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Periprosthetic joint infection after total hip arthroplasty induces histological degeneration of the gluteus medius tendon

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Aims

A revision for periprosthetic joint infection (PJI) in total hip arthroplasty (THA) has a major effect on the patient's quality of life, including walking capacity. The objective of this case control study was to investigate the histological and ultrastructural changes to the gluteus medius tendon (GMED) in patients revised due to a PJI, and to compare it with revision THAs without infection performed using the same lateral approach.

Methods

A group of eight patients revised due to a PJI with a previous lateral approach was compared with a group of 21 revised THAs without infection, performed using the same approach. The primary variables of the study were the fibril diameter, as seen in transmission electron microscopy (TEM), and the total degeneration score (TDS), as seen under the light microscope. An analysis of bacteriology, classification of infection, and antibiotic treatment was also performed.

Results

Biopsy samples from the GMED from infected patients revealed a larger fibril diameter than control patients, as seen in the TEM ($p < 0.001$). Uninfected patients were slightly older and had their revisions performed significantly later than the infected patients. Histologically, samples from infected patients revealed significantly more vascularity ($p < 0.001$), the presence of glycosaminoglycans ($p < 0.001$), and a higher TDS ($p = 0.003$) than the control patients. The majority of patients had staphylococcal infections of various species.

Conclusion

More histological degeneration in the GMED was found in patients undergoing THA revision surgery due to PJI than in patients undergoing THA revision surgery due to other reasons.

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Introduction

Periprosthetic joint infection (PJI) has a substantial effect on patients' health and life, making it one of the most feared complications after total hip arthroplasty (THA). It has been associated with more re-admissions, subsequent revisions, poorer quality of life (QoL), and even increased mortality compared with the revision of hip prostheses for other reasons.[1,2] EuroQol five-dimension (EQ-5D) index scores indicate that patients with PJI experience a loss of independence in their lives and a greater need for ambulatory aid.[2,3] Furthermore, poor postoperative results for hip function, as measured using the Oxford Hip Score (OHS) or the Western Ontario and McMaster Universities Osteoarthritis index (WOMAC),[4,5] with limping and pain emphasizes the severity of this condition.[6,7]

Gait deficiency originating from the hip is often related to the gluteus medius tendon (GMED) and muscle infirmity.[8] Tendons are dense collagenous tissues that transmit

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Table I. Evaluation of biopsy samples with a semi-quantitative four-point scoring system.

Sample	Grade 0	Grade 1	Grade 2	Grade 3
Fibre structure	Straight, parallel, packed fibres, with slight waviness	Slight separation of fibres, increased waviness	Separation of fibres, deterioration of fibres	Complete loss of fibre structure and hyalinisation
Cellularity	< 100 cells/high-power field (HPF)	100 to 199 cells/HPF	200 to 299 cells/HPF	> 300 cells/HPF
Vascularity	Vessels running parallel to the collagen fibre bundles in the septa	Slight increase in vessels, including transverse vessels in the tendon tissue	Moderate increase in vessels within the tendon tissue	Markedly increased vascularity with clusters of vessels
Glycosaminoglycans	No alcianophilia	Slight alcianophilia between the collagen fibres	Moderate increase in alcianophilia	Markedly increased alcianophilia forming blue lakes

HPF, high-power field.

Table II. Comparison of clinical data and self-reported patient outcome measurements.

Variable	Infected patients (n = 8)	Non-infected patients (n = 21)	p-value
Sex, n			0.408
Male	6	11	
Female	2	10	
Age, yrs			0.119
Mean (SD)	67 (9.1)	73 (10.8)	
Median (range)	66 (52 to 80)	74 (46 to 90)	
BMI, kg/m2			0.327
Mean (SD)	28 (4.9)	30 (5.7)	
Median (range)	27.4 (20 to 37)	28.3 (24 to 45)	
Preoperative EQ-5D-3L score			0.881
Mean (SD)	0.46 (0.31)	0.41 (0.31)	
Median (range)	0.69 (0.09 to 0.8)	0.55 (-0.18 to 0.8)	
Missing values	1	2	
Preoperative Oxford Hip Score			0.728
Mean (SD)	19 (11.4)	21 (7.7)	
Median (range)	20 (3 to 40)	21 (9 to 44)	
Years from index operation			**0.004**
Mean (SD)	3.6 (4.5)	11.6 (6.7)	
Median (range)	1.7 (0.2 to 14)	11.1 (1 to 23)	

Significant p-values are marked in bold.
EQ-5D-3L, EuroQol five-dimension three-level; SD, standard deviation.

