Published in final edited form as:

Biomaterials. 2006 February ; 27(5): 752–757. doi:10.1016/j.biomaterials.2005.06.011.

Correlating subjective and objective descriptors of ultra high molecular weight wear particles from total joint prostheses

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Abstract

A total of 750 images of individual ultra-high molecular weight polyethylene (UHMWPE) particles isolated from periprosthetic failed hip, knee, and shoulder arthroplasties were extracted from archival scanning electron micrographs. Particle size and morphology was subsequently analyzed using computerized image analysis software utilizing five descriptors found in ASTM F1877-98, a standard for quantitative description of wear debris. An online survey application was developed to display particle images, and allowed ten respondents to classify particle morphologies according to commonly used terminology as fibers, flakes, or granules. Particles were categorized based on a simple majority of responses. All descriptors were evaluated using a one-way ANOVA and Tukey–Kramer test for all-pairs comparison among each class of particles. A logistic regression model using half of the particles included in the survey was then used to develop a mathematical scheme to predict whether a given particle should be classified as a fiber, flake, or granule based on its quantitative measurements. The validity of the model was then assessed using the other half of the survey particles and compared with human responses. Comparison of the quantitative measurements of isolated particles showed that the morphologies of each particle type classified by respondents were statistically different from one another ($p < 0.05$). The average agreement between mathematical prediction and human respondents was 83.5% (standard error 0.16%). These data suggest that computerized descriptors can be feasibly correlated with subjective terminology, thus providing a basis for a common vocabulary for particle description which can be translated into quantitative dimensions.

Keywords

Wear debris; Arthroplasty; Polyethylene; Joint replacement

1. Introduction

Aseptic loosening is the most frequent long-term complication in prosthetic total joint replacements and is the most common cause of component failure requiring revision [1,2]. This complication has been shown to be closely associated with osteolysis and the

generation of wear debris from the joint prosthesis [3,4], with ultra-high molecular weight polyethylene (UHMWPE) particles appearing to play a particularly significant role [5]. Previous studies have shown that UHMWPE wear debris particles generated from the liner are deposited in periprosthetic tissues surrounding the bone where they are engulfed by local tissue macrophages [6]. Phagocytosis results in the activation of macrophages and the release of cytokines such as IL-1 β and TNF- α which promote local inflammation at the interfacial membrane, osteoclastogenesis, and secondary osteolysis [7]. The result of these processes is a local environment which favors net bone resorption and subsequent aseptic loosening of the joint prosthetic. Systemic dissemination of UHMWPE particles is also common with particles being found in extra-articular reticuloendothelial tissues such as the spleen and paraaortic lymph nodes [8].

The pathogenesis of UHMWPE particle-induced inflammation and resulting osteolysis is not fully understood; however, it has been shown that factors such as size, quantity, and morphology of wear particles play important roles in determining the magnitude of these cellular responses. Several previous studies have shown that the majority of particles generated from hip, knee, and shoulder arthroplasties are submicron in size, with a mean particle size of 0.5 μ m, and greater than 90% of particles less than 1 μ m [9]. Green et al. [10] demonstrated that these submicron sized particles stimulated murine peritoneal macrophages to generate significantly higher levels of bone-resorbing activity than larger particles. Recently, studies have also investigated the role of UHMWPE particle morphology in the response to wear debris of periprosthetic tissue and up-regulation of gene products involved in osteoclastogenesis [11]. Ren et al., using a murine pouch model, showed that elongated UHMWPE particles induced significantly higher expression of RANK, RANK-L, IL-1 β , TNF- α , and CK gene products as compared with more globular shaped particles [12].

Due to the importance of particle characteristics in the quantity and quality of biological response, great emphasis has been placed on developing techniques to extract and study the quantity, size, and morphology of UHMWPE wear particles. Campbell et al. [13] and others have demonstrated the feasibility of isolating submicron UHMWPE particles from periprosthetic tissue retrieved at the time of revision without altering particle morphology, and scanning electron microscopy has been extensively used to examine individual submicron particles. However, despite these advances, a uniform set of terminology for describing particle characteristics has been elusive. Over the years, various descriptors have been used to characterize particles. For example, McKellop et al. [14] categorized particles as either *rounded* or *elongated*. Later, Schmalzried et al. [15] used a system designating beads, *granules*, *fibrils*, *shreds*, and *flakes* as distinct descriptors of particle morphology. In an effort to quantify particle characteristics, Stachowiak et al. [16] used a computerized image analysis program to generate a set of numerical descriptors to characterize particles. These descriptors included outline fractal dimension (OFD), form factor (FF), roundness (R), and aspect ratio (AR). Landry et al. [17] refined this set to include equivalent circular diameter (ECD) as a measure of particle size and elongation factor (EF). The American Society for Testing and Materials later adopted these six descriptors as part of ASTM Standard F1877-98 for quantitative characterization of wear particles [18]. ASTM F1877-98

has been successfully used to characterize wear debris from failed hip, shoulder, and knee arthroplasties [19].

