

Factors influencing changes in articular cartilage following hemiarthroplasty in sheep

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Abstract

This study examined the relationship between acetabular cartilage properties after hemiarthroplasty surgery and surgical variables including femoral head size and position. Nineteen sheep received unilateral hip arthroplasties and were euthanized one year post-operatively to harvest the femora and acetabula. Cartilage histology, biochemistry and material properties were determined from samples located in the superior load-bearing region. Femoral head size mismatch, leg length difference, anterior–posterior and medial–lateral offset and anteversion were measured. In the acetabulum, substantial cartilage degradation occurred with widespread fibrillation and significant changes in the biochemical and material properties compared to the intact contralateral joint. Regression analyses on the surgical variables explained 75–80% of the changes in tissue biochemistry but did not explain the material changes. Head size mismatch and leg length difference were the most significant contributors of the five variables examined and therefore may be critical to successful outcome in hemiarthroplasty. © 2002 Orthopaedic Research Society. Published by Elsevier Science Ltd. All rights reserved.

Keywords: Articular cartilage; Hemiarthroplasty; Sheep cartilage biochemistry; Cartilage material properties

Introduction

Hemiarthroplasty is a well-established treatment for femoral neck fractures. Approximately one third of the hip replacements performed in the United States annually are hemiarthroplasties [1]. Despite shorter surgical time and lower cost than total hip replacement surgery, concerns remain regarding the long-term performance of hip hemiarthroplasty. Complications related to hemiarthroplasty generally occur on the acetabular side of the hip joint, and are believed to result from the articulation of the metal femoral prosthesis with the natural articular cartilage of the acetabulum [17].

Acetabular cartilage erosion and acetabular protrusion have been reported following hemiarthroplasty both clinically [2,5,10,11,29,32] and experimentally [8,9]. The factors contributing to these failure modes are not understood. In addition to the metal–cartilage articulation, the amount of degeneration may be related to the prosthesis location. Decisions made in the operating room determine prosthesis location and head size and may contribute directly to cartilage wear. Operative factors which have been suggested to contribute to acetabular cartilage degeneration and wear include prosthesis head size mismatch and improper femoral neck length [10,12,18].

The goal of this study was to elucidate the factors that affect the clinical outcome and longevity of hip hemiarthroplasty. We focused on the acetabular side of the hip joint as maintaining the integrity of the acetabulum

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and acetabular cartilage is critical to the success of hemiarthroplasty surgery. In particular we addressed two research questions: (1) what histological, biochemical and material changes occur in acetabular cartilage following hemiarthroplasty? and, (2) how are these properties affected post-hemiarthroplasty by head size and location? These questions were examined in sheep after one year of implantation. Variations in head size, neck length and anteversion angle were examined within the range of normal surgical variation.

Materials and methods

Study design

Twenty-one skeletally mature male sheep (Polypay; Thomas Ranch, Winters, CA, USA) received a unilateral hemiarthroplasty of the left hip. The contralateral hip remained intact. At the time of surgery all animals were between 1.5 and 2 years old. The femoral implants were custom designed for the sheep femur. The prosthesis was a modular design with a cobalt chromium head (26 or 28 mm) and a titanium alloy stem (Kirshner Medical Company, Timonium, MD, USA). All surgeries were performed by an orthopaedic surgeon using a standard craniolateral approach, and all prostheses were fixed with cement. Based upon the training of the surgeon, oversizing the femoral head was intentionally avoided. Immediate post-operative radiographs were taken to document prosthesis location, orientation and cement technique. Follow-up radiographs were taken six months post-operatively to confirm absence of fracture, migration or dislocation. The protocol was approved in advance by the Institutional Animal Care and Use Committee.

One year after implantation, 19 sheep were euthanized by an intravenous overdose of pentobarbital (Repose, Syntex Inc., Palo Alto, CA, USA). Two sheep did not complete the study; one was euthanized at six months due to a loose prosthesis and a second was found dead in the pasture at nine months. In the remaining 19 sheep, the acetabula and femora were immediately removed for analysis following euthanasia. Analysis of the joint included evaluation of cartilage morphology, biochemistry and mechanical properties (Fig. 1). The entire acetabu-

lum was fixed in 10% neutral buffered formalin following sample removal.

