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Potential Lubricating Mechanism of Hyaluronic Acid for a Reduction of Albumin-Mediated Friction in the Artificial Joint System

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Abstract: The average lifespan of artificial joints is 15–25 years, but it is still too short for young and active patients. Human synovial albumin is easily adsorbed on the surfaces of artificial joint materials and has increased friction when subjected to conformational changes. Most studies have focused on the interaction between synovial fluid components and artificial joints when protein conformation has not been modified, but not on how to reduce friction and wear caused by denatured proteins. This study aimed to investigate whether hyaluronic acid could provide lubrication for albumin-mediated friction when high friction was caused by the disrupted secondary structure of albumin. Thermally processed human synovial albumin was used as denatured protein while friction testing, measurement of conformation, adsorption, and viscosity analysis were investigated. The results demonstrated that adding fresh hyaluronic acid to thermally processed albumin solution could reduce 50% of the friction coefficient caused by totally disrupted albumin. The viscosity of thermally processed albumin with fresh hyaluronic acid increased 40 times more than denatured albumin alone, and the adsorbed albumin area with fresh hyaluronic acid increased twice. The results showed hyaluronic acid provided lubrication by increasing the viscosity for friction mediated by denatured albumin, and it may provide a potential solution for prolonging the lifespan of artificial joints.

Keywords: lubricating mechanism; artificial joint system; hyaluronic acid; albumin

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1. Introduction

Osteoarthritis (OA) is a common condition that increases with age, and the end-stage treatment is mainly total knee arthroplasty (TKA) [1]. The main material for artificial joint system is ultra-high molecular weight polyethylene (UHMWPE), because of its high mechanical strength and wear resistance [2]. Although the lifespan of an artificial joint system has been reported to range between 15 and 25 years, the aseptic loosening induced by wear particles of UHMWPE is still one of the major causes for TKA revision [3]. For older patients, a 25-year lifespan of an artificial joint system might be sufficient. However, for younger and active users, more durable artificial joints are needed so as not to affect the quality of patients' lives. In order to reduce UHMWPE wear particles, a reduction of friction or an increase of lubrication in the artificial joint system could be potential solutions.

The synovial fluid still functions as a lubricant after TKA; thus, the interaction between the components of synovial fluid and the artificial joint materials may affect the tribological properties of UHMWPE.

Human synovial fluid contains biological components that can act as lubricants, such as albumin, globulin, mucinous glycoproteins (mainly lubricin), and hyaluronic acid (HA) [4]. Previous studies have shown that the synovial fluid compositions differ between a healthy joint and an OA joint; mainly, the concentration of HA is decreased from 2.5~4 mg/mL to 0.83~2 mg/mL in OA patients [5]. Therefore, increasing HA might be useful for improving lubrication in the artificial joint system. Forsey et al. and Mabuchi et al. have shown that adding HA could decrease friction for damaged joints in human or animal models through increasing the viscosity of lubricant, resulting in HA being adsorbed on the joint surface to reduce friction [6,7]. For the artificial joint system, adding HA was not absolutely beneficial for a reduction of the friction coefficient. Although raising the concentration of HA (molecular weight was 2–4 $\times$ 10^6 Dalton) could decrease the high friction coefficient caused by the presence of albumin, HA was not a good lubricant when the concentration was higher than 5 mg/mL in the UHMWPE–CoCrMo artificial joint system [8]. The results suggest that the interaction between HA and albumin should be taken into account for decreasing friction in order to extend the lifespan of artificial joints.

Bovine serum albumin could be adsorbed on the surface of UHMWPE–CoCrMo artificial joint material, resulting in a lower friction coefficient compared with Hanks' balanced salt solution as a lubricant [9]. Although Serro's group observed no conformational changes of albumin in their experimental conditions, it has been shown that the surface temperature of UHMWPE could reach 60 °C during friction [10]. Temperature could affect the conformational changes of proteins. Das et al. showed that human serum albumin (HSA) became aggregates or fibrils when the temperature was raised to 56 °C or 70 °C [11]. Fang et al. demonstrated that when HSA was thermally processed at 90 °C, the α-helix content of albumin was decreased, resulting in an increased friction coefficient of the UHMWPE–CoCrMo sliding system [12]. In addition, the adsorption rate of thermally processed albumin was higher than naïve albumin, suggesting that more denatured albumin was adsorbed on the surface of UHMWPE and subsequently resulted in a higher friction coefficient [12]. If denatured albumin causes high friction of the artificial joint system and shortens its lifespan, whether adding HA can decrease the friction coefficient caused by the denatured albumin becomes critical. However, such an issue has not yet been investigated.

