



Biocompatibility testing of domestically produced ultra-high molecular weight polyethylene with vitamin E through manufacturing and design evaluation with analysis of toxicity, inflammatory response, and tissue reaction in an *Oryctolagus cuniculus* rabbit model

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Abstract

Introduction: Life expectancy in Indonesia will increase along with economic and health advancements. Osteoarthritis is a degenerative disease that can affect joints in various parts of the human body, including the hip joint, one of the most frequently affected areas. Significant pain can lead to impaired mobility and dependence on support devices or assistance from others. **Objective:** To assess and compare the safety and biocompatibility of domestically produced vitamin E-stabilized UHMWPE (GUR® 1050-E) against commercial UHMWPE as acetabular liner material in the Total Hip Arthroplasty system.

Methods: *In vivo* experimental study with a comparison of 2 groups. Laboratory of the Faculty of Veterinary Medicine, Airlangga University, 1 August–12 September 2025 (observation period 6 weeks). A total of 12 male rabbits aged 3–6 months (1500–2000 g) were divided into 2 groups (each n=6): domestically produced UHMWPE + vitamin E and commercial UHMWPE (control). After 7 days of acclimatization, sterile 6 × 5 mm UHMWPE implants were implanted into the right femur near the periosteum under ketamine–xylazine anesthesia. Outcomes included Draize Test and Body Condition Score (weeks 0, 3, 6), serum IL-6 and TNF-α levels by ELISA (weeks 0 and 6), and histopathology of the tissue around the implant

(H&E) with Modified ISO 10993-6 assessment after euthanasia. Statistical analysis used SPSS 25.0.

Results: All Draize scores at weeks 0, 3, and 6 were 0 in both groups without erythema or edema, and there were no significant differences across time points or between groups ($p=1.000$). IL-6 and TNF-α levels decreased significantly intragroup from week 0 to week 6 in both groups. The decrease in IL-6 in the UHMWPE + vitamin E group was greater than in the control group (Δ IL-6: 221.03 ± 200.91 vs. 21.26 ± 12.44 ; $p=0.035$), while the change in TNF-α between groups was not significantly different ($p=0.073$). The BCS was relatively stable without significant differences between groups. Local tissue response scores based on Modified ISO 10993-6 did not differ significantly between groups ($p=0.945$). **Conclusion:** Domestically produced vitamin E-stabilized UHMWPE has equivalent biocompatibility to commercial UHMWPE with no evidence of additional adverse effects.

Keywords: Biocompatibility. Draize Test. IL-6. ISO 10993-6. Rabbit model. TNF-α. UHMWPE. Vitamin E.

Introduction

Life expectancy in Indonesia will increase along with economic and health advancements. Osteoarthritis is a degenerative disease that can affect joints in

various parts of the human body, including the hip joint, one of the most frequently affected areas. Significant pain can lead to impaired mobility and dependence on support devices or assistance from others [1]. Total hip replacement is a widely performed surgical procedure for the treatment of hip osteoarthritis, providing excellent long-term results and making it one of the most reliable orthopedic surgical procedures. Over one million patients worldwide require total hip arthroplasty (THA) each year, with demand continuing to rise as the aging population and the increasing life expectancy of patients lead to a need to remain physically active [2].

The success of this procedure depends heavily on the performance and biocompatibility of the prosthetic component materials used. Prosthetic products used in Indonesia are generally imported from abroad, increasing surgical costs. Another obstacle is that the size of these prostheses is based on the average bone dimensions of foreigners or Caucasians, which can affect surgical success rates and postoperative complications [3]. A relevant solution is the development of domestic prostheses that are more compatible and appropriate to the anatomy and morphometry of the Indonesian population, while simultaneously reducing dependence on imported products and expanding access to more affordable and high-quality orthopedic care.

Ultra-High Molecular Weight Polyethylene (UHM) is a biomaterial that has proven important in hip arthroplasty due to its good mechanical properties, high wear resistance, and proven biological compatibility in various studies [4]. Innovation in the development of Ultra-High Molecular Weight Polyethylene (UHMWPE) continues to be carried out to improve oxidative stability, reduce wear rates, and extend implant life, thereby increasing the long-term success of hip arthroplasty [5]. Ultra-High molecular Weight Polyethylene has the potential to become a primary material in the development of local hip prostheses in Indonesia, but biocompatibility testing is still required to ensure safe interaction with tissue and prevent complications. This study is the initial stage of biomaterial safety screening through the evaluation of biological responses in the form of tissue toxicity, inflammatory reactions, immune responses, physical conditions, and tissue histopathology in *in vivo* tests using *Oryctolagus cuniculus* rabbits for 6 weeks to support the development of hip arthroplasty prosthesis technology that is in line with Indonesian national standards or Domestic Component Levels as well as the need for biocompatibility evaluation before the advanced pre-clinical stage and clinical applications, including in the context of fulfilling the regulatory aspects of the Food and Drug Supervisory Agency.