tensile forces between muscle and skeleton. They consist primarily of collagen fibres of differing quality oriented in the direction of the load. Ultrastructurally, fibers form a cluster of fibrils composed of collagen type III instead of collagen type I, resulting in tendinopathic tendons exhibiting smaller diameters.[9] Proteoglycans and glycoproteins form the dense ground substance surrounding a small yet important cellular matrix including tenocytes. Disorganized fibre arrangement, increased non-cellular ground substance, poor vascularity, and an increase in glycosaminoglycans (GAGs) constitute degenerated tendons, in addition to fatty deposits and ectopic ossifications, which can be studied in the microscope. However, the pathogenesis and repair mechanisms are only understood to a limited degree, although the importance of mechanical tendon loading, in particular regarding the Achilles and supraspinatus tendons, has been recognized.[10,11]

THA is performed using different surgical approaches, with the lateral and the posterior approaches being the most common.[12] Large registry studies,[13,14] as well as histological and ultrastructural studies of THA patients,[15] have revealed differences between the outcome and tendon appearance of the different approaches. A recent study of infected patients has also shown that the lateral approach was associated with inferior postoperative patient-reported outcome measures (PROMs) when used in a single debridement, antibiotics, implant retention (DAIR) procedure compared with the posterior approach.[16]

The objective of this case control study was to investigate the histological and ultrastructural appearance of the GMED in a group of eight patients revised due to a PJI, who had their primary THA operated via a lateral

Table III. Fibril diameter as seen in the transmission electron microscope.

GMED tendon fibrils	Infected patients (n = 8)	Non-infected patients (n = 21)	p-value*
N	800	2,100	
Mean diameter, nm (SD)	62.7 (17.0)	56.1 (15.5)	< 0.001
Median, nm (range)	60.0 (30 to 170)	59.0 (18 to 150)	

n = the number of fibrils in areas showing transversely sectioned collagen fibrils; p-value is significant.
*Unpaired t-test.
GMED, gluteus medius tendon; SD, standard deviation.

Table IV. Stratified distribution of biopsy samples pursuant to the semi-quantitative four-point scoring system.

Variable		Infected patients (n = 8 × 2)	Non-infected patients (n = 21 × 2)
Fibre structure	0	1 (6)	1 (2)
	1	4 (25)	12 (29)
	2	11 (69)	20 (48)
	3		8 (19)
Cellularity	0	2 (13)	4 (10)
	1	5 (31)	21 (50)
	2	1 (6)	10 (24)
	3	8 (50)	6 (14)
Vascularity	0		11 (26)
	1	3 (19)	18 (43)
	2	4 (25)	10 (24)
	3	9 (56)	2 (5)
Glucosaminoglycans	0		15 (36)
	1	2 (13)	14 (33)
	2	11 (69)	5 (12)
	3	3 (19)	7 (17)
Missing values, %			1 (2)

Two samples were collected from each patient. The total number for each score is listed as whole numbers and percentages are given in parentheses.

approach, and compare it with a group of 21 revised THAs without infection performed using the same approach.

The hypothesis was that more ultrastructural and histological tendon degeneration would be found in infected patients than in non-infected patients undergoing THA revision surgery. The primary variables of the study were the fibril diameter, as seen in the transmission electron microscopy (TEM), and the total degeneration score (TDS), as seen in the light microscope.

Methods

Originally, patients undergoing surgery at our institution (orthopaedic department, Uddevalla Hospital, NU Hospital Group, Sweden) between 2015 and 2018 were recruited to a case control study with the aim of studying histological and ultrastructural changes in the GMED tendon in patients with primary THA due to osteoarthritis (OA), cervical neck fracture, or revision THA, where the index operations had been performed using a lateral or posterior approach.[15] The exclusion criteria in the revision group were previous non-implant hip surgery and neuromuscular diseases (polio, stroke, multiple sclerosis). In addition, patients with multiple illnesses, including insulin-requiring diabetes, dementia, widespread malignancy, and systemic corticosteroid treatment, as well as previous surgery due to PJI, were excluded.

Nevertheless, a revised subgroup of eight patients had suffered PJI and undergone index surgery using a lateral approach. In the revision group, 21 of the non-infected patients had undergone index surgery through the same lateral approach. In these patients, samples for both the light and electron microscope were suitable and were analyzed according to methods previously used at our institution.[15] All patients gave their written informed consent prior to their study inclusion, and had prospectively been asked to complete self-assessment forms for a EuroQol five-dimension three-level (EQ-5D-3L) report and Oxford Hip Score (OHS) prior to revision surgery. Ethical approval for the study was approved by the Human Ethics Committee at the medical faculty at the University of Gothenburg Dnr 381/15.