Articular morphology and histology

For each of the acetabula, the extent of cartilage erosion (% loss of cartilage surface area) and condition of the remaining cartilage (% fibrillation) were determined visually using four levels of grading: no loss (0–10% loss or fibrillation); moderate (10–50% loss or fibrillation), widespread (50–90% loss or fibrillation) or complete (90–100% loss or fibrillation). Each evaluation was performed by two independent observers and averaged.

Cartilage integrity was assessed from Safranin-O staining of 5 µm thick sections. Samples for histological analysis were removed from the superior load-bearing region adjacent to the removed cores. The samples were decalcified with formic acid and embedded in paraffin for sectioning. For each sample a single section was examined and four categories were assessed based on a modification of the system of Mankin et al. [21]: articular surface structure, cellular organization, clone formation and tidemark integrity (Table 1). Grading was performed on a scale of zero to nine, where normal healthy cartilage received the minimum score (0) and the maximum possible score was nine. The characteristic elements of the Mankin score are tied to the presence of intact extracellular matrix and normal cellularity on the joint surface. The components of the Mankin rating scale include presence of fibrillation which has been correlated with loss of proteoglycan content as depicted by Safranin-O staining [27] and toluidine-blue staining [24]. The loss of the superficial zone or deep zone is associated with loss of cellularity. Further progression of severe destruction of cartilage includes loss of tidemark integrity and progressively deeper vertical cleft formation [7,20]. The correspondence of extracellular matrix loss with the resultant loss of proteoglycan (glycosaminoglycan (GAG) and collagen) would inversely follow the increase in score for the Mankin scoring system [20–22]. In some instances, an elevated Mankin score reflects a complete eburnation of bone if there is no material on which one can do biochemical analyses.

Surgical variables

Femoral length and head size, offset and anteversion were measured on the excised left and right femora. For the right femur, femoral head size was measured with calipers anterior–posterior (AP) across

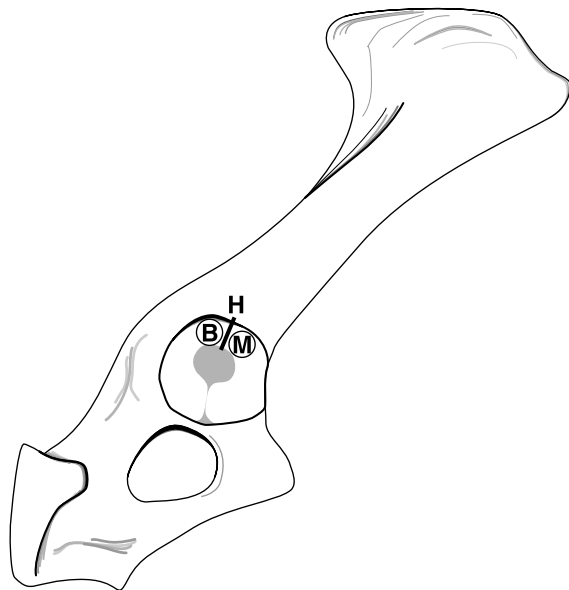


Fig. 1. Lateral view of the right sheep pelvis with tissue sampling sites indicated in the acetabulum. Sample notation: B = biochemistry (6 mm core), H = histology (radial full thickness section), M = mechanical testing (6 mm core).

Table 1
Histological–histochemical grading system

Category	Grade
<i>I. Articular surface structure</i>	
Normal	0
Focal fibrillation	1
Moderate fibrillation	2
Widespread fibrillation	3
<i>II. Cellular organization</i>	
Normal	0
Loss of superficial zone	1
Loss of deep zone	2
<i>III. Clone formation</i>	
None	0
Minimal	1
Moderate	2
Severe	3
<i>IV. Tidemark integrity</i>	
Intact	0
Crossed by blood vessels	1

Minimum score = 0 (normal, healthy cartilage).

Maximum score = 9.

