribility [1]. Newer clinical formulations of UHMWPE offer potential for enhanced longevity in total joint replacements (TJR); yet there is an ongoing need to understand in-vivo oxidation and concomitant degradation mechanical properties [2]. *In vivo* loading conditions may also elucidate microstructure evolution and propensity for localized UHMWPE wear or fracture [3]. Adhesive and abrasive wear are more prevalent in conforming TJR while less conforming joints such as knees are prone to fatigue (delamination) [4]. The high contact stresses in many tibial component designs may exacerbate wear rates and can promote fatigue mechanisms in UHWMPE [4-6].

The articulating surface of retrieved components, may provide researchers with a better understanding of wear mechanisms and associated changes in mechanical behavior resulting from *in vivo* conditions. Characterization of the surface mechanical properties provides insight into the local material properties and offers benefits over macroscale testing that may lack ability to detect localized mechanical property variations across the articulating surface of an implant [7]. Thus, testing techniques such as small punch testing and micro-indentation techniques have been widely used to measure the local behavior of retrievals [8–10]. Notably, Edidin and colleagues used small punch testing to relate UHMWPE properties to the wear mechanisms in acetabular bearings [11]. Similarly, Kurtz et al established the suitability of small punch testing for mechanical characterization of retrievals [12]. By contrast, Wernele et al highlighted the usefulness of microindentation for correlating mechanical properties to oxidation levels for retrieved tibial knee bearings [10]. Micro-length scale mechanical testing has been shown to be beneficial as a characterization technique for retrievals [8,13]; yet, there is an ongoing need to develop relations between the surface behavior and wear mechanisms. Nano-scale characterization techniques enable the opportunity to map both the nanomechanical heterogeneity on the articulating surface as well as in the cross-section of an UHMWPE TJR component. Furthermore, nanomechanical mapping may provide the opportunity to observe oxidation and cyclic loading effects on the local mechanical properties of explants.

The objective of this research is to develop a modulus map of the articulating surface of tibial inserts to: establish nanoindentation as a suitable surface characterization technique and to better understand and quantify the changes in mechanical properties at the articulating surface. The nano-modulus map may also provide insight into wear mechanisms on tibial inserts.

Methods and Materials: In this study, two retrieved Prolong® Highly Crosslinked Polyethylene tibial inserts were nano-mechanically characterized. The retrieval in Fig. 1a is a long-term implanted retrieval, while retrieval Fig. 1b is a short-term implanted retrieval (Zimmer Biomet).

Nanomechanical analysis was performed on section B of the tibial inserts, as shown in Figure 1a,b. The implants were sectioned using a bandsaw; this allowed a TriboIndenter to reach into and contact the implants.

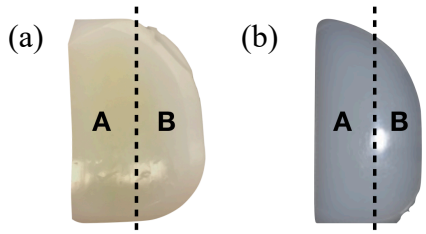

Fig. 1: (a) Long-term implanted and (b) Short-term implanted Prolong tibial insert.

Nanoindentation – Testing Parameters & Data Analysis

A Ti-900 TriboIndenter (Hysitron, Minneapolis, MN) was used to perform indentations at ambient temperature using a Berkovich diamond tip with a 100 nm radius. The indentations were load-controlled with a rate of 30 μN/s. A trapezoidal loading-unloading function was used. Each indent was prescribed a maximum load of 400 μN.

The modulus value was calculated according to the Oliver and Pharr method [14].

Results: The locations of indentations on section B for both short and long-term implanted tibial inserts are illustrated Fig. 2a and 3a (demarcated as red and black dots). Fig. 2b and 3b highlights the modulus heterogeneity across the surface of section B for both long and short-term implanted inserts, respectively. The average elastic modulus for section B of the long-term implanted tibial insert is 0.59 ± 0.41 (GPa). By contrast the average elastic modulus of section B for the short-term implanted tibial insert is 1.15 ± 0.66 (GPa).