In this study, the tribological effect of HA on albumin-mediated friction was investigated in the UHMWPE–CoCrMo artificial joint system. The friction coefficients of thermally processed HSA at 75 °C or 90 °C alone or combined with thermally processed HA or fresh HA was analyzed. The reason for selecting 75 °C or 90 °C was to maintain disrupted structures of albumin during analysis, which has been previously predicted by molecular dynamics simulation approaches [12]. In addition, Mishina et al. observed a broken structure of albumin after longer friction testing (24 h) [13], suggesting that parts of albumin would be denatured after extensive use by artificial joint patients. To maintain the consistency of each testing condition, a mixture of normal and denatured albumin that may mimic the clinical situation was not used in this study. The secondary structure, adsorption area on a CoCrMo alloy disc, and viscosity of thermally processed HSA with or without HA were also investigated. The results can then provide a potential lubricating mechanism of HA that can decrease the friction of the UHMWPE–CoCrMo artificial joint system and possibly increase its lifespan.

2. Materials and Methods

2.1. Preparation of Solutions

Human serum albumin (HSA, Sigma-Aldrich, St. Louis, MI, USA) was dissolved in phosphate buffer saline (PBS, Sigma-Aldrich, St. Louis, MI, USA) and the final concentration was 12.5 mg/mL. Hyaluronic acid sodium salt (HA, molecular weight is 2–4 $\times$ 10^6 Dalton, Sigma-Aldrich, St. Louis, MI, USA) was either dissolved in PBS only or in albumin solution

(HSA–HA), and the final concentration of HA was 4.5 mg/mL. When preparing thermally processed HSA, HA, or HSA–HA solution, 6 mL of solution was poured into a caped vial and heated at 75 ± 1 °C or 90 ± 1 °C in the constant temperature water bath for 5 min. The vial was then placed at 22 °C for another 5 min, and the procedures were repeated 3 times for a total period of 30 min.

2.2. Friction Testing

A pin-on-disc rotational motion was used for friction testing, and the articulating materials were fixed onto the universal micro-tribometer-2 (CETR, UMT-2) tester. The highly crosslinked GUR1050 ultra-high molecular weight polyethylene pin (UHMWPE) and cobalt—chromium–molybdenum (CoCrMo) alloy disc were used as the articulating materials, and both were provided by the United Orthopaedic Corporation (Taipei, Taiwan). The size of the UHMWPE pin was 6.35 mm in diameter and 25.4 mm in height, and the mean roughness of the end surface was 0.82 μm. The surface of the CoCrMo alloy disc (50 mm in diameter and 5 mm in height) was polished and the surface roughness was 0.11 μm. The condition of friction testing was described as follows: normal load was 159 Newton (the contact pressure was 5.0 MPa), rotational speed was 20 rpm (revolutions per minute; the equivalent velocity was 20.93 mm/s), rotational radius was 10 mm, and the duration of friction was 15 min. Each solution was tested 3 times. The friction coefficient was friction force divided by normal force, and the friction coefficient from the last 5 min was averaged for comparison. The contact pressure of knee cartilage could range between 2.3 and 7.4 MPa during walking [14]; thus, the median normal load was conducted in this study. In addition, the knee speed during walking on the treadmill could range from 0.28 to 0.81 m/s [15]. Since the friction of artificial joints is boundary lubrication, a rotational speed lower than the knee speed was selected.

2.3. Measurement of the Structural Changes of Thermally Processed Albumin

The native and thermally processed structures of HSA in PBS or in HA solution were measured using circular dichroism (CD). The CD was operated at room temperature over a wavelength range between 190 nm and 250 nm, and the scan speed was 20 nm/min. The α-helix content was the value of the CD signal (mdeg) at 208 nm and 222 nm [12,16], and each spectrum was tested 3 times. Once 3 measurements were obtained and averaged, the α-helix content of HSA at 25 °C was considered as 100%. The value of the other solution was then compared with HSA at 25 °C to obtain the relative percentage of α-helix content.