Ultrastructural analysis. Specimens were collected at surgery by cutting 5 to 7 mm pieces with a surgical knife and immediately fixed in 2% glutaraldehyde and 1% paraformaldehyde in 0.1 M sodium cacodylate buffer containing 0.1 M sucrose and 3 mM $CaCl_2$ (pH 7.4) at room temperature for 30 minutes, followed by storage at 4 °C.

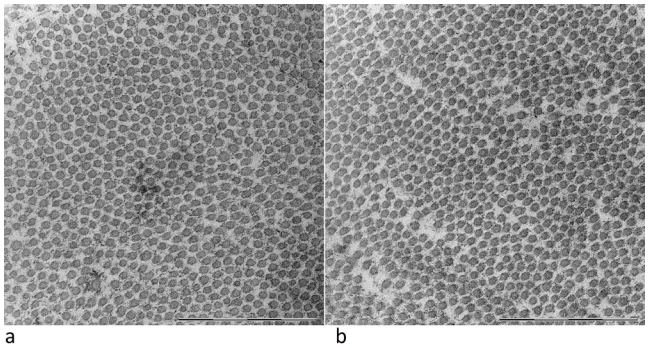

Fig. 1

a) Tendon from a standard revision due to loosening eight years postoperatively in a 73-year-old female patient. b) Tendon from an infected 52-year-old male patient with an infection duration of one year. The images appear to have similar fibril diameter distribution, with slightly more ECM between the fibrils in the infected image to the right. Scale bars 1 µm.

were used for image analysis and fibril diameter measurement. The fibril diameters were measured manually on images acquired at x49.000 magnification (1.14 nm/px) using Fiji software[17] and the Bio-Formats plugin.

In all, 100 fibrils were analyzed in each specimen and the mean value was calculated with an accuracy of 1/10th of a nanometre. Two biopsy specimens from each patient were scanned. However, the fibril diameters were only measured in the biopsy with the best transverse orientation, while the other biopsy was left unmeasured. The micrographs were evaluated by an independent technician (LH) with extensive experience of using transmission electron microscopy (TEM). The technician was not informed of the group affiliation of the specimens.

Histological analysis. The samples for light microscopy were fixed in 10% neutral-buffered formalin, embedded in paraffin blocks and sectioned at 4 to 5 µm. The sections were stained with haematoxylin-eosin (HE) to evaluate the fibre structure, cellularity and vascularity. Alcian blue (pH 2.5)-periodic acid Schiff (AB/PAS) was used to detect GAG-rich areas. The histological evaluations of two samples from each patient were performed by a pathologist (NP) and an orthopaedic surgeon (TM) with a special interest in pathology, together using a light microscope (Leica DMRBE, Germany). The examiners were blinded in terms of the group to which the patient belonged.

Table V. Histological results of biopsy sample system.

Variable	Revision infection (n = 8 × 2)	Revision lateral (n = 21 × 2)	p-value*
Fibre structure			0.360
Mean (SD)	1.6 (0.62)	1.9 (0.76)	
Median (range)	2.0 (0 to 2)	2.0 (0 to 3)	
Missing values		1	
Cellularity			0.119
Mean (SD)	1.9 (1.18)	1.4 (0.87)	
Median (range)	2.5 (0 to 3)	1.0 (0 to 3)	
Missing values		1	
Vascularity			**< 0.001**
Mean (SD)	2.4 (0.81)	1.1 (0.85)	
Median (range)	3.0 (1 to 3)	1.0 (0 to 3)	
Missing values		1	
Glucosaminoglycans			
Mean (SD)	2.1 (0.57)	1.1 (1.091)	**< 0.001**
Median (range)	2.0 (1 to 3)	1.0 (0 to 3)	
Missing values		1	
TDS			**0.003**
Mean (SD)	8.0 (2.71)	5.5 (2.49)	
Median (range)	8.5 (3 to 11)	5.0 (1 to 10)	
Missing values		1	

Significant p-values are in bold.
*Mann-Whitney U test.
SD, standard deviation; TDS, total degeneration score.