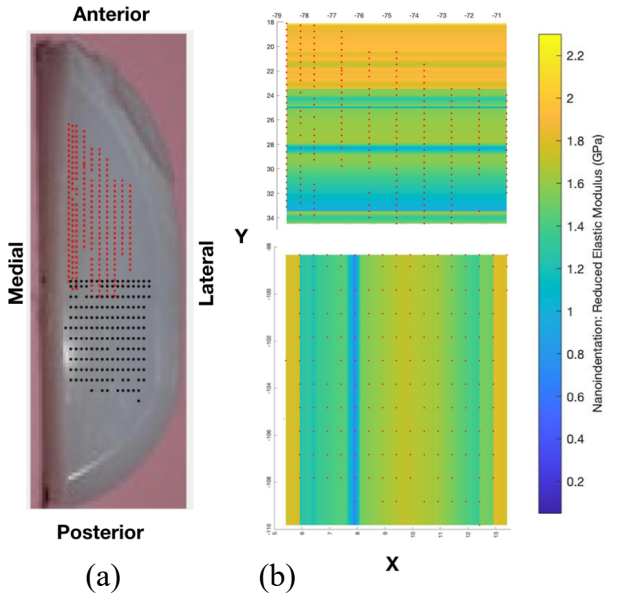

Fig. 2: (a) Section B from the long-term implanted Prolong tibial knee insert overlaid with indent location (b) Top and bottom – Color map of reduced elastic moduli across the surface of section B.

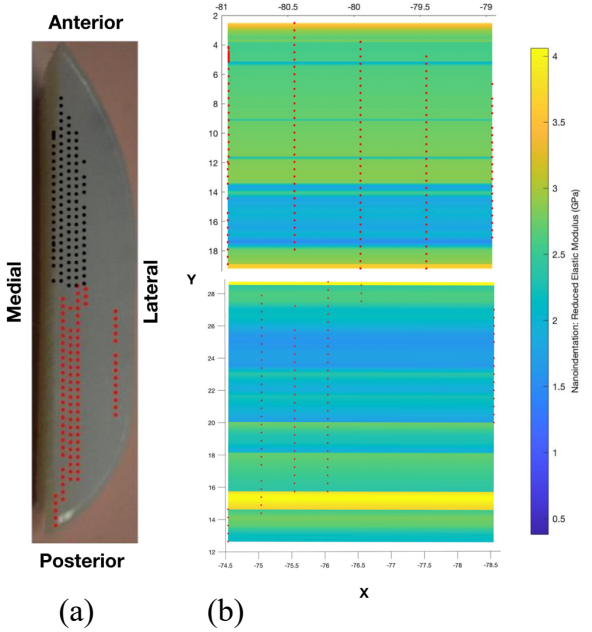

Fig. 3: (a) Section B from the short-term implanted Prolong tibial knee insert overlaid with indent location (b) Top and bottom – Color map of reduced elastic moduli across the surface of section B.

Discussion: This study utilizes nanoindentation methods to examine the articulating surface of retrievals. Based on the nanoindentation modulus data of section B, the short-term implant exhibited a larger nanomechanical modulus value than the long-term implant. These results agree with previous studies [11], which observe a softening in mechanical properties resulting from the accumulation of plastic strains. Researchers believe that *in vivo* articulation leads to molecular chain alignment at the surface; resulting in localized anisotropy and strain softening in the direction transverse to the oriented molecular chains [11,15]. This phenomenon may provide a better understanding of wear and its relation to surface mechanical properties.

Future studies will include the nano-modulus mapping of section A for both long-term and short-term retrievals. This will enable a better understanding of the areas that exhibited larger changes in modulus. We predict that nanoindentation can determine which areas have undergone the most articulation based on the local modulus values. Furthermore, a nano-modulus mapping of the retrieval's cross-sections may assist in correlating the oxidative degradation to nanomechanical properties.

In summary, assessing the nano-scale properties of retrievals provides an opportunity to understand structure-property evolution owed to *in vivo* conditions.