2.4. Adsorption of Fluorescent-Labeled HSA on CoCrMo Alloy Disc

HSA or thermally processed HSA was labeled with fluorescein isothiocyanate by using FluroTag™ FITC Conjugation Kit (FITC1, Sigma-Aldrich, St. Louis, MI, USA) according to the manufacturer's instructions. The mechanism of fluorescent labeling is that FITC combines with free amino acid groups of protein to form a stable thiourea bond [17]; thus, both undenatured and denatured albumin can be labeled and detected. The CoCrMo alloy disc was immersed in 10 mL of labeled HSA with or without HA solution for 1 min, and the extra solution was wiped after taking out the disc. The CoCrMo alloy disc was then placed in 30 mL of PBS and rotated at 150 resolutions per minute (rpm) for 2 min and rinsed with 10 mL of PBS. After drying the disc, the labeled alloy disc was observed with a fluorescence microscope (Nikon eclipse 50i, Tokyo, Japan). Three random areas of each labeled alloy disc were imaged, and the fluorescent area was quantified by ImageJ software (National Institute of Health, Bethesda, MD, USA). The average areas of adsorbed albumin on the CoCrMo alloy disc in different solutions under the same thermally processed temperature were compared.

2.5. Viscosity Analysis of Different Solutions

The viscosity of various solutions was measured by a programmable rheometer (DV-III ultra, Brookfield, Middleboro, MA, USA), which was equipped with a cone-on-plate fixture

in the steady-shear mode. Then, 0.5 mL of HSA, HA, HSA–HA, thermally processed HSA, thermally processed HSA–HA, and thermally processed HSA with fresh HA solutions were measured, and each solution was repeated 3 times at 25 °C. A sweep of rotation speeds was performed, and the viscosity of each solution at different shear rates was recorded.

2.6. Statistical Analysis

All data were represented as the means of three independent samples. The differences in friction testing, structural changes, adsorption, and viscosity were assessed by the two-tailed Student's t-test. Differences were only compared between different solutions at the same temperature. A p value less than 0.05 was considered statistically significant.

3. Results

3.1. Thee Effect of Thermally Processed Albumin with or without HA on Friction Coefficient

The UHMWPE pin was sliding against the CoCrMo alloy disc in various solutions to investigate the friction coefficient, and the results are shown in Figure 1. The friction coefficient of human serum albumin (HSA) was significantly higher than HA at 25 °C but was reduced in the presence of HA (Figure 1a). A similar phenomenon was observed when HSA was thermally processed. The friction coefficient of thermally processed HSA was higher than that of HA, no matter whether HSA was treated at 75 °C (Figure 1b) or at 90 °C (Figure 1c). The presence of HA could decrease the friction coefficient significantly, and adding fresh HA showed a lower friction coefficient that the HSA–HA group (Figure 1b,c).

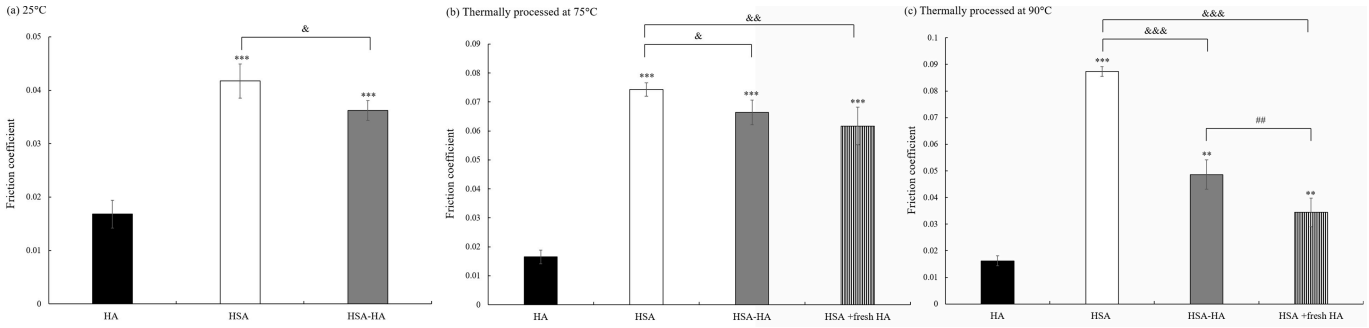

Figure 1. The friction coefficient of HA (black bar), HSA (white bar), HSA–HA (grey bar), and thermally processed HSA with fresh HA (stripe bar). Solutions are not thermally processed (**a**), or thermally processed at 75 °C (**b**) or 90 °C (**c**). Each bar is shown as mean ± standard deviation. ** $p < 0.01$ or *** $p < 0.001$ when comparing friction coefficients of different solutions versus HA. $^{\&}$ $p < 0.05$, $^{\&\&}$ $p < 0.01$, $^{\&\&\&}$ $p < 0.001$ when comparing friction coefficients of different solutions versus HSA. $^{\#\#}$ $p < 0.01$ when comparing friction coefficients of thermally processed HSA with fresh HA versus thermally processed HSA–HA.