Even with the advent of standardized criteria for describing wear debris, and computerized image processing, much of the terminology used to describe particles in current literature relies on commonly used subjective terms such as those stated earlier. Several issues are immediately apparent in this schema. First, the use of subjective terms has the potential for presenting a barrier to comparing results across different studies. Next, standardized dimensions have been successfully used to quantify important information about particle morphology but they may fail to communicate the gestalt of the particle in simple, understandable terms.

The goal of the present study was to analyze UHMWPE particles using computerized image analysis to generate quantitative dimensions, and then categorize particles using subjective responses from individuals. Quantitative analysis was then performed to develop a computational model which will be useful in classifying particles according to appropriate subjective category. This information may be useful for developing a common vocabulary for describing particles which incorporates both formal dimensions and subjective impression.

2. Materials and methods

Digital images of individual UHMWPE particles obtained from periprosthetic tissue of failed total hip, shoulder and knee arthroplasties were extracted from archival scanning electron micrographs. These particles had previously been obtained from digested tissue using a protocol described by Mabrey et al. [19] Particles were filtered on 0.2 μm Nucleopore poly-carbonate filters (Whatman Inc., Clifton, NJ) and dried. Each filter was then sputter-coated with gold palladium and digitally imaged on a Zeiss LEO 435VP scanning electron microscope (Oberkochen, Germany). Individual particle images were selected on the basis of a clear view of an isolated particle, variability in morphology, and variability in magnification. Magnification ranged from 2500 $\times$ to 10,000 $\times$ with the vast majority of particles imaged at either 5000 $\times$ or 10,000 $\times$.

Particle analysis was conducted on Macintosh computers (Apple, Cupertino, CA), using a custom application based on the public domain image-processing and analysis program, NIH Image. This application was developed at the Research Services Branch of the National Institute of Mental Health (NIMH), part of the National Institute of Health (NIH), and is publicly available on the Internet at <http://rsb.info.nih.gov/nih-image>. Particles were outlined on each micrograph and analysis was performed to produce five shape and size parameters contained in ASTM F1877-98: FF, R, AR, ECD, and E for each particle. Both images and data were entered into a custom relational database.

ECD is a measure of size defined as the diameter of a circle with area equivalent to the area of the particle, and has units of length. Thus, first the area (A) of the particle is determined using image analysis and then the ECD is calculated using the following relationship:

$$ECD=2(A/\pi)^{1/2}.$$

The remaining descriptors are dimensionless ratios which describe aspects of particle morphology. AR is the ratio of the major diameter (longest straight line drawn between any two points on the particle) to the minor diameter (longest line perpendicular to the major diameter). Elongation (E) is the ratio of the particle's actual length to average width. R is a measure of how closely the particle resembles a circle, with a perfect circle having a value of 1. FF is a measure of how closely the particle resembles a circle based on perimeter. The sixth parameter, OFD, was omitted for this study.

A survey application was developed to allow questionnaire data to be entered over the Internet. The survey asked respondents to classify themselves as *Surgeon*, *Researcher*, *Resident*, or *Other* according to their experience in the field of medicine. The respondents comprised researchers, surgeons, medical residents, or medical students all working in the orthopedic field. Next, respondents were shown images of individual particles along with magnification, and asked to classify each particle as a *fiber*, *flake*, or *granule* based on terminology commonly used in particle analysis literature. An example of the survey and images presented to respondents is shown in Fig. 1. In all, ten respondents from the clinical field classified each particle according to subjective preference and previous experience. Each particle was designated as a specific type based on a simple majority of these responses. Particles for which there was no majority classification were excluded from further analysis. Frequency distributions of different particle types were plotted using Microsoft Excel 2002 (Microsoft Corporation, Redmond, WA) and analyzed with respect to the five variables via one-way ANOVA, and then compared among particle classes by the Tukey–Kramer multiple comparisons test at $p = 0.05$.