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Influence of artificial aging on the delamination risk of different TKA polyethylene materials under a High Demanding Activities Knee Wear Simulation

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Introduction: Total knee arthroplasty (TKA) is a well established treatment for degenerative joint disease with good clinical results. Currently, there is an increasing demand on the performance of these implants, as this treatment is also performed in young and middle-aged adults who have a significant physical activity and higher life expectancy [1]. However, complications may occur due to severe wear of the polyethylene gliding surfaces as well as to the biological response to the wear particles, which lead to aseptic loosening [2].
In order to reduce wear and osteolysis, highly crosslinked polyethylene was introduced and showed improvements in total hip arthroplasty [3]. However, these benefits have not been seen in vivo in TKA [4, 5], even though it showed favorable results in vitro [6]. Material fatigue and delamination of tibial inserts is caused by a combination of high contact stresses and subsurface stress concentration in combination with degradation of the polyethylene due to oxidation. One major limitation of the current ISO 14243 wear testing is that it only simulates the abrasive-adhesive surface wear produced during level walking and not the delamination produced due to the high contact stresses generated during high demanding activities (HDA) such as climbing stairs or standing up form a chair. More recently, vitamin E has been added to the polyethylene in order prevent its oxidation and therefore stabilize its mechanical properties.
The purpose of this study was to analyze the wear behavior, particularly the risk of delamination, of several clinically relevant polyethylene materials as well as vitamin E stabilized polyethylene materials under a high demanding activities wear simulation in combination with different grades of artificial aging.

Methods and Materials: A cruciate retaining fixed bearing TKA design (Columbus® CR, Aesculap AG, Tuttlingen, Germany) with several artificially aged (ASTM F2003-02 parameters: 70°C, pure oxygen at 5 bar, 2 or 6 weeks) polyethylene gliding surfaces were tested. The different polyethylene materials were:

- Standard polyethylene (STD-2w): 30 kGy, γ-irradiated in nitrogen, 2 weeks artificially aged
- Highly-crosslinked and remelted polyethylene (REM-2w and REM-6w): 75 kGy, γ-irradiated in nitrogen, 2 and 6 weeks artificially aged
- Vitamin E (0.1 %) blended polyethylene (VitE-6w): 30 kGy, γ-irradiated in nitrogen, 6 weeks artificially aged
- Non-irradiated Vitamin E (0.1%) blended polyethylene (N-VitE-6w): 6 weeks artificially aged
- Non-irradiated polyethylene (N-PE-6w): 6 weeks artificially aged

The wear simulation was performed on a load controlled 4 station knee wear simulator (EndoLab GmbH) capable of reproducing loads and movement of stairs up, stairs down, level walking, chair raising and deep squatting. Daily patient activities measured by Bergmann et al. [7] in vivo, were applied in a combination of 40 % stairs up, 40 % stairs down, 10% level walking, 8% chair raising and 2% deep squatting with up to 100° flexion [8]. The load profiles were applied for 5 million HDA cycles, test serum was changed every 0.5 million HDA cycles and all the components were cleaned and analyzed according to ISO 14243-2:2009 to measure gravimetric wear. The gliding surfaces were inspected optically with a microscope and analyzed for abrasive-adhesive and delamination wear modes.

Results: The combination of artificial aging and HDA knee wear simulation lead to visible signs of delamination in the articulating surfaces of the STD-2w material [9]. Small delamination signs started to appear after 2.5 million HDA cycles and progressed to severe signs after 3 million HDA cycles (Fig. 1). The REM-2w has only shown slight signs of surface delamination after 3 million HDA cycles (Fig. 1), (ongoing test). However, the REM-6w material showed severe signs of delamination since the first 0.5 million HDA cycles (Fig. 2).
On the other hand, the VitE-6w material showed no signs of delamination during the whole HDA wear test (Fig. 2), only striated patterns and abrasion, and had a wear rate of 2.4 ± 0.3 mg/million HDA cycles. Same was seen with the N-VitE-6w material (Fig. 3), which showed a wear rate of 3.6 ± 1.4 mg/million HDA cycles.
Finally, the N-PE-6w material showed severe signs of delamination and was completely damaged after only 0.14 million HDA cycles (Fig. 3).

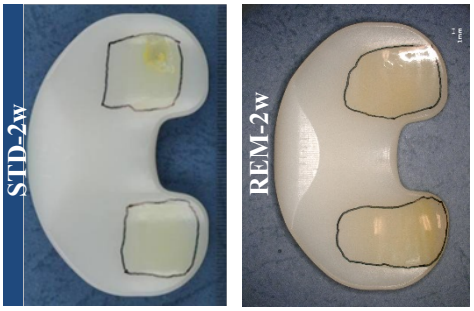

Fig. 1: Severe signs of delamination started to appear in the STD-2w material after 3 million HDA cycles [9], but have not been seen in the REM material after 3 million HDA cycles (ongoing test).