3.2. Thermally Processed Albumin Reduces Its α-Helix Content

In order to investigate the effect of temperature on the secondary structure of albumin, the α-helix content of HSA in various solutions was analyzed. The results showed that α-helix of HSA was decreased at 75 °C at wavelengths of 208 nm (Figure 2a) and 222 nm (Figure 2b), and it reduced more when HA was also thermally processed with HSA. However, the α-helix content of thermally processed HSA at 75 °C with fresh HA was similar to thermally processed HSA alone. When HSA was thermally processed at 90 °C, the α-helix content was lower than 16%, and adding thermally processed HA or fresh HA did not affect the secondary structures of albumin.

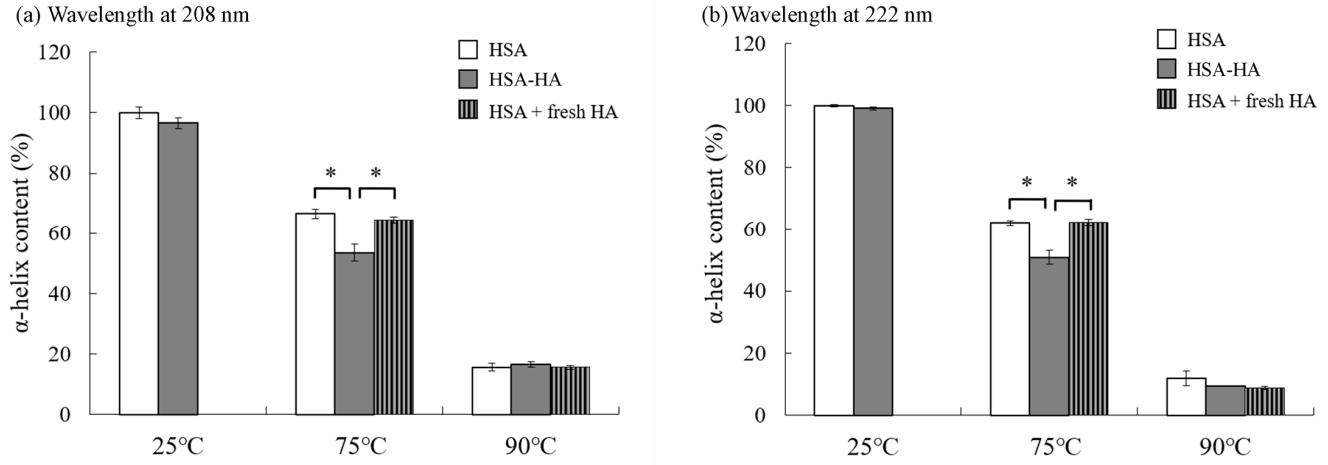

Figure 2. The α-helix content of HSA (white bar), HSA–HA (grey bar), and thermally processed HSA with fresh HA (stripe bar) is measured at wavelengths of 208 nm (**a**) or 222 nm (**b**). * $p < 0.5$ when comparing the α-helix content between thermally processed HSA and HSA–HA at 75 °C, or between thermally processed HSA–HA and thermally processed HSA at 75 °C with fresh HA.

3.3. Thermally Processed Albumin Is More Easily Adsorbed on the Surface of CoCrMo Alloy Disc

Previous studies have shown that when the amount of adsorbed albumin is increased, the friction coefficient of the artificial joint system is also increased [12,18]. HSA or thermally processed HSA was then labeled with fluorescein isothiocyanate, and the adsorption behavior was observed. When HSA or HSA–HA was not thermally processed, the adsorption area was 721.5 ± 53.0 or 1116.7 ± 66.3 μm^2, respectively (Figure 3a). When HSA was thermally processed at 75 °C, the adsorption area increased to 1832.2 ± 140.3 μm^2, and it increased even more in the presence of thermally processed HA or fresh HA (Figure 3b–d). When HSA was thermally processed at 90 °C, the adsorption area became 9840.1 ± 568.1 μm^2 (Figure 3e). Interestingly, the adsorption area was reduced when HA was also thermally processed at 90 °C (Figure 3f). The area of HSA was largely covered on the disc when HSA was thermally processed at 90 °C and fresh HA was added (Figure 3g), suggesting that the low friction coefficient of thermally processed HSA at 90 °C with fresh HA did not result from less adsorbed HSA on the CoCrMo alloy disc.