Materials and Methods

Study Design

This study is an *in vivo* experimental evaluation of the biocompatibility of domestically produced UHMWPE (GUR® 1050-E) compared with commercial UHMWPE as a control. Evaluation was carried out through local toxicity parameters, systemic inflammatory and immune responses, physical conditions, and histopathological responses of tissues around the implant in a rabbit model for 6 weeks, and following the ARRIVE checklist: (Available on: <https://arriveguidelines.org/arrive-guidelines>. Accessed on: March 18, 2025).

Ethical Approval

The study was conducted at the Laboratory of the Faculty of Veterinary Medicine, Airlangga University, Surabaya, from August 1st to September 12th, 2025 (Ethical approval number 2.KEH.102.07.2025).

Animal model and eligibility criteria

The test animals were male rabbits (*Oryctolagus cuniculus*) aged 3–6 months, weighing 1500–2000 g, divided into 2 groups (n=6 each). This study used the absence of harmful effect approach and applied the 3R principle (Reduction, Refinement, Replacement), so that the number of 5–6 animals/group was considered adequate for initial safety screening and in line with related methodological recommendations/standards [6,7]. Inclusion criteria included active, healthy rabbits, as determined by clinical examination, without infectious/metabolic diseases, without musculoskeletal disorders, able to tolerate anesthesia and surgery, maintained in a controlled laboratory environment, and not showing excessive aggressiveness. Exclusion criteria included active or parasitic infections, immune/autoimmune disorders, cardiovascular or respiratory disorders that increase anesthetic risk, history of previous trauma/orthopedic surgery, severe stress/high aggressiveness that interferes with standard care, and intraoperative death.

Study variables

The independent variable was the type of implant (domestic UHMWPE GUR® 1050-E stabilized with vitamin E vs commercial UHMWPE). The dependent variables included local toxicity (Draize Skin Irritation Test), physical/nutritional condition (Body Condition Score/BCS), inflammatory response (serum IL-6 level), immune response (serum TNF- α level), and local tissue response (H&E histopathology with Modified ISO 10993-6 scoring system). The control variables included rabbit species/type (age and uniform weight), cage and feedwater conditions, operator and surgical technique, evaluation time, blood collection procedure,

and histological processing and staining techniques.

Study procedures

Domestically produced UHMWPE is made based on GUR® 1050 with a very high molecular weight (± 4.7 – 8.7 million g/mol) determined through an intrinsic viscosity approach (Margolies formula), then mixed with vitamin E (α -tocopherol) at around 1000 ppm to increase oxidative stability, processed by compression molding/direct compression molding, and undergoing irradiation (gamma or electron beam) for sterilization and optimization of mechanical properties; the product is claimed to meet related material standards (ASTM F648, ISO 5834-1/2, ASTM F2965) before biocompatibility testing [8]. The implant is cut to size and sterilized (autoclave 121°C, 15 minutes). After 7 days of acclimatization, implantation was performed on the right thigh: anesthesia with ketamine 100 mg/kg and xylazine 5 mg/kg intramuscularly, surgical field preparation with povidone-iodine and 70% alcohol, incision in the biceps femur muscle, then a 6 mm $\times$ 5 mm implant was placed intramuscularly near the femoral periosteum with minimal fixation (Figure 1), wound closure with resorbable suture, and administration of cefazolin 25 mg/kg and meloxicam 0.2 mg/kg postoperatively. Daily monitoring was performed to assess activity, signs of infection, and complications.