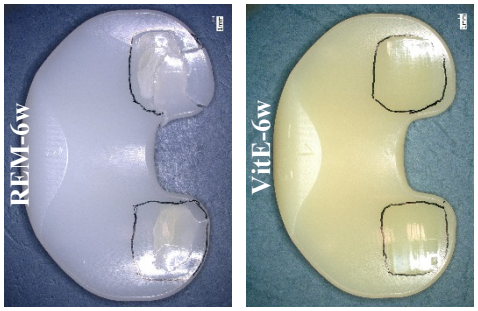

Fig. 2: Severe delamination occurred after only 0.5 million HDA cycles in the REM-6w material, but did not occurred in the VitE-6w material after 5 million HDA cycles.

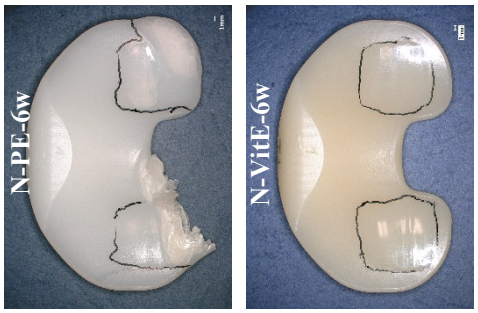

Fig. 3: Severe delamination occurred after only 0.14 million HDA cycles in the N-PE-6w material, but did not occurred in the N-VitE-6w material after 5 million HDA cycles.

Discussion:

This study showed the influence of the different degrees of artificial aging in combination with a HDA knee wear simulation on the delamination risk of several TKA polyethylene materials. While no severe signs of delamination were detected on the REM-2w material at the same time point they appeared on the STD-2w material, delamination did occurred when increasing the duration of artificial aging (REM-6w).

Moreover, this study demonstrated that vitamin E stabilized materials are able to prevent material fatigue and delamination, even under severe artificial aging and testing conditions.

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Bupivacaine-eluting polyethylene as an alternative to systemic opioid after total knee arthroplasty

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INTRODUCTION: Postoperative pain is a major side effect of total joint arthroplasty and improvements in pain management have the potential to shorten length of stay and reduce hospital readmission rates [1]. In this study, we aim to develop a novel pain management strategy that employs the use of analgesic-eluting polyethylene as an alternative to systemic opioid administration to provide targeted therapy at the surgical site and reduce the likelihood of opioid dependence after total joint arthroplasty. Specifically, we investigate the effectiveness of bupivacaine-loaded ultra-high molecular weight polyethylene in providing pain relief against systemic opioid pain treatment in a preclinical rat model of total knee replacement.

METHODS: The following experimental procedures were approved under MGH IACUC protocols 2015N000068 and 2018N000196. 24 Sprague Dawley rats received a simulated total knee arthroplasty surgery involving implantation of a titanium screw in the tibial plateau and press fitting of an ultra-high molecular weight polyethylene 3.0x3.0mm cylindrical implant transcondylarly. All rats were given pre-operative buprenorphine 30 minutes before surgery and were anesthetized using isoflurane. Postoperatively, pain management varied by group: Group I (n=8) received systemic buprenorphine every 12 hours for 3 days, while Group II (n=8) received a bupivacaine-loaded polyethylene implant (composition: 10% bupivacaine hydrochloride) during surgery to provide sustained local pain relief. Endpoint measurements included gait analysis (AGATHA, Orthopaedic Biomedical Engineering Laboratory, University of Florida) using videos recorded at 400 frames per second (PROMON U750, AOS Technologies), von Frey hindlimb reflex response (Electronic Von Frey, Bioseb), and static weight bearing (Walkway, Tekscan, Inc.). Kruskall-Wallis test was used to assess whether there were any differences between the groups by day ($p<0.05$).

RESULTS SECTION: All animals showed a greater hindlimb duty factor imbalance after surgery which did not recover to the healthy range (database of 140 animals) until postoperative week 3 and there were no significant difference between Group I and II. Hindlimb spatial symmetry dropped below the healthy range for days 1 and 3 for animals in the 10% bupivacaine group while the buprenorphine control group remained in the healthy range for the entire course of the study. Phase dispersion (right hind-left fore) increased after surgery and all post-operative measurements were comparable between the two groups. Right-left weight bearing ratio dropped after the operation indicating that animals were applying a greater force to the unoperated (left) limb and the groups were similar for all days. 1-5 toe spread values dropped after surgery and did not return to the healthy range by the end of the study for all animals. von Frey readings appeared mostly within the healthy range for both groups on the operated and unoperated limbs; however, left control leg readings were higher for the 10% bupivacaine group on most days (although not significantly).

