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Brief communication

Tobacco Exposure Is Associated With Extremely Low Polyethylene Oxidation in Total Knee Arthroplasty Components

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ABSTRACT

Background: We evaluate whether patient exposures such as tobacco use are associated with high systemic or local in vivo oxidative state and with increased in vivo polyethylene oxidation.
Methods: We performed a case-control study which evaluated clinical factors associated with high systemic or local in vivo oxidative state among patients whose implants have been identified as demonstrating either extreme or minimal oxidation by our implant retrieval laboratory. Analysis of more than 2500 tibial inserts from explanted total knee arthroplasty demonstrated a wide spectrum of polyethylene oxidation. Components from some patients exhibited extremely high oxidation rates (super-oxidizers), and components from other patients demonstrated negligible oxidation (nonoxidizers). Patients' clinical data were retrospectively investigated from a prospectively collected institutional database.
Results: Eighteen patients met criteria as either super-oxidizers (9) or nonoxidizers (9). Average time in vivo was 6.6 (±4.4) years. Reasons for removal were aseptic loosening (10), instability (3), infection (2), component malposition (1), massive osteolysis (1), and other (1). Chi-square for categorical predictors demonstrated that nonoxidizer patients were significantly more likely to be current smokers than super-oxidizers (6 vs 0, $P = .012$). No other free radical–associated variables were significantly different across oxidation groups.
Conclusion: There was a significant association between extremely low ultra-high-molecular-weight polyethylene oxidation and current smoking.

Introduction

Oxidative damage to ultra-high-molecular-weight polyethylene (UHMWPE) arthroplasty components has been demonstrated to contribute to failure of total knee arthroplasty (TKA) [1]. Irradiation is used in UHMWPE manufacturing for sterilization or to increase implant wear-resistance through cross-linking. Oxidative damage results from chain scissioning as free radicals react with oxygen [2]. Several steps in the manufacturing processes, such as gamma-inert sterilization and barrier packaging, prevent exposure to oxygen and limit oxidative damage during storage before implantation [3]. However, there is no method to prevent in vivo exposure of polyethylene to oxygen and reactive oxygen species (ROS).

Inflammation is associated with the generation of free radicals and destructive proteolytic enzymes, which create a strong in vivo oxidative environment [4]. Moreover, studies of UHMWPE in culture media from inflamed synoviocytes demonstrate that ROS created by inflamed synovial tissue may induce oxidative implant degradation, resulting in a positive feedback loop yielding additional tissue inflammation, cytokine production, and ultimately polyethylene breakdown [4]. It remains unclear whether this process is impacted by patient clinical characteristics.

Through prospective retrieval analysis of TKA implants, we identified 2 cohorts, one with very high oxidation of the UHMWPE components and one with minimal or no oxidation of the UHMWPE components. In this investigation, we aimed to identify patient exposures and characteristics associated with increased

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in vivo polyethylene oxidation. We hypothesized that patient factors associated with the generation of ROS would have a positive association with UHMWPE oxidation.

Methods

We performed a case-control study evaluating clinical factors that are known to be associated with high systemic or local in vivo oxidative states among patients whose implants have been identified as demonstrating either extreme or minimal oxidation by our institutional review board–approved implant retrieval laboratory. Our analysis of more than 2500 tibial inserts from explanted TKAs demonstrated a wide spectrum of oxidation within polyethylene components. Components from some patients exhibited extremely high oxidation rates (super-oxidizers), and components from other patients demonstrated negligible oxidation (nonoxidizers). To test our hypothesis, we compared characteristics and exposures of patients in these 2 groups.

Our retrieval database was queried for all polyethylene tibial implants from a single institution for which oxidation magnitude and oxidation rate were known. Separate trend lines of expected oxidation were identified depending on the type of polyethylene used in the tibial insert: gamma-sterilized, annealed highly cross-linked, or remelted highly cross-linked. These devices were further sorted by in vivo duration and processing techniques (ie, manufacturing, sterilization, and cross-linking treatment). Devices with identical processing and similar in vivo duration were selected for further analysis (Fig. 1). Retrievals in the study were received between 2010 and 2018, representing 3 manufacturers. For our study, each retrieval was compared to the oxidation trend with time for that material. Implants identified as high-rate oxidizers had oxidation indices that on average were 7 times the expected oxidation index for their time in vivo. Retrievals identified as low-rate oxidizers had oxidation indices that on average were a factor of 5 less than the expected oxidation index for their time in vivo. The patients from whom the components were explanted made up our study sample. Investigators were blinded to the oxidative state of the retrieved implants from these patients (whether super-oxidizers or nonoxidizers) during data collection and analysis.