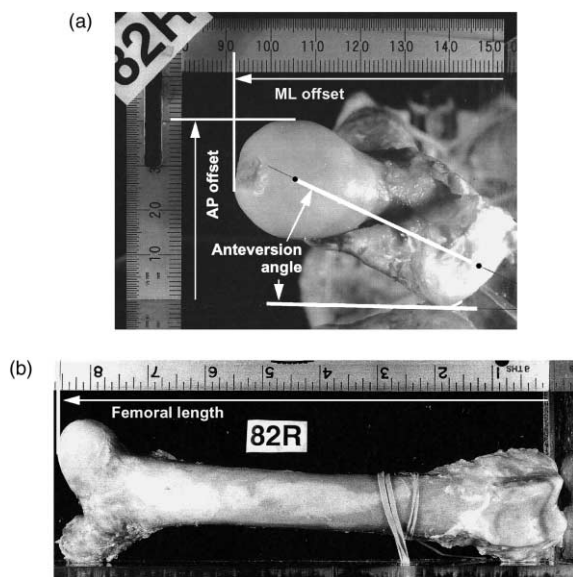


Fig. 2. (a) Proximal and (b) medial photographs of sheep femur with reference points and femoral measurements indicated.

the head perpendicular to the neck axis. The average value was calculated from three independent measurements. The results were expressed as head size mismatch: the difference between the implant head diameter (26 or 28 mm) and the intact femoral head width. Therefore, a negative head size mismatch indicates an undersized implant relative to the contralateral limb.

AP and medial–lateral (ML) radiographs as well as photographs of anterior, medial and superior views were taken of the femora after dissection to determine femoral length and head location. Prior to radiography and photography, each femur was mounted in an acrylic fixture to assure consistent orientation. A ruler was included in each field of view and measurements were taken from enlarged photographs. Femoral length was measured from the distal condyles to the most proximal point on the femoral head (Fig. 2(b)). Leg length difference was determined relative to the right, intact femur. Head location and anteversion were obtained from the proximal photographs (Fig. 2(a)). Femoral head location was defined by AP and ML offsets measured from the standard fixture to the most cranial and medial points of the femoral head, respectively. Using the same view, anteversion was defined as the angle between the standard fixture and a line drawn from the center of the femoral head through the bisector of the trochanter. The offset and anteversion results were expressed as a percentage of the intact value.

Cartilage tissue properties

For the biochemical analyses, 6 mm diametrical full thickness cartilage samples were removed from the subchondral bone immediately after specimen removal. Each sample was dried at 60 °C for 12 h and weighed to obtain the dry weight (dw). Each cartilage sample was then digested with papain. Total GAG content was quantified using the dimethylmethylene blue assay [13]. This assay measures sulfated GAGs using chondroitin sulfate as a standard. Collagen content was determined from hydroxyproline (HYP) content [6]. The papain-digested samples were acid hydrolyzed, and HYP was measured using the diaminobenzoic acid assay [30,31]. GAG and HYP per dw and the GAG-to-HYP ratio were calculated.

Cartilage material properties were determined from in situ creep and recovery indentation tests performed on 6 mm cylindrical osteochondral samples. The specimens were tested using an automated creep indentation apparatus [3] and the tissue material properties were interpreted by linear biphasic constitutive theory [4,25]. At the time of dissection, the mechanical testing samples were wrapped in saline-soaked gauze and stored at –70 °C until testing. At the time of testing, each specimen was thawed for 1 h in normal saline solution with

protease inhibitors. Specimens were mounted onto an aluminum base plate and submerged in saline throughout testing. Loads were applied perpendicular to the articular surface using a 1.5 mm diameter porous plane-ended indenter. A tare load of 0.01 N was applied until the tissue reached creep equilibrium, defined as a slope of less than 1×10^{-6} mm/s of the displacement–time curve. After tare equilibrium, a test load of 0.49 N was applied to the surface until the tissue reached creep equilibrium. The load was removed and the tissue recovery was monitored until equilibrium was reached. The thickness (h) of the cartilage was then measured at the center of the plug with a needle-probe system.

From the experimental creep compressive displacement vs. time curve the three biphasic material properties were obtained by fitting the data using biphasic finite element analysis and optimization techniques [3]. The material properties obtained were the aggregate modulus (H_A), the shear modulus (μ) and the permeability (k).