DISCUSSION: Deviation from the healthy range for all animals for postoperative hindlimb duty factor imbalance indicates that animals experience some pain despite local or systemic pain medication administration. While there are not significant differences between groups for hindlimb spatial symmetry and weight bearing ratio, the slight delay in recovery to normal for the 10% bupivacaine group could indicate that a higher dose of the drug is needed. The slightly higher von Frey readings on the unoperated limb for the group receiving local bupivacaine could be due to the animals resting more on the unoperated side because of increased sensitivity and might also suggest a larger bupivacaine dose. Overall, the lack of significant differences between groups for postoperative gait metrics, von Frey reflex response, and static weight bearing suggests that locally delivered bupivacaine from polyethylene is comparable to systemic buprenorphine in relieving post-operative pain.

SIGNIFICANCE/CLINICAL RELEVANCE: Analgesic-eluting polyethylene shows promise as an alternative to systemic opioids in a rat model of total knee arthroplasty and proper dosing will be investigated in the future.

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ACKNOWLEDGEMENTS: This work was in part supported by the Office of the Assistant Secretary of Defense for Health Affairs, through the Peer Reviewed Medical Research Program under Award No. W81XWH-17-1-0614.

IMAGES AND TABLES:

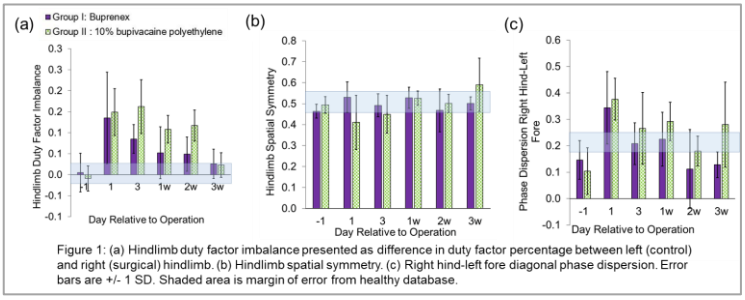

Figure 1: (a) Hindlimb duty factor imbalance presented as difference in duty factor percentage between left (control) and right (surgical) hindlimb. (b) Hindlimb spatial symmetry. (c) Right hind-left fore diagonal phase dispersion. Error bars are +/- 1 SD. Shaded area is margin of error from healthy database.

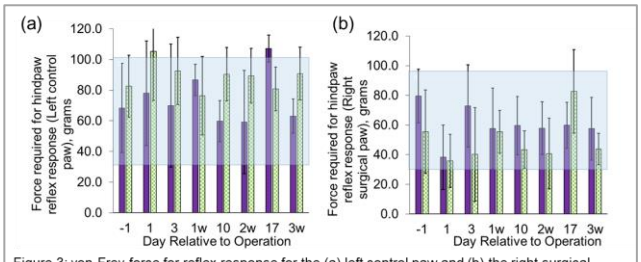

Figure 3: von Frey force for reflex response for the (a) left control paw and (b) the right surgical paw. Error bars are +/- 1 SD. Shaded area is margin of error from healthy database.

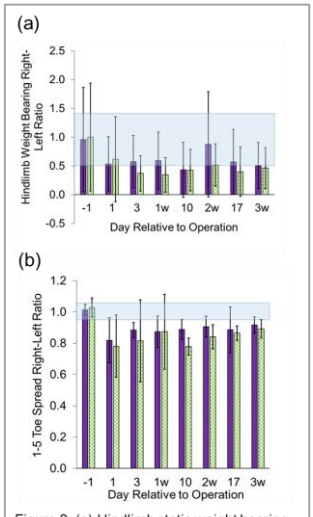

Figure 2: (a) Hindlimb static weight bearing surgical to control ratio. (b) Hindlimb 1-5 toe spread surgical to control ratio. Error bars are +/- 1 SD. Shaded area is margin of error from healthy database.