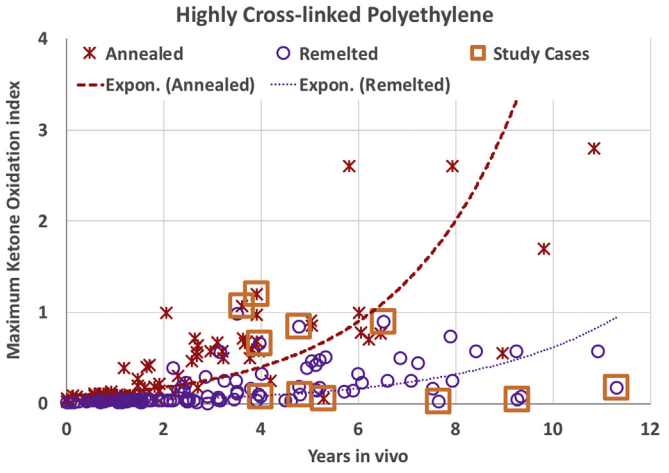

Figure 1. Maximum ketone oxidation index measured for highly cross-linked retrieved tibial inserts is plotted vs time in vivo. Trend lines of expected oxidation are shown separately for annealed highly cross-linked and remelted highly cross-linked inserts. The highly cross-linked retrievals included in the statistical analysis are highlighted by the orange boxes.

Review of available literature identified numerous clinical factors which may be related to systemic and local oxidative state. Eight hundred twenty-five diagnoses were determined to be potential contributors to oxidation state and were searched against the patient sample. These were defined by ICD-10 codes relating to various free radical–associated diseases (eg, cancer, hypertension, cirrhosis, asthma, autoimmune diseases) and exposures (eg, tobacco, pesticides) [5,6]. Patient clinical data were retrospectively investigated from a prospectively collected institutional database. Chi-square difference tests for categorical and independent samples t-tests for continuous outcomes were used for primary analysis. Data were analyzed using the R 3.6.1 statistical analytic software. Statistical significance was set at $P < .05$.

Results

Analysis of explanted polyethylene components identified 18 patients who met criteria as either super-oxidizers (9) or nonoxidizers (9). The average time in vivo was 6.6 (±4.4) years (high-rate oxidizers averaged 5.5 years in vivo, the nonoxidizers 7.5 years in vivo.) The reasons for removal were aseptic loosening (10), instability (3), infection (3), component malposition (1), and massive osteolysis (1). Table 1 demonstrates comparative data from group 1 (super-oxidizers) and group 2 (nonoxidizers). We found that age and gender were not significantly different across oxidation groups. Chi-square for categorical predictors demonstrated that nonoxidizer patients were significantly more likely to be current smokers than super-oxidizers (6 vs 0, $P = .012$). No other free radical–associated variables were significantly different across oxidation groups (Table 2). In addition, no differences were found across groupings in the mean number of free radical–associated variables (Tables 1 and 2).

Table 1
Comparative data from super-oxidizers and nonoxidizers

Patient characteristics	Super-oxidizers	Nonoxidizers	*P* value
N	9	9	
Age, mean (SD)	66.04 (10.71)	66.84 (10.85)	.877
Gender = male (%)	3 (33.3)	5 (55.6)	.635
Race = white (%)	9 (100)	9 (100)	NA
Left/Right = R (%)	4 (44.4)	6 (75.0)	.433
Endometrial cancer = yes (%)	1 (11.1)	0 (0.0)	NA
Lung cancer = yes (%)	0 (0.0)	1 (11.1)	NA
Tongue cancer = yes (%)	0 (0.0)	1 (11.1)	NA
Cancer = yes (%)	0 (0.0)	1 (11.1)	NA
Hypertension = 1 (%)	7 (77.8)	5 (55.6)	.617
Tobacco use[a] = yes (%)	0 (0.0)	6 (66.7)	**.012**
Tobacco use[b] = yes (%)	3 (33.3)	8 (88.9)	.053
Alcohol use = yes (%)	7 (77.8)	5 (55.6)	.617
Cataract = yes (%)	1 (11.1)	0 (0.0)	NA
Centrilobular emphysema = yes (%)	0 (0.0)	1 (11.1)	NA
High blood pressure = yes (%)	1 (11.1)	0 (0.0)	NA
Posterior capsular opacification = yes (%)	1 (11.1)	0 (0.0)	NA
Asthma = yes (%)	2 (22.2)	1 (11.1)	NA
Psoriasis = yes (%)	0 (0.0)	1 (11.1)	NA
Reactive airway disease = yes (%)	1 (11.1)	0 (0.0)	NA
Hypertensive retinopathy = yes (%)	0 (0.0)	1 (11.1)	NA
Analgesic allergy = yes (%)	0 (0.0)	1 (11.1)	NA
Narcotic allergy = yes (%)	0 (0.0)	1 (11.1)	NA
All cancer = yes (%)	1 (11.1)	3 (33.3)	.571
Free radical disease, mean (SD)	1.11 (0.60)	1.00 (1.00)	.779
Free radical exposure, mean (SD)	1.11 (0.78)	1.44 (0.73)	.363
Total, mean (SD)	2.67 (1.12)	3.00 (1.87)	.653

The bold values indicate statistical significance.
[a] Smokers defined as only current smokers.
[b] Smokers defined as either currently smoking or having a history of smoking.