From this data, statistical analysis was performed to generate a logistic regression model to predict a particle type, given the five standard variables previously described. This would allow a subjective determination of how the particle type depended on these quantitative measurements. The multinomial logistic regression model we chose stipulates that each particle has certain probabilities, denoted by p_{fla} , p_{gra} , p_{fib} , to be of three types: flakes, granules, fibers. These probabilities satisfy the system of equations

$$\begin{aligned} \log(p_{fla}/p_{fib}) &= a + b_1 \cdot ECD + b_2 \cdot AR + b_3 \cdot E + b_4 \cdot R + b_5 \cdot FF, \\ \log(p_{gran}/p_{fib}) &= c + d_1 \cdot ECD + d_2 \cdot AR + d_3 \cdot E + d_4 \cdot R + d_5 \cdot FF, \\ p_{fla} + p_{gra} + p_{fib} &= 1, \end{aligned}$$

where a , c , and b_i ; d_i ; $i = 1 \dots 5$ are unknown parameters that need to be estimated from the data based on the maximum likelihood principle. This was performed using built in functions in the StatView software package (SAS Institute Inc., Cary NC). Once these probabilities for a given particle are calculated, its type can be determined to be the one with the highest probability. In order to test how well this prediction scheme corresponds to human classification, an agreement test was performed by randomly taking half of the classified particles ($n = 346$) to construct the model which was then used to predict the type

of the remaining half of the particles. This result was then compared with the particle classifications assigned by survey respondents by vote.

3. Results

A total of 750 particles comprising three groups of 250 particles from hip, knee, and shoulder arthroplasties were analyzed in this study. The results of qualitative analysis are presented in Table 1 as mean value±standard error. By vote, survey respondents classified 93 particles as fibers, 252 particles as flakes, and 347 particles as granules. An additional 58 particles were excluded because no particle type was selected by a majority of respondents. Mean ECD, AR, E, R, FF values were significantly different among particle types ($p<0.05$, ANOVA). Post-hoc tests (Tukey–Kramer) showed each particle type to be different from other particle types based on quantitative descriptors. Frequency distributions for equivalent circular diameter based on particle type are shown in Fig. 2. For size measurement, it is apparent that larger particles (mean ECD: $2.03\pm0.04\ \mu\text{m}$) tended to be classified as flakes. The smallest particles (mean ECD: $1.24\pm0.02\ \mu\text{m}$) were classified as granules, with particles classified as fibers having intermediate values (mean ECD $1.86\pm0.01\ \mu\text{m}$). As might be expected, mean AR and E measurements indicate that elongated particles tended to be classified as fibers (mean AR: 4.04 ± 0.02 ; mean E: 12.43 ± 0.05). Particles classified as flakes tended towards higher ARs (1.94 ± 0.03) and E values (4.32 ± 0.03) than granules (mean AR: 1.54 ± 0.02 ; mean E: 2.55 ± 0.07). However, as shown in Figs. 3 and 4, significant overlap in relative frequency distribution exists for these dimensions among granules and flakes. Analysis of R values showed that particles classified as granules tended to be more circular (mean R: 0.66 ± 0.02) and fibers were the least circular (mean R: 0.23 ± 0.01). Particles classified as flakes occupied a distinct but intermediate ground between fibers and granules (mean R: 0.50 ± 0.01). Similar results were seen with FF measurements for fibers (0.29 ± 0.01), flakes (0.60 ± 0.01), and granules (0.78 ± 0.01). Relative frequency distributions for particle types based on R and FF are shown in Figs. 5 and 6, respectively.

For statistical analysis, the following explicit expressions were obtained to allow the calculation of the probability of each particle type from the five parameters:

$$\begin{aligned} X &= \exp(2.35 + 0.62 \cdot \text{ECD} - 0.87 \cdot \text{AR} - 0.32 \cdot \text{E} + 2.35 \cdot \text{R} + 2.31 \cdot \text{FF}), \\ Y &= \exp(-0.55 - 0.42 \cdot \text{ECD} - 1.11 \cdot \text{AR} - 0.14 \cdot \text{E} + 3.87 \cdot \text{R} + 7.87 \cdot \text{FF}), \\ p_{fla} &= X / (1 + X + Y), \\ p_{gra} &= Y / (1 + X + Y), \\ p_{fib} &= 1 / (1 + X + Y). \end{aligned}$$

This model was generated based on the particles used for the survey. In order to test the validity of the model in predicting the types of other particles outside this data set, we carried out 100 test-runs. In each test-run half of the particles were randomly selected to generate a multinomial logistic regression model which was then used to predict the types of the other half of the particles. In these 100 test-runs, the average agreement between the particle type predicted by the model and that chosen by survey respondents was 83.5% with a standard error of 0.16%.