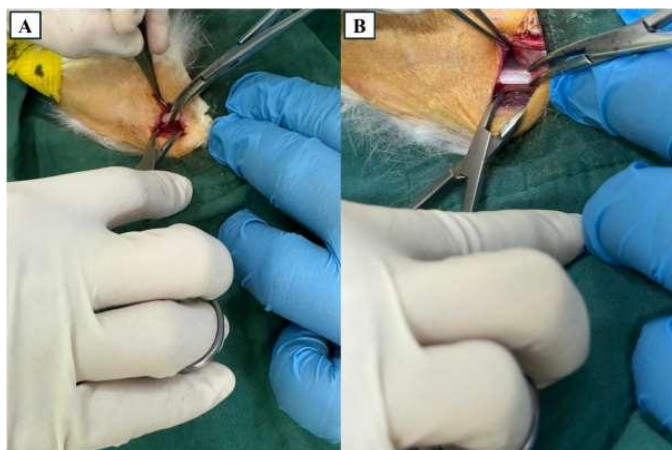


Figure 1. Surgical procedure and implantation process using commercially available UHMWPE in Indonesia (A) before placement and (B) after placement. Source: Own authorship.

Data collection

The Drainage Test was performed at weeks 0, 3, and 6, assessing erythema and edema around the surgical area on a scale of 0–4, accompanied by photographic documentation when necessary, and categorizing the level of irritation based on the cumulative total score. BCS was assessed periodically using a scale of 1–5 by palpation of the spine, ribs, base of the tail, flanks, and shoulders to monitor changes in nutritional status/general condition throughout the

study. Blood samples were drawn at weeks 0 and 6 via the marginal auricular vein (or a suitable alternative), processed by centrifugation at 3000 rpm for 10 minutes, and serum was stored at -80°C until analysis. IL-6 and TNF- α levels were measured by ELISA according to the antigen-antibody principle. Serological evaluation at the specified time points refers to the practice of evaluating inflammatory biomarkers in animal models [8]. After the study period was completed, euthanasia was performed according to animal welfare protocols, then the tissue around the implant was excised, fixed in 10% buffered formalin, processed by paraffin, sectioned at 4–5 μm , stained with H&E, and assessed using Modified ISO 10993-6 (ISO, 2016), including parameters of inflammation, foreign body response, fibrosis, and bleeding.

Statistical analysis

Analyses were performed to compare between groups and across time points according to measurement points. Draize scores and BCS at weeks 0, 3, and 6 were analyzed as repeated data. IL-6 and TNF- α levels were compared between groups at weeks 0 and 6 using an independent t-test, while intragroup changes from week 0 to 6 were analyzed using a paired t-test. Draize scores and BCS were analyzed using the Friedman test for intragroup comparisons across time points. Modified ISO 10993-6 histopathology scores at the end of observation were compared between groups according to the study's analytical plan. All analyses were performed using SPSS version 25.0.

Results

Draize Skin Irritation Test

The Draize Skin Irritation Test was conducted to evaluate the potential for local irritation of the skin around the UHMWPE biomaterial implantation area, which was observed serially at week 0, week 3, and week 6 post-implantation. Based on the observation results, all experimental animals in the control and treatment groups showed a score of zero at all evaluation times. No signs of erythema, edema, or other skin irritation reactions were found in the area around the implant, either immediately after implantation or during follow-up observations up to week 6. The results of the Mann-Whitney test at each time point and the Friedman test in each group showed a p-value of 1.000, indicating no statistically significant difference. Thus, neither domestically produced UHMWPE with added vitamin E nor commercial UHMWPE without vitamin E caused skin irritation or inflammation during the observation period (Table 1).

Table 1. Draize Skin Irritation Test Scores for Each Group

Groups	Week 0	Third week	Sixth week	p-value
UHMWPE	0	0	0	1.000 ^b
UHMWPE + Vit E (GUR® 1050-E)	0	0	0	1.000 ^b
p-value	1.000 ^a	1.000 ^a	1.000 ^a	

*Analysis using the following tests: ^aMann Whitney U-Test, ^bFriedman. Significant results if the p-value is ≤ 0.05 . Source: Own authorship.

Differences in Inflammatory Response (IL-6 and TNF- α) between UHMWPE + Vit E and UHMWPE Implant Groups

The Shapiro-Wilk test results showed that all data were normally distributed ($p \geq 0.05$). The difference in IL-6 pre and post was used a paired t-test because the data on the difference in IL-6 in the UHMWPE + Vitamin E and UHMWPE implant groups were normally distributed. The difference in IL-6 pre and the difference between the UHMWPE + Vit. E and UHMWPE implant groups used a 2-sample independent t-test because the data of the two groups being compared were normally distributed (**Table 2**).