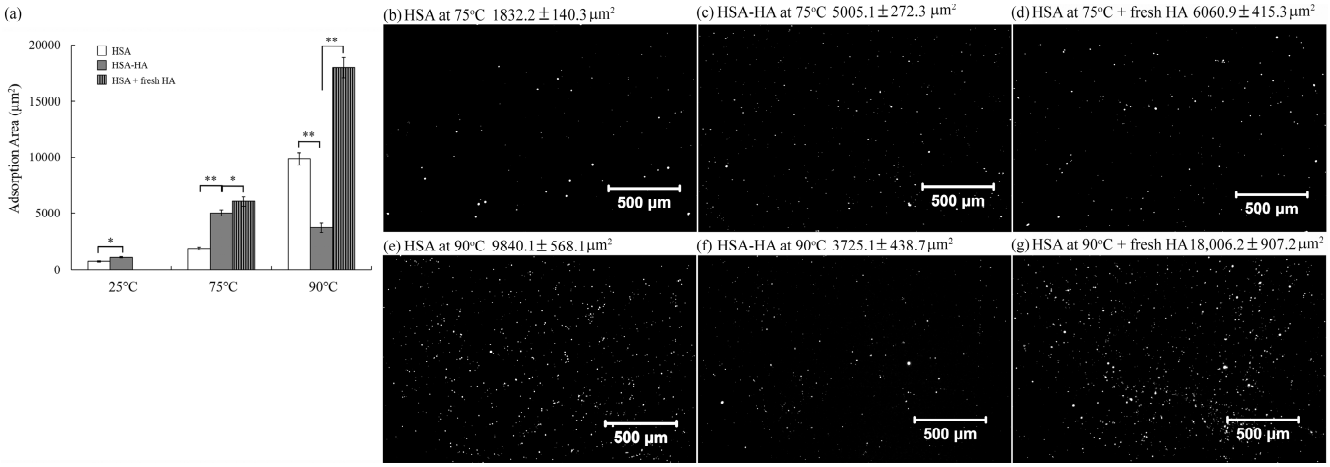

Figure 3. (**a**) The adsorption area of various HSA (white bar), HSA–HA (grey bar), or thermally processed HSA with fresh HA (stripe bar) solutions is quantified. * $p < 0.5$ or ** $p < 0.01$ when comparing adsorption areas between two different solutions at the same temperature. (**b**–**g**) The representative images of thermally processed HSA, HSA–HA, and HSA with fresh HA at 75 °C (**b**–**d**) or at 90 °C (**e**–**g**) after being adsorbed on the CoCrMo alloy disc.

3.4. Viscosity Characteristics of HSA and HA after Being Thermally Processed

The friction of artificial joints is boundary lubrication according to Stribeck's curve, and the physical–chemical properties of the lubricant are critical because it will form a thin layer to protect the joints [19]. To understand the physical–chemical properties of thermally processed HSA, or HSA–HA, a viscosity analysis was performed. The viscosities of HA were decreased when the thermally processed temperatures were increased (Figure 4a). The viscosities of HSA were low at 25 °C and 75 °C but increased 80 times when HSA was thermally processed at 90 °C (Figure 4b). However, the viscosities of thermally processed HSA at 90 °C was reduced with an increase in shear rates, suggesting that the solution was not viscous. The group of thermally processed HSA–HA at 25 °C or 75 °C also showed low viscosity, but the viscosity of HSA–HA at 90 °C increased 40 times more (Figure 4c). The same outcome was observed in thermally processed HSA with fresh HA, with the viscosity increasing approximately 40 times more when the thermally processed temperature was 90 °C (Figure 4d). The solution of thermally processed HSA at 90 °C with fresh HA was fluidity while shear rates were increased (Figure 4d), but the solution of thermally processed HSA–HA at 90 °C might be sticky since the viscosities were not reduced dramatically (Figure 4c).