Local delivery of pain medication in an infected joint replacement model

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INTRODUCTION: A costly complication of joint replacement is periprosthetic infection, which occurs in 2% of total joint replacement patients [1]. We propose using a drug-eluting UHMWPE implant to deliver analgesic compounds locally to address post-surgical pain and to reduce the risk of infection [2]. Our approach involves studying the effect of pain medication (bupivacaine and tolfenamic acid) as non-conventional antibacterial compounds for this purpose in a clinically relevant infection in the rat model.

METHODS: This study was approved by MGH IACUC, under the protocol 2018N000196. Male Sprague-Dawley rats were given buprenorphine before isoflurane anesthesia. A 3.0x3.0 mm polyethylene cylindrical implant was implanted transcondylarly in the femur. 10 µL of saline was injected through the tibial plateau before insertion of a 1.3 mm diameter titanium maxillofacial screw. An additional 40 µL of saline was injected into the joint space. Two groups were performed: Group I (n=8) received saline with 10^8 CFU/50µL *S. aureus* (Xen29, ATCC 12600) with virgin polyethylene, and Group II (n=8) received saline with 10^8 CFU/50µL *S. aureus* with 5 % bupivacaine/5% tolfenamic acid polyethylene. Postoperative data collection occurred on days 1, 3, 7, 14, 21, 24, and 28. Animal weight, core temperature, and local knee temperature were recorded, blood collection performed, and x-rays captured. Spatiotemporal gait analysis was performed using AGATHA [3] and videos were recorded at ~400 fps (PROMON U750, AOS Technologies). Static weight bearing (Walkway, Tekscan, Inc.), hindpaw reflex response (Electronic Von Frey, Bioseb USA) and toe spread were also measured. At day 28, bone samples were collected, and retrieved screws were placed in sterile PBS. Screws were then sonicated for 45 minutes and the spread-plate method was used to determine adherent bacteria count. Micro-CT was performed *ex vivo* to determine the bone loss.

RESULTS: Following the surgery, the bodyweight of both groups declined. But the recovery rate of bupivacaine treated group (Group II) was faster than that of the control group. For Group II, the difference in skin temperature between surgical and non-surgical knees was significantly decreased at days 3 and day 7 (Figure 1). Post-sacrifice bacterial count was not significantly higher for Group II. Surgical:non-surgical hindlimb weight bearing ratio for Group II increased rapidly after surgery and recovered to baseline at POD 14. There were statistically significant differences between groups on days 1 and 3 (Figure 2). The infection was assessed by X-ray observation of osteolysis and implant migration (Figure 3). The bone loss was observed in both groups by micro-CT.

CONCLUSIONS: We showed previously that a chronic periprosthetic infection was established for in this model. After the 5 % bupivacaine/5% tolfenamic acid treatment, weight bearing was improved, demonstrating effective pain relief in this model by the locally delivered drugs. The bacterial count was decreased, and the postoperative skin temperature was also improved commensurate with out in-vitro findings of moderate antibacterial activity for these analgesics. However, the presence of implant migration and lysis at day 28 suggested that further study should focus on optimizing dosing and duration to treat infection.

SIGNIFICANCE/CLINICAL RELEVANCE: We established a preclinical infected joint surgery model in which postoperative recovery can be monitored by assessing gait, weight-bearing, and x-ray. This model can be used to study the efficacy of different combinations of implant materials and medication regimens.

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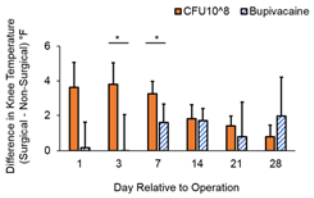

Figure 1. Mean difference in skin temperature between the surgical and non-surgical knees. Asterisks indicate difference between groups ($p<0.05$). Error bars are +/- 1 SD.

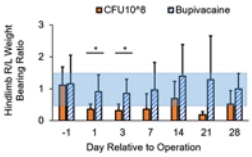

Figure 2. Weight bearing right:left (surgical:non-surgical) ratio for hind limbs. Asterisks indicate difference between groups ($p<0.05$). Shaded area is the margin of error from database of healthy animals. Error bars are +/- 1 SD.

Figure 3. Sample post-surgical x-ray images for infected and non-infected groups. Radiographs for infected rats show features of septic loosening including periosteal reaction (red arrows), and implant migration (asterisks)