Statistical analyses

Left–right differences in femoral measures and surgical variables were assessed by paired t -tests. For the histological grading, left–right pairs were compared using the Wilcoxon signed rank test; unpaired comparisons were made using the Mann–Whitney U test. The effect of articulation with metal on cartilage properties was determined from paired t -tests between the intact (right) and implanted (left) sides. Relationships were examined between the percent changes, relative to intact, in the cartilage properties and the surgical variables using a regression model including all five surgical variables (head size mismatch, % intact AP and ML offset, % intact anteversion, femoral length difference). Stepwise linear regression analyses were performed when significant relationships existed to determine the primary contributing parameters. For these regressions, only animals were included for whom a complete set of measurements was obtained ($n = 13$). For all analyses, significance was at $p = 0.05$.

Results

Morphology and histology

From visual examination, the left acetabula of 12 (63%) sheep demonstrated moderate loss of cartilage (10–50%), and seven (37%) acetabula had widespread (50–90%) cartilage loss. In the animals that exhibited regions of cartilage remaining in the acetabulum, close examination of the tissue revealed widespread or complete fibrillation. No cartilage loss or fibrillation was visible in the acetabula from intact joints.

Histological scores for the intact (right) joints ranged from 0 to 3 with a mean value of 1.1 (0.9 SD). In contrast, remaining cartilage from the acetabula with implants exhibited significantly increased cartilage scores that ranged from 1 to 9 with a mean score of 7.1 (2.2 SD). A score of 1–3 would indicate no to moderate fibrillation in the morphological examination.

Surgical variables

Head size mismatch (mean = –0.80 mm, 0.759 SD), AP-offset (mean = 76% of intact) and anteversion (mean = 33% of intact) were significantly different between the intact and implanted hips. In this study, 17 of 19 femoral heads were undersized. No significant difference was found in femoral leg length (mean = –0.76 mm) and ML-offset (mean = 99% of intact).

Table 2
Biochemical and material properties of acetabular articular cartilage

Parameter	N	Intact right, mean (SD)	Implant left, mean (SD)	Implant as % intact
<i>Biochemistry</i>				
Dry weight (dw, mg)	14	15.4 (6.59)	10.1 (4.62)	66 ^a
Total GAG (GAG, µg)	16	1540 (480)	536 (374)	34 ^a
GAG/dw (µg/mg)	14	105 (28.6)	56.1 (35.7)	55 ^a
Total HYP (HYP, µg)	14	1330 (387)	860 (606)	59 ^a
HYP/dw (µg/mg)	14	98.6 (40.8)	87.2 (42.5)	93
GAG/HYP (µg/µg)	13	1.13 (0.41)	0.730 (0.48)	64 ^a
<i>Material properties</i>				
Aggregate modulus	18	0.407 (0.204)	0.163 (0.177)	53 ^a
Permeability	8 ^b	4.74 (4.20)	26.5 (33.1)	804
Shear modulus	8 ^b	0.213 (0.081)	0.076 (0.049)	41 ^a
Thickness	17	1.11 (0.432)	0.507 (327)	48 ^a

All samples obtained from the superior load bearing region of intact and implanted acetabula of sheep. N = number of paired samples. Implant as percent intact value determined pairwise for each individual animal.

^aSignificantly different from intact, $p < 0.05$.

^bThe sample sizes for the permeability and shear modulus are reduced due to an error in a subset of our samples.

Cartilage tissue properties

Biochemical analysis of the remaining cartilage from the superior weightbearing region comparing intact and implant values showed decreases ($p < 0.01$) in dw, total GAG content, total HYP content and GAG/dw (Table 2).

Material property analysis of the cartilage from implanted and intact joints showed significant side-to-side differences for all material properties and for thickness (Table 2). In the implanted hip, the aggregate modulus was decreased and the permeability increased. The cartilage on the implanted side was thinner than the tissue on the contralateral side. The shear modulus of the implanted side was reduced relative to the intact side.

No significant correlations were present between the biochemical and material properties.

Relationships between properties and surgical variables

When relationships were examined between the cartilage biochemical and material properties from the implanted hips and the five surgical variables, significant relationships were found for biochemical measures, but not for any material properties (Table 3). For GAG/dw

Table 3
Coefficients of variation and significance for multiple regressions: cartilage property = function of (head size mismatch; % intact AP and ML offset; % intact anteversion; femoral length difference); 13 pairs examined

Property (% intact)	R ²	p-value
GAG/dw	0.756	0.040
HYP/dw	0.338	0.632
GAG/HYP	0.809	0.019
Aggregate modulus	0.188	0.856
Thickness	0.432	0.383

and GAG/HYP, the model explained 75–80% of the variance. For the non-significant regressions, 20–50% of the variance in the cartilage properties was explained by the surgical measures.