4. Discussion

The characterization of UHMWPE wear debris particle size and morphology has been an evolutionary process. It is clear that an understanding of characteristics such as size and morphology of particles can be critical to the development of models to elucidate the etiology and progression of osteolytic processes at the implant–bone interface. The process of particle analysis and characterization has been greatly aided by the advent of computerized image-analysis software which has allowed the transition from particle descriptions based on crude dimensions and subjective impression to more objective quantification by integrating descriptors which take into account the complex morphologies present in retrieved samples. These efforts have allowed standardization and a common platform for particle descriptions. However, a significant disconnect continues to exist when attempting to communicate between the vagaries of subjective morphological descriptors and objective dimensions produced by computer.

In terms of size and morphology, the character of UHMWPE wear debris obtained for this study compares favorably with debris obtained by other investigators from other failed hip, knee, and shoulder arthroplasties. [15,19] This data suggests that particles classified as “fibers”, regardless of size, tend to have larger AR and E values with smaller R and FF values. Particles classified as flakes have larger relative ECD values and intermediate FF and R values. Particles classified as granules tend to have smaller ECD and elongation values, but relatively larger R and FF values. The distributions for AR and E show the most significant separation between particles described as fibers and those described as granules or flakes, suggesting that these descriptors may be the most useful in differentiating these particle types. The distributions for R and FF show significant separation between all three particle types. However, the inter-quartile ranges for equivalent circular diameter in the fiber and flake categories overlap substantially. Overall, these plots indicate that the measurements of the five descriptors may be useful in classifying particles into an appropriate category using a suitable mathematical model.

We based this study on the assumption that individuals attempting to describe particles would use a common set of subjective impressions to guide their categorization of a particle as a particular type. Using logistic regression we generated a model which was able to predict the particle type which was chosen by human observers approximately 83% of the time. This result suggests that there is significant inter-observer agreement as to what constitutes a fiber, flake, or granule, and that these observations can be translated into valid numerical estimates of particle properties. The computational model developed as part of this investigation may be viewed as a tool for bridging sometimes disparate terminology with data derived from computer analysis in order to allow researchers to better characterize particle morphology.

This is the first study known to the authors to investigate the role of subjective terminology in classifying various types of UHMWPE particles. More research is necessary to determine the impact of a higher sample population of respondents on how particles are classified and to refine the accuracy of the mathematical model. The methodology presented here is not

limited to UHMWPE particles but can be used to classify wear debris from other polymeric and non-polymeric biomaterials.

5. Conclusions

In summary, a methodology based on statistical techniques has been developed to correlate quantitative shape and size descriptors of UHMWPE wear particles to qualitative descriptors often used in the literature. This technique will provide the foundation for a common vocabulary for wear particle descriptions and their understanding.

Acknowledgments

The authors would like to thank DePuy Orthopaedics for providing the funding for this work.

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Fig. 1.
Sample electron micrographs of UHMWPE particles with accompanying survey text.

Fig. 2. Frequency distribution for equivalent circular diameter of UHMWPE particles classified as granules, flakes, and fibers. In general there was significant inter-quartile overlap between particle types.

Fig. 3.

Frequency distribution for aspect ratio of UHMWPE particles classified as granules, flakes, and fibers. Particles classified as fibers were more elongated, while flakes and granules had similar values.

Fig. 4. Frequency distribution for elongation of UHMWPE particles classified as granules, flakes, and fibers. Particles classified as fibers were clearly the most elongated, followed by flakes and then granules.

Fig. 5. Frequency distribution for roundness of UHMWPE particles classified as granules, flakes, and fibers. Particles showed distinct separation based on classification, with granules tending to more closely approximate a circular shape.

Fig. 6. Frequency distribution for form factor of UHMWPE particles classified as granules, flakes, and fibers. Particles showed significant separation based on classification, with granules tending to be more rounded.

Table 1

Size and shape descriptors for UHMWPE wear debris particles

	N	ECD (μm)	AR	E	R	FF
Fiber	93	1.86 ± 0.07	4.04 ± 0.169	12.43 ± 0.48	0.23 ± 0.01	0.29 ± 0.01
Flake	252	2.02 ± 0.04	1.94 ± 0.033	4.32 ± 0.03	0.50 ± 0.01	0.60 ± 0.01
Granule	347	1.24 ± 0.02	1.54 ± 0.02	2.55 ± 0.07	0.66 ± 0.01	0.78 ± 0.01
Total	692	1.67 ± 0.03	2.03 ± 0.04	4.56 ± 0.14	0.53 ± 0.01	0.64 ± 0.01

All values expressed as mean ± standard error.