Table 2. Results of Normal Distribution Testing of IL-6 Data.

Variable	Groups	p-value	
		UHMWPE + Vit. E (n = 7)	UHMWPE (n = 6)
Pre		0.120	0.328
Post		0.706	0.074
Delta		0.149	0.204
Variable	Groups	Pre (p-value)	Post (p-value)
IL-6	UHMWPE + Vit E (GUR® 1050-E)	0.159	0.092
IL-6	UHMWPE	0.055	0.092
TNF- α	UHMWPE + Vit E (GUR® 1050-E)	0.047*	0.064
TNF- α	UHMWPE	0.053	0.076

*Analysis using the Shapiro-Wilk test. Results are significant if the p-value is ≤ 0.05 . Source: Own authorship.

Furthermore, a comparison of changes in cytokine levels between groups was carried out by calculating the difference between post and pre values (Δ = post - pre) and analyzed using the Mann-Whitney test. The results of the analysis showed that the decrease in IL-6 levels in the UHMWPE + vitamin E (GUR® 1050-E) group was significantly greater than in the UHMWPE alone group, with a p value of 0.035. In contrast, the results of TNF- α measurements did not show a statistically significant difference between the treatment and control groups (p value = 0.073) (**Table 3**).

Table 3. Mean Difference Test on Differences in IL-6 and TNF- α Level Measurement Results at Weeks 0 and 6.

Variable	Δ UHMWPE + Vit E (Mean $\pm$ SD)	Δ UHMWPE (Mean $\pm$ SD)	p-value
IL-6	-206.29 ((-615.12) – 53.65)	-17.24 ((-43.17) – (-10.75))	0.035*
TNF- α	-10.02 ((-79.30) – (-0.98))	-16.75 ((-21.33) – (-12.94))	0.073

*Analysis using the Mann-Whitney U-Test. Results are significant if the p-value is ≤ 0.05 . Δ : difference in measurement results at week 0 and week 6. Source: Own authorship.

Based on intra-group analysis related to changes in IL-6 and TNF- α levels from before and after treatment in each group, it showed that both in the treatment group and the control group, there was a statistically significant decrease in IL-6 and TNF- α levels. In the UHMWPE + vit E group, the decrease in IL-6 levels (369.64 ± 187.19 vs 148.61 ± 27.86) and TNF- α (22.56 ± 26.32 vs 3.84 ± 2.61) showed a statistically significant decrease with a p value of 0.028 in the results of IL-6 level measurements and 0.018 in the results of TNF- α level measurements. Furthermore, in the UHMWPE group, the decrease in IL-6 levels (92.57 ± 6.31 vs 71.31 ± 7.88) and TNF- α (19.84 ± 3.87 vs 2.87 ± 0.81) showed a statistically significant decrease with a p value of 0.028 in the results of measuring IL-6 and TNF- α levels (**Table 4**).

Table 4. Test of Differences in Mean IL-6 and TNF- α Levels in Each Group

Variable	Groups	(Mean $\pm$ SD) Week 0	(Mean $\pm$ SD) Sixth week	p-value
IL-6	UHMWPE + Vit E	369.64 ± 187.19	148.61 ± 27.86	0.028*
IL-6	UHMWPE	92.57 ± 6.31	71.31 ± 7.88	0.028*
TNF- α	UHMWPE + Vit E	22.56 ± 26.32	3.84 ± 2.61	0.018*
TNF- α	UHMWPE	19.84 ± 3.87	2.87 ± 0.81	0.028*

*Analysis using the Wilcoxon Test. Results are significant if the p-value is ≤ 0.05 . Source: Own authorship.

Body Condition Score (BCS)

Based on the results of the BCS assessment conducted at week 0, week 3, and week 6 in the UHMWPE and UHMWPE + vitamin E (GUR® 1050-E) groups, the BCS scores in both groups showed relatively stable values with a tendency for a slight increase until week 6 for each experimental animal (**Table 5**).

Table 5. Body Condition Score of Experimental Animals at Each Measurement Time.