Stepwise elimination of surgical parameters for the two significant regressions revealed a strong relationship with head size mismatch and leg length difference for changes in GAG/dw ($p = 0.007$, $R^2 = 0.63$) and GAG/HYP ($p = 0.002$, $R^2 = 0.71$). For the 13 animals from which samples were obtained for all analyses, all femoral heads were undersized. Changes in anteversion and AP- and ML-offset did not contribute significantly to the regressions. When individual regressions were examined with these two surgical parameters, GAG/dw correlated most strongly with head size mismatch ($p = 0.038$, $r^2 = 0.336$) and GAG/HYP correlated most strongly with leg length difference ($p = 0.007$, $r^2 = 0.494$) (Fig. 3). These individual regressions explained less of the variance in the biochemical data than the multiple regression with both parameters included.

Discussion

The study results show severe acetabular cartilage degradation at one year following hemiarthroplasty in sheep that is characterized by changes in the morphological integrity, material properties and biochemical integrity of the extracellular matrix.

Our findings are consistent with previous studies of hemiarthroplasty in other animal models [8,9,19]. In all cases, the time course is rapid and accelerated when compared to similar findings in humans at comparable post-operative periods. Cruess et al. [9] observed progressive degeneration of acetabular cartilage over time until 24 weeks after unilateral hemiarthroplasties of the

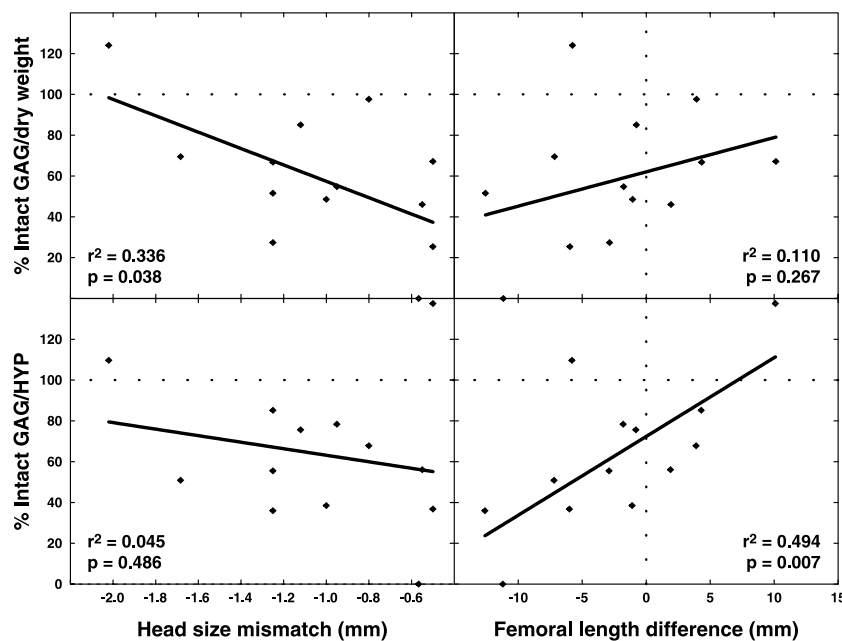


Fig. 3. Individual regressions of GAG/dw and GAG/HYP against head size mismatch and leg length difference. The multiple regressions for these two biochemical parameters on both surgical variables were highly significant (see text). 13 complete sets of samples examined.

hip in mongrel dogs. In their study, the changes started with loss of metachromatic staining, followed by surface fibrillation, subchondral bone activity, pannus formation and, finally, cartilage destruction. LaBerge et al. created custom canine patellofemoral implants in an attempt to remove the influence of geometric mismatch on hemiarthroplasty outcome [19]. However, even in the presence of precise control of implant geometry, histological and mechanical degeneration of the articular cartilage occurred and increased progressively from 3 to 6 months. Cook et al. examined the effect of material modulus on articular cartilage degeneration following hemiarthroplasty in 45 dogs and showed that articular cartilage survivorship was only 20% probable in joints articulating with metal compared to 92% for carbon implants after 18 months [8]. In their study, survivorship was defined by the extent of eburnation.