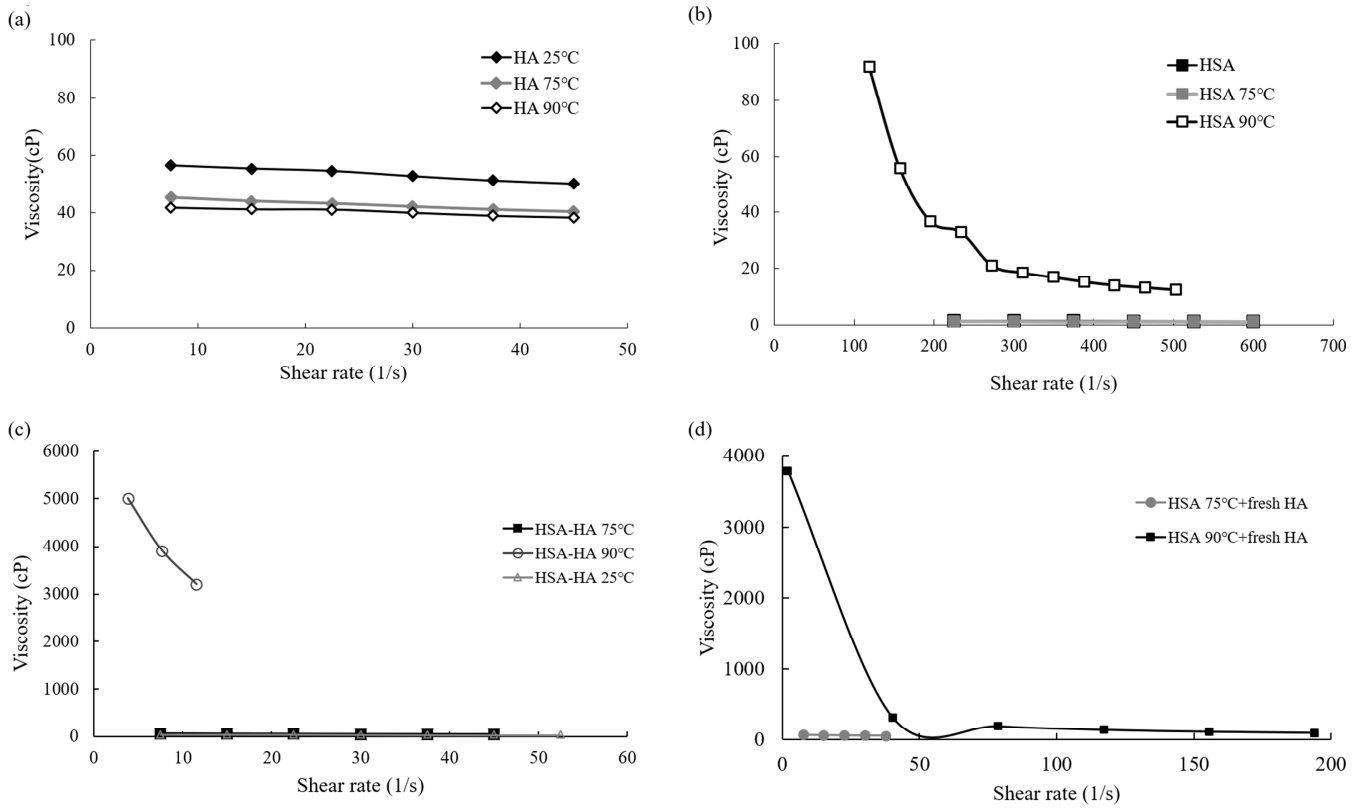

Figure 4. Viscosities of HA (**a**), HSA (**b**), HSA–HA (**c**), and thermally processed HSA with fresh HA (**d**) at different shear rates.

4. Discussion

The most abundant protein in synovial fluid is albumin, which acts as a lubricant in the healthy joint. However, albumin has been shown to be easily adsorbed on the surface of UHMWPE–CoCrMo artificial joint materials, resulting in an increased friction coefficient [12,18]. Although adsorbed proteins resulted in higher friction, the wear rate was reduced because of protection of the artificial joint material surfaces [20,21]. Since wear and lubrication are related [22], the current study focused on investigating the lubricating mechanism of artificial joint systems (Figure 5). When HSA–HA was thermally processed at 90 °C or HA was freshly added into thermally processed HSA at 90 °C, the

viscosity increased dramatically and the friction coefficient decreased. It is possible that the UHMWPE–CoCrMo sliding mechanism was switched to the mixed lubrication from the boundary lubrication, resulting in a reduced friction coefficient.