Code	Groups	Week 0	Third week	Sixth week
P01	UHMWPE	3	3	3
P02	UHMWPE	2	3	3
P03	UHMWPE	3	3	4
P05	UHMWPE	3	3	4
P06	UHMWPE	2	2	3
P07	UHMWPE	3	3	3
E01	UHMWPE + Vit E	3	3	4
E02	UHMWPE + Vit E	3	3	3
E03	UHMWPE + Vit E	2	3	3
E04	UHMWPE + Vit E	3	3	4
E05	UHMWPE + Vit E	2	2	3
E06	UHMWPE + Vit E	3	3	3

Source: Own authorship.

Based on the mean difference test, the mean BCS score in the UHMWPE group was 2.86 ± 0.38 at week 0, increased to 3.14 ± 0.38 at week 3, and 3.43 ± 0.53 at week 6, while in the UHMWPE + vitamin E (GUR® 1050-E) group the mean BCS score was 2.86 ± 0.38 at week 0, 3.00 ± 0.38 at week 3, and 3.14 ± 0.38 at week 6. The Friedman test in each group showed a p value of 0.043 in the UHMWPE group and 0.368 in the

UHMWPE + vitamin E (GUR® 1050-E) group. Furthermore, the Mann-Whitney test between groups at each observation time showed a p-value of 1.000 at week 0, 0.705 at week 3, and 0.220 at week 6 (Table 6).

Table 6. Difference Test of Mean BCS Scores.

Groups	Week 0	Third week	Sixth week	p-value
UHMWPE	2.86 ± 0.38	3.14 ± 0.38	3.43 ± 0.53	0,043 ^b
UHMWPE + Vit E	2.86 ± 0.38	3.00 ± 0.38	3.14 ± 0.38	0,368 ^b
p-value	1,000 ^a	0,705 ^a	0,220 ^a	

*Analysis using the following tests: aMann Whitney U-Test, bFriedman. Significant results if the p-value is ≤0.05. Source: Own authorship.

Histopathological Analysis Using the Modified ISO 10993-6 Scoring System

Fisher's exact test results showed no difference in bleeding and foreign body responses between the UHMWPE + Vitamin E implant group and the UHMWPE group ($p \geq 0.05$). The Mann-Whitney test results showed no difference in inflammatory and fibrotic responses between the UHMWPE + Vitamin E implant group and the UHMWPE group ($p \geq 0.05$) (Table 7).

Table 7. Differences in histopathological responses between the SUHMWPE + Vit. E and UHMWPE groups.

Histopathological response	UHMWPE + Vit E	UHMWPE	p-value
Bleeding			0,592
None	3 (42.9%)	4 (66.7%)	
Mild	4 (57.1%)	2 (33.3%)	
Inflammation			0.815
None	3 (42.9%)	4 (66.7%)	
Rare, 1-5 cells per HPF	1 (14.3%)	0 (0%)	
Rare, 5-10 cells per HPF	2 (28.6%)	0 (0%)	
Heavy infiltration	1 (14.3%)	1 (16.7%)	
Very heavy infiltration (full)	0 (0%)	1 (16.7%)	
Foreign body response			0.192
None	7 (100%)	4 (66.7%)	
Rare, 1-2 cells per HPF	0 (0%)	2 (33.3%)	
Fibrosis			0.940
None	2 (28.6%)	3 (50%)	
Narrow band	1 (14.3%)	0 (0%)	
Medium band	3 (42.9%)	1 (16.7%)	
Thick band	1 (14.3%)	2 (33.3%)	

Source: Own authorship.

Based on histopathological evaluation of the tissue around the implantation site using H&E staining, differences in tissue response patterns were observed between the UHMWPE + Vitamin E (GUR® 1050-E) and UHMWPE groups. In the UHMWPE + Vitamin E (GUR® 1050-E) group, the histological appearance was dominated by relatively organized fibrous tissue with densely and homogeneously arranged collagen fibers around the implant area. Inflammatory cell infiltration was minimal, consisting primarily of sparse mononuclear cells, without a predominance of neutrophils or dense infiltration. The presence of macrophages and multinucleated giant cells was very limited, and no severe infiltration or cell sheets were observed. Furthermore, signs of tissue hemorrhage

were almost absent, and no necrosis or extensive tissue damage was observed around the implant site. In contrast, in the UHMWPE group, histopathology showed tissue around the implant appearing more irregularly arranged with muscle fibers and connective tissue, accompanied by areas of fibrosis that were more prominent and varied in thickness. Mononuclear inflammatory cell infiltration was more pronounced than in the UHMWPE + vitamin E (GUR® 1050-E) group, although it remained mild to moderate. Furthermore, more macrophages and indications of a foreign body response were observed around the implant area, although not yet reaching the level of severe infiltration. In some areas, tissue changes suggestive of local remodeling were also observed, with residual mild hemorrhage around the implant tissue (Figure 2).