The specimens were rinsed in 0.1 M sodium phosphate buffer (pH 7.4) prior to post-fixation in 2% osmium tetroxide in 0.1 M sodium phosphate buffer (pH 7.4) at 4 °C for 2 h. The specimens were then dehydrated stepwise in ethanol, followed by acetone and LX-112 (Ladd) embedding. Ultrathin sections (approximately 60 to 80 nm) were prepared and contrasted with uranyl acetate followed by lead citrate and examined in a Tecnai G2 Spirit BioTWIN electron microscope (FEI) operated at 80 kV and equipped with a 2kx2k Veleta CCD camera (Olympus Soft Imaging System, USA). Four randomly acquired images in areas showing transversely sectioned collagen fibrils

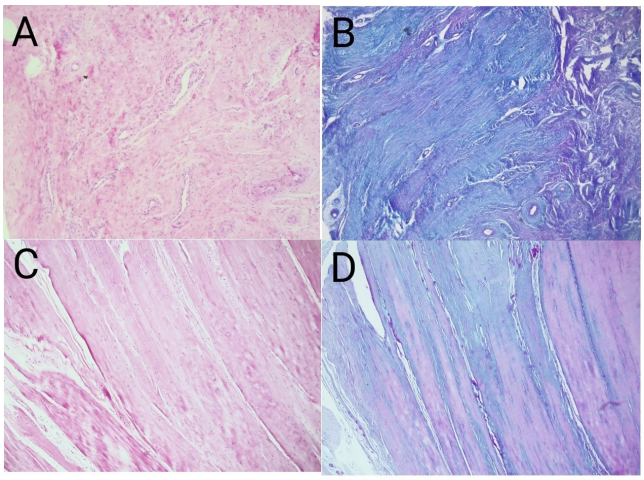

Fig. 2

Biopsy specimens a) and b) were obtained at revision from a 78-year-old male patient with a periprosthetic joint infection after total hip arthroplasty performed using a lateral approach. a) depicts the deterioration of fibres, with several vessels within the dense connective tissue. b) Rich glycosaminoglycan content with markedly increased alcianophilia in the connective tissue. Biopsy specimens c) and d) were obtained at revision from a 77-year-old male patient with cup and stem loosening, who had previously undergone a hip joint arthroplasty via a lateral approach. The light-microscopic views show c) slight separation of fibres and few vessels. d) A moderate increase in alcianophilia (blue staining) between the pink-stained collagen fibres.

The fibre structure, cellularity, and vascularity and the presence of GAGs were classified according to a semi-quantitative scoring system (Table I).[15,18] It consists of four different elements, each of which is between 0 and 3 points. This procedure and evaluation system have also been used in multiple previous studies.[19–23]

The TDS was therefore calculated by adding the values from the two biopsies for the four constituents, which can result in values between 0 (no degeneration) and 12 points (extremely high degeneration). The TDS is similar to a scoring concept previously described and used in a biopsy analysis of the Achilles tendon. The score has also undergone satisfactory intraobserver reliability testing.[24]

Bacteriological analysis. Analyses of bacteriology, the definition of infection and antibiotic treatment, were performed by a specialist in infectious diseases (JK) in accordance with previously published data from the same institution.[25] A PJI was reckoned by the major criterium of two or more positive cultures with growth of the same microbiological organism in joint fluid or collected tissue samples. In the non-infected group, PJI was ruled out by ten collected tissue samples at revision surgery. A PJI was considered to be eradicated when there were no inflammatory signs, including normalized ESR and/or CRP or symptoms from the hip joint for a minimum of two years after the termination of antibiotic treatment.[26]

Statistical analysis. Median (range) and mean (standard deviation (SD)) values are presented for the clinical data and the TEM findings. For the histological findings, a stratified distribution is presented. The unpaired *t*-test and the Mann-Whitney U test were used for comparisons of clinical data, fibril diameters, and the histological findings of the TDS, respectively, between the study groups.

The power analysis was based on the assumption that it would be meaningful to detect a difference of 5 nm in fibril diameter between the study groups in accordance with previously published studies. If the SD was as large as 40 nm, then 800 fibrils from infected patients and 2,100 control fibrils would reach a power of over 80%. The value of α used in the power analysis was 0.05.

Results

Background clinical and outcome data in the infected and the non-infected revision groups are presented in Table II. The non-infected patients had their revisions performed significantly later after the index operation than the infected patients.

The biopsy samples from the GMED of infected patients revealed a significantly larger diameter than those of the control patients, as seen in the TEM ($p < 0.001$) (Table III). However, the relative fibril distribution was similar.

Representative TEM images showing both the fibril diameter and the composition of fibrils in transversely sectioned tendons are presented in Figure 1.