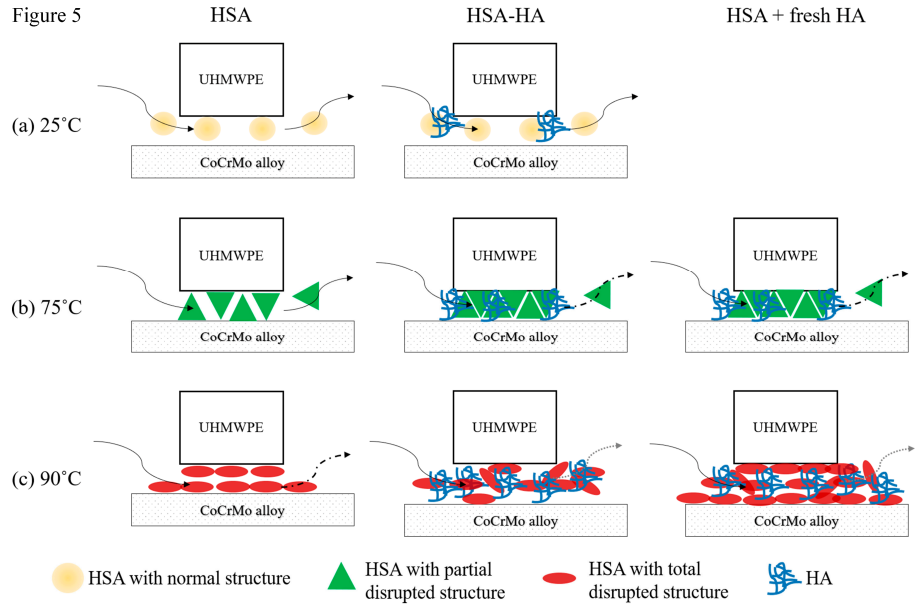

Figure 5. The potential lubricating mechanism of HA in the UHMWPE–CoCrMo artificial joint system. (**a**) The viscosity (black arrows) and adsorption area of HSA with normal structure in HSA or HSA–HA solution at 25 °C is low, resulting in a low friction coefficient. (**b**) When HSA is thermally processed at 75 °C, the secondary structure is partially denatured, resulting in more adsorption of albumin on the surfaces of sliding materials and a higher friction coefficient. In thermally processed HSA–HA or thermally processed HSA with fresh HA group, the intramolecular interaction between HA and HSA increases viscosity slightly (dashed arrows) and reduces the friction coefficient. (**c**) Thermally processed HSA at 90 °C causes a dramatically higher friction coefficient due to a large area of adsorbed albumin with denatured structure on the surfaces. In the presence of HA, the strong interaction between HA and denatured HSA forms a gel-like mixture to increase viscosity significantly (grey dashed arrows). The lubrication then switches to mixed lubrication from boundary lubrication, resulting in a greatly reduced friction coefficient.

The viscosity of HA was reduced while the thermally processed temperature was increasing (Figure 4a); thus, the high viscosity of thermally processed HSA–HA or thermally processed HSA with fresh HA was not caused by HA alone. It has been shown that the intermolecular interaction between albumin and HA serves an important role in lubricating joint cartilage models, although both molecules are negatively charged under physiological conditions [23]. It has been proposed that globular proteins (such as albumins or globulin) in healthy synovial fluid aggregate (possibly caused by conformational changes of proteins) to form a weak network, and HA would entangle with this network to maintain the rheopectic characteristics of synovial fluid [24]. The network of proteins and HA would increase the viscosity of synovial fluid to make it become gel-like, resulting in a low friction coefficient of articular cartilage [25]. Therefore, a potential mechanism is proposed here that the intramolecular interaction between denatured HSA at 90 °C and HA resulted in a gel-like mixture with high viscosity to separate the surfaces of the UHMWPE pin and CoCrMo alloy disc (Figure 5c). Subsequently, the friction coefficient of the UHMWPE–CoCrMo artificial joint system was reduced.

The unexpected result was that when HA was thermally processed with HSA at 90 °C, the adsorbed area of protein was lower than the area when HA was freshly added into a thermally processed HSA solution. It is possible that when HA was thermally processed with HSA at 90 °C, the secondary structures of HSA were disrupted and aggregated,

resulting in stronger affinity between HA and albumin than between denatured albumin and the hydrophobic surface of the CoCrMo alloy disc (Figure 5c). In contrast, thermally processed HSA at 90 °C almost disrupted its secondary structure, resulting in it being more attracted to the hydrophobic surface. Once fresh HA was added into the thermally processed HSA solution, HA would entangle with HSA both on the surface and in the solution, resulting in high viscosity and a low friction coefficient (Figure 5c).