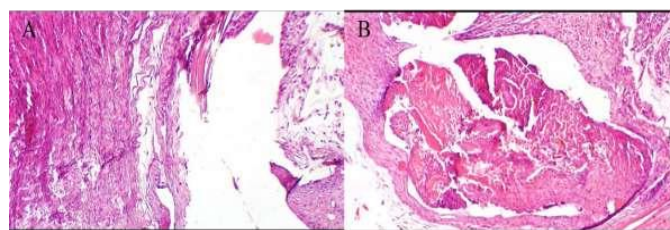


Figure 2. **A)** Histological examination results of the UHMWPE + vitamin E group (GUR® 1050-E), **B)** Histological examination results of the UHMWPE group. Source: Own authorship.

Discussion

This study showed that both UHMWPE materials were well tolerated during the 6-week observation in the rabbit model. The Draize test at weeks 0, 3, and 6 consistently showed a score of 0 in both groups without erythema or edema, IL-6 and TNF- α levels decreased from week 0 to week 6, BCS was relatively stable with a slight upward trend, and Modified ISO 10993-6 histopathology scores were comparable between groups with a tendency for more organized fibrosis and minimal inflammatory infiltration in UHMWPE + vitamin E. The consistent outcome pattern in several of these domains supports the interpretation that the emerging biological response is controlled and tends to resolve over time. These findings are also in line with the objectives of early-stage safety screening in the absence of a harmful effect approach, so that the focus is on the absence of clear toxicity/adverse reaction signals during the subacute period [9,10].

Regarding local toxicity outcomes, the absence of a reaction in the Draize Test confirms that the modification of domestically produced UHMWPE does not increase the risk of irritation compared to commercial products. Previous evidence by Pietrzak and Pietrzak positioned UHMWPE as a relatively inert orthopedic polymer that rarely triggers significant soft

tissue reactions. This finding is consistent with the biological characteristics of the material [5,9,10]. The skin irritation test also serves as a sensitive baseline for detecting potential acute local toxicity, so a persistent score of 0 has strong confirmatory value for local safety. Hypersensitivity reactions are more commonly associated with metal-based implants through ion release and delayed-type hypersensitivity mechanisms, whereas polymers like UHMWPE are less likely to trigger these pathways [11,12].

The decrease in IL-6 in the systemic inflammatory response, in both groups, indicates resolution of post-implantation inflammation and does not support the presence of persistent inflammation due to the biomaterial. IL-6 is known as one of the key cytokines that plays a role in the early to subacute phase of foreign body reaction, so its decrease over time supports tissue adaptation to the presence of the implant.⁹ The greater decrease in IL-6 in the UHMWPE + vitamin E group is in line with evidence that vitamin E stabilization can suppress inflammatory pathways related to oxidative stress and reduce the production of pro-inflammatory cytokines upon exposure to UHMWPE [13,14]. The mechanism of free radical stabilization after irradiation in UHMWPE described in the literature also provides a biological rationale for why the microenvironment can become less pro-inflammatory in vitamin E-stabilized materials [15,16]. The literature also emphasizes that prolonged IL-6 elevation may contribute to undesirable remodeling, making this decreasing trend biologically relevant [17].

The decrease in TNF- α in both groups indicates transient acute immune activation followed by a resolution phase, consistent with TNF- α 's role as an early mediator of foreign body reactions, which are generally milder in polymers than in metals [9,10]. The lack of significant differences between groups supports that domestically produced UHMWPE does not trigger a stronger systemic immune response than commercial products in the phases evaluated. The wider variation in initial TNF- α values in the vitamin E group may occur because TNF- α is highly dynamic and sensitive to the degree of tissue trauma and wound healing response, allowing biological variation between animals to widen the distribution [14]. The timing of measurements that do not capture the very early phase after implantation may also explain why differences between materials are not clearly visible, especially if biological differences are more pronounced in exposure to wear debris particles than in intact implants [14,18].