A number of retrospective clinical studies confirm that severe cartilage degradation follows hemiarthroplasty. In a study of 161 patients, an 11% incidence of acetabular erosion was observed after an average of three years post-operatively, with a greater incidence in younger patients [10]. Acetabular protrusion was observed in 26% of 214 patients followed by Søreide et al. [29]. Both patient age and length of follow-up have been shown to be important factors. Patients over 75 years were nearly twice as likely to develop acetabular protrusion, with length of follow-up (1–84 months) being the most significant predictive factor. Dalldorf et al. examined the histology of acetabular articular cartilage

at the time of hemiarthroplasty revision in 12 patients and found a strong relationship between duration of implantation and acetabular cartilage loss [11]. They found that all hips implanted for more than seven years had complete loss of acetabular cartilage. The most severe cases may have been selectively represented, however, as these were the patients being revised to total arthroplasties.

The surgical variables we examined represent alterations in femoral geometry relative to the natural hip and result from decisions made by the surgeon as part of the hemiarthroplasty procedure. These geometric variations were the outcome of standard surgical procedures and are, therefore, presumably within the range of normal variability. In this study, surgical variables impacted the biochemistry of the remaining cartilage (Table 3). In other clinical studies, radiographs have been reviewed retrospectively to examine surgical variables that may contribute to hemiarthroplasty outcome. Kwok and Cruess reviewed the incidence of “technical complications” in 286 radiographs and found the following [18]: 25% had unsatisfactory head size; 47% had inappropriate neck length; 29% of the femoral stems were varus; and, 25% had unsatisfactory calcar seating of the component. Gebhard et al. conducted a retrospective review of 56 patients for relative head size and found only 5.4% were correctly sized [15]. In addition to geometry, joint loading may be critical to post-operative success and would be affected by altered geometry. In a single individual with a pressure-instrumented

hemiarthroplasty, McGibbon et al. found a significant positive correlation between in vivo acetabular contact pressure and histology grade and a negative correlation between the contact pressure and MRI-based acetabular cartilage thickness after 34 months of implantation [23].

Of the surgical variables evaluated in this study, previous research has focused on femoral head size mismatch. Obtaining a perfect match between the natural and prosthetic femoral heads is unlikely, given the discrete head size increments available and hospital inventory limitations. Laboratory studies using fundamentally different methods to examine head size have produced conflicting results. In vitro bone strain studies suggest that undersized heads produce decreased strains relative to the natural head in cadavers [14,26]. However, in vitro pressure measurements of hemiarthroplasties in cadavers have demonstrated less increase in peak pressures with over-sized heads [16,28]. Our results suggest that, if a choice must be made, a smaller head size should be chosen (Fig. 2). Because this conclusion is based primarily on undersizing the femoral head, further investigation of head size mismatch and its impact on in vivo contact pressure, fluid lubrication and bone strains is clearly warranted.

While geometric factors related to femoral head location were focused on here, we were unable to control for geometric variations as others have done [19]. In the sheep model in particular, head shape mismatch may also play a role in cartilage degradation. While the human femoral head approximates a sphere, replacing the natural elliptical or tear drop geometry of the sheep femoral head (Fig. 2) with a spherical implant alters joint conformity and contact areas. The extent of this influence could not be assessed here; however, bony remodeling of the acetabulum was evident on radiographs taken following necropsy.

In conclusion, of the variables examined in this study, head size mismatch and leg length difference contribute most significantly to the degenerative changes following hemiarthroplasty in sheep. Regressions based on all five surgical variables explained 75–80% of the variation in tissue biochemistry. In this study, material properties did not relate to the surgical parameters, but this may be explained by the extreme extracellular matrix degradation. The substantial matrix damage may have completely compromised load-bearing function. Previous studies have demonstrated that loss of mechanical integrity precedes visual evidence of cartilage damage [19]. Therefore, examination of earlier, progressive time points prior to complete material destruction may provide additional insights regarding how the course and nature of articular cartilage degeneration in joints with a metal prosthesis are influenced by surgical factors.

Acknowledgements

This study was supported by the Orthopaedic Research and Education Foundation (grant #95-026) and the Department of Veterans Affairs (grant #A652-RA).

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