When HSA was thermally processed at 75 °C, the secondary structure of albumin was partially disrupted, resulting in a high adsorption area and high friction coefficient. When HA was thermally processed with HSA at 75 °C or was added freshly, the friction coefficient of the UHMWPE–CoCrMo sliding materials was reduced, although the adsorption area of albumin was increased. The increased adsorption area could be explained by the disruption of the secondary structure of albumin, but the reduced friction coefficient could not be simply explained by viscosity since the viscosities of HSA–HA at 75 °C were low with the increase of shear rates. The intramolecular interactions between albumin and HA might still be a reason for decreased friction in this condition, but the gel-like network between HA and the partially disrupted HSA at 75 °C was not as strong as at 90 °C, resulting in a less-reduced friction coefficient of the UHMWPE–CoCrMo sliding materials (Figure 5b). The results demonstrated that adding fresh HA into a thermally processed HSA solution resulted in better lubrication, regardless of the thermally processed temperatures. However, whether the HA-induced low friction coefficient of the UHMWPE–CoCrMo sliding materials also results in a low wear rate will require further investigation.

A potential lubricating mechanism of HA on albumin-mediated friction is proposed (Figure 5), but there are other components in the synovial fluid that might also interact with albumin. The biggest limitation of the current study was that only the interaction between HA and albumin was investigated. Kruszewska et al. showed that there is interaction between albumin and two types of chondroitin sulfate (CS-4 and CS-6): the interaction of albumin:CS-4 is stronger than albumin:CS-6 by the molecular dynamics approach and the result suggests that albumin:CS-4 can provide better lubrication [26]. Since the percentage of CS-4 is much lower than CS-6 in ill cartilage, it will be beneficial to investigate whether CS-4 could also reduce denatured albumin-mediated friction. Gamma-globulin is another synovial fluid protein, and Yang et al. demonstrated that increased globulin concentrations also increase the friction coefficient of UHMWPE–CoCrMo artificial joints [27]. HA also functioned as a lubricant to reduce the high friction coefficient caused by γ-globulin, but it is unknown whether the structure of γ-globulin would change during friction and whether HA could also reduce denatured γ-globulin-mediated friction. Necas et al. even demonstrated that γ-globulin forms a thin layer and is reinforced by phospholipids and HA on the surface of PMMA–CoCrMo to provide lubrication, and this lubricating layer is caused by layers of albumin [28]. Therefore, how all the synovial fluid components contribute to the tribological properties of UHMWPE–CoCrMo artificial joint materials when the structures of albumin and/or γ-globulin are modified will require further investigation.

In addition, the materials and the designs of artificial joint systems have been improved greatly to minimize the complications and to provide better quality of life for patients [29]. The degree of cross-linked UHMWPE and coating antioxidants on the surface of HUMWPE are both under investigation, to improve the performance of UHMWPE in TKA application [2]. It will also be interesting to investigate whether HA can provide better lubrication in these artificial joint systems. Many studies have focused on increasing the lubrication of artificial joints by investigating the interactions among synovial fluid components, but little research has focused on reducing friction caused by denatured synovial fluid proteins. The current study provided a fundamental mechanism where the effect of denatured proteins on the friction of artificial joints after extensive use was considered; thus, the lubrication provided by HA might be applied ultimately in clinical applications.

5. Conclusions

The lubricating properties of HA have been investigated in this study under the UHMWPE–CoCrMo artificial joint materials. Thermally processed HSA was used to mimic denatured protein after a long friction duration, resulting in an increase of the friction coefficient. The main findings are as follows:

(1) When HSA was thermally processed at 75 °C, the secondary structure was partially disrupted. The friction coefficient increased compared to that of HA.

(2) The viscosity of thermally processed HSA at 75 °C was not higher than the viscosity of HSA at 25 °C. The area of adsorbed HSA was increased, suggesting that a higher friction coefficient resulted from more denatured HSA on the surface of artificial joint materials.

(3) When HSA was thermally processed at 90 °C, the secondary structure was totally disrupted. The friction coefficient also increased, caused by large adsorption of denatured protein.

(4) When HA was thermally processed with HSA or fresh HA was added into thermally processed HSA at 90 °C, the friction coefficient decreased. The viscosity of the HSA–HA solution was greatly increased, suggesting that the lubrication of artificial joints might switch from boundary lubrication to mixed lubrication.

(5) The similar effect of HA was also observed when HA was thermally processed with HSA or fresh HA was added into thermally processed HSA at 75 °C, but the mechanism might be distinct from HSA–HA at 90 °C.

This outcome may provide a potential solution for achieving better lubrication on albumin-mediated tribological process, and ultimately for prolonging the lifespan of artificial joint systems to provide better quality of life for TKA patients.

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