The stability of the BCS in both groups supports that UHMWPE implantation did not impose a significant physiological burden over 6 weeks. The BCS serves as an integrative indicator that captures changes in

nutritional status, postoperative recovery, and physiological stress, thus its stability corroborates the findings of systemic safety from cytokine output. The literature suggests that responses to UHMWPE are generally limited to the local environment surrounding the implant, except under extreme conditions such as heavy wear and high particle accumulation, so the stability of the animals' body condition is consistent with the systemic inert profile of UHMWPE [4,5,9,10]. Vitamin E is also reported to have a good biocompatibility profile and acts as an antioxidant that can reduce tissue oxidative stress without disrupting systemic homeostasis, so it is not expected to reduce the animals' body condition during the monitoring period [13,15]. Limited observation duration still needs to be considered because very subtle systemic changes may require longer monitoring to be detected consistently [5].

Comparable Modified ISO 10993-6 quantitative scores indicate equivalence of local tissue responses between materials in terms of inflammation, fibrosis, bleeding, and foreign body response. The literature suggests that tissue responses to UHMWPE fall along a spectrum of mononuclear inflammation, fibrosis, and foreign body response, influenced by material stability, oxidation, and particulate matter. Therefore, the tendency for more organized fibrosis and less inflammatory infiltration in UHMWPE + vitamin E remains significant, although not always fully quantified by numerical scores [9,18]. Mechanistic evidence regarding oxidative stabilization of UHMWPE by vitamin E and reduced free radical formation provides a biological basis for a more organized pattern of tissue remodeling [15,17,19,20]. Furthermore, Thomas et al stated that highly cross-linked polyethylene had a significantly lower steady-state wear rate than conventional UHMWPE at 7 years in a double-blind randomized controlled trial using radiostereometric analysis, reinforcing that material modification can reduce wear, which is a key upstream driver of late particle-mediated inflammation and osteolysis [21]. A study by Cang et al reported that dendritic cells enhance UHMWPE wear particle-induced osteoclast differentiation of macrophages, with augmented NF- κ B activation and higher TNF- α levels, supporting that the most discriminative inflammatory differences between materials may emerge under wear-particle exposure rather than intact implantation [22]. However, evidence regarding vitamin E-containing wear particles remains mixed: Bichara et al found reduced osteolytic potential of vitamin E-diffused highly cross-linked UHMWPE particles in a murine calvarial model, whereas Neuerburg et al observed no significant difference in osteolysis between UHMWPE and vitamin E-blended

UHMWPE particles in a murine particle-induced osteolysis model, indicating ongoing controversy and model dependence [23,24].

The strength of this study lies in its controlled in vivo design with multiparameter outcomes that assessed local, systemic, and histological safety in parallel. Limitations include a small sample size, a 6-week duration, and an implantation model that does not represent the THA joint environment and has not evaluated the outcomes of wear debris, osteolysis, bone integration, and long-term performance.

Conclusion

This study shows that domestically produced UHMWPE is well tolerated for 6 weeks in a rabbit model and has a safety profile comparable to commercial UHMWPE, characterized by a Draize score of 0, decreased IL-6 and TNF- α without signs of persistent systemic inflammation/immunity, stable BCS, and similar histopathological responses around the implant without severe reactions. Further studies need to extend the follow-up and add evaluation of oxidative stress, osteolysis, wear debris, and bioavailability testing, before proceeding to advanced pre-clinical and controlled clinical trials for widespread use.

CRedit

Author contributions: All authors contributed to the conception and design of the study. Material preparation, data collection, and laboratory analyses were performed by all authors. The first draft of the manuscript was prepared by the corresponding author, and all authors critically reviewed, edited, and approved the final version of the manuscript for submission.

Acknowledgment

Not applicable.

Ethical Approval

The study was conducted at the Laboratory of the Faculty of Veterinary Medicine, Airlangga University, Surabaya, from August 1st to September 12th, 2025 (Ethical approval number 2.KEH.102.07.2025), and following the ARRIVE checklist: (Available on: <https://arriveguidelines.org/arrive-guidelines>. Accessed on: March 18, 2025).

Informed Consent

Not applicable.

Funding

Not applicable.

Data Sharing Statement

The datasets generated and analysed during the current study are not publicly available because of confidentiality of patient information, but are available from the corresponding author on reasonable request, subject to institutional approval and compliance with applicable data-protection regulations.

Publication Statement

All authors have agreed to the publication of this article.

Conflict of Interest

The authors declare no competing interests.

Similarity Check

It was applied by Ithenticate®.

Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

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