Table 2
Comparison of free radical associated variables for super-oxidizers and nonoxidizers

Patient characteristics	Super-oxidizers		Nonoxidizers		
	No free radical	Free radical	No free radical	Free radical	*P* value
n	3	6	5	4	
Age, mean (SD)	68.07 (7.35)	65.03 (12.58)	70.59 (12.28)	62.15 (7.76)	.689
Gender = male (%)	2 (66.7)	1 (16.7)	2 (40.0)	3 (75.0)	.259
Race = whte (%)	3 (100)	6 (100)	5 (100)	4 (100)	NA
Left/Right = R (%)	1 (33.3)	3 (50.0)	4 (80.0)	2 (66.7)	.573
Endometrial cancer = yes (%)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Lung cancer = yes (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	NA
Tongue cancer = yes (%)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	NA
Cancer = yes (%)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	NA
Hypertension = yes (%)	3 (100.0)	4 (66.7)	4 (80.0)	1 (25.0)	.17
Tobacco use[a] = yes (%)	0 (0.0)	0 (0.0)	2 (40.0)	4 (100.0)	**.006**
Tobacco use[b] = yes (%)	2 (66.7)	1 (16.7)	4 (80.0)	4 (100.0)	**.04**
Alcohol use = yes (%)	3 (100.0)	4 (66.7)	2 (40.0)	3 (75.0)	.358
Cataract = yes (%)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	NA
Centrilobular emphysema = yes (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	NA
HBP = yes (%)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	NA
Posterior capsular opacification = yes (%)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	NA
Asthma = yes (%)	1 (33.3)	1 (16.7)	0 (0.0)	1 (25.0)	NA
Psoriasis = yes (%)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	NA
Reactive airway disease = yes (%)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	NA
Hypertensive retinopathy = yes (%)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	NA
Analgesic allergy = yes (%)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	NA
Narcotic allergy = yes (%)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	NA
All cancer = yes (%)	1 (33.3)	0 (0.0)	2 (40.0)	1 (25.0)	.414
Free radical disease, mean (SD)	1.67 (0.58)	0.83 (0.41)	1.00 (0.71)	1.00 (1.41)	.562
Free radical exposure, mean (SD)	1.67 (0.58)	0.83 (0.75)	1.20 (0.84)	1.75 (0.50)	.214
Total, mean (SD)	3.33 (0.58)	2.33 (1.21)	3.20 (2.17)	2.75 (1.71)	.764

The bold values indicate statistical significance.
[a] Smokers defined as only current smokers.
[b] Smokers defined as either currently smoking or having a history of smoking.

Conclusion

Our analysis demonstrated a significant association between extremely low UHMWPE oxidation and current smoking. Conversely, extremely high oxidation rates were present only in nonsmokers. No other free radical–producing disease states or exposures were associated with oxidation rate. These findings are unexpected as smoking is known to promote oxidative damage in other organ systems [7].

In vivo oxidation appears to be related to the local fluid environment [8,9]. *In vivo* ROS that diffuse into UHMWPE react with free radicals residing in irradiated polyethylene or may initiate oxidation in polyethylene with no initial free radicals [8]. Superoxide dismutase is an endogenous antioxidant enzyme that is believed to serve a protective role in the progression of inflammatory and degenerative arthritis [10,11]. This and other antioxidant enzymes are regulated by the transcription factor nuclear factor erythroid 2–related factor 2 (Nrf2). One plausible explanation for our findings is upregulation of Nrf2 in smokers. Prior literature evaluating Nrf2 activation in the lungs of smokers has demonstrated increased expression of Nrf2-modulated genes, likely as a cellular defense against the oxidative stress of smoking [12]. If present in the joint, this could lead to increased levels of superoxide dismutase resulting in a protective antioxidant environment that might decrease oxidative stress to polyethylene implants by reducing in vivo exposure to ROS.

The present study has several limitations. The small sample size limits the ability to further evaluate other factors which may contribute to in vivo UHMWPE oxidation and may confound results. Our small sample size also precluded evaluation of whether reason for implant removal was a contributing factor. While smoking status was determined at the time of retrieval, smoking status of all patients at the time of index surgery was unable to be determined from our current data as many of the patients underwent their index surgery at outside facilities. Furthermore, as the majority of the index joint replacement surgeries for patients in the sample were performed at outside institutions, we are limited in our evaluation of shelf-life of implants before implantation, which may also affect outcomes related to oxidative damage. We are currently proceeding with broader investigations to address these limitations.

Despite these limitations, we believe our preliminary findings are noteworthy and merit early communication as they may be of interest to other investigators. With additional investigation we hope to determine the molecular basis for the complex interaction between the in vivo environment and arthroplasty components. This information could lead to improvements in arthroplasty component longevity by understanding the relationship between transcription factors and oxidation which could further our understanding of the role of oxidative injury in the progression of arthritis.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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