The distribution of the histological findings for the four elements of the TDS is reported in Table IV. Histologically, the samples from infected patients revealed significantly more vascularity ($p < 0.001$), presence of GAGs ($p < 0.001$, Mann-Whitney U test), and a higher TDS ($p = 0.003$, Mann-Whitney U test) than the samples from control patients (Table V).

Photomicroscopic views of biopsy specimens obtained from repair tissue of the gluteus medius tendon are presented in Figure 2. Views a and c are stained with haematoxylin and eosin, with b and d with Alcian blue-PAS, and all the views have a magnification of approximately x 50. Loss of fibre structure, increased vascularity, and pronounced blue staining indicates degeneration.

Bacteriological findings, surgical treatment, subsequent antibiotic therapy, and the outcome of the treatment of the infection are listed in Table VI. The majority of patients had staphylococcal infections of various species. Patient number six differed from the others since he had had a temporary implant prior to revision. Intravenous antibiotics were given for an average of ten days and were followed by oral therapy for just over three months.

Discussion

The main finding in the present study was that more histological degeneration was found in the GMED tendon in patients undergoing THA revision surgery due to a PJI

Table VI. Clinical and bacteriological data in infected patients.

No.	Sex	Age, yrs	Time from index op (years)	Primary pathogen	Secondary pathogens	Surgical treatment	Intravenous therapy	Oral therapy	Outcome
1.	Male	70	0.7	*CoNS*		One-stage revision	Vancomycin	Ciprofloxacin/rifampicin	Eradication
2.	Male	59	0.3	*Staphylococcus saccharolyticus*		One-stage revision	Piperacillin-tazobactam	Clindamycin/penicillin V	Eradication
3.	Female	80	6.4	*Escherichia coli*		One-stage revision	Cefotaxime	Ciprofloxacin	Eradication
4.	Male	78	3.9	*CoNS*		Two-stage revision	Vancomycin	Clindamycin/rifampicin	Lifelong antibiotic suppression (flucloxacillin)
5.	Male	58	14.2	*Cutibacterium acnes*	*Staphylococcus aureus, CoNS*	One-stage revision	Vancomycin	Clindamycin/amoxicillin	Eradication
6.	Male	72	0.2	*S. aureus*		One-stage revision	Cloxacillin	Flucloxacillin	Eradication
7.	Female	64	2.4	*S. aureus*		DAIR + cup revision	Vancomycin	Sulphametoxazol/ trimethoprim	Lifelong antibiotic suppression (Sulpha-Trimethoprim)
8.	Male	52	1.0	*S. saccharolyticus*		One-stage revision	Vancomycin	Clindamycin	Eradication

CoNS, coagulase-negative *Staphylococci*; DAIR, debridement, antibiotics and implant retention.

than in patients undergoing THA revision surgery for other reasons.

GMED tendon changes among patients with a PJI appear to be particularly associated with the vascularization and changes in the extracellular matrix (ECM). GAG are complex carbohydrates in the ECM that are thought to form cross-links between collagen molecules, and play a role in the mechanical properties of tendons. A correlation between an abnormal Achilles tendon fibre structure with tendinosis and a substantial histopathological increase in the volume of GAG-rich areas was presented decades ago,[24] and the excess amounts of GAGs in the present study indicate more tendinosis and thereby degeneration.

The formation of the ECM and the pathophysiology of GAGs have recently attracted increasing interest in cellular research. Although the normal mechanical function depends on the precise alignment of collagen fibrils, it is proteoglycans that regulate collagen fibrillogenesis and thus, indirectly, tendon function.[27] GAG depletion in tendons increases fascicle stress relaxation, but not recovery.[28] Certain GAG formation, as well as GAG-depleted tendons, affect tenocyte morphology and nanostructural properties, and facilitate both load transfer and sliding between fibrils.[29] Tissue engineering and regenerative medicine research are also able to produce constructs by using bioreactors on stem and progenitor cell populations that will improve tendon repair. However, in spite of being needed for seamless tendon function, an increasing amount of GAGs indicates tendon degeneration.[30]

Ultrastructurally, the group of infected patients had more collagen fibrils with a larger diameter than the uninfected group, which is inconsistent with our hypothesis. However, the difference is not striking, and the diameter in both groups is smaller than in non-infected patients previously undergoing surgery through a posterior approach and considerably less than in patients with OA and cervical hip fracture.[15] Both groups in the present study had previously undergone surgery using the lateral approach, thereby cutting the insertion of the GMED tendon. This procedure itself might induce a shift towards smaller fibril diameters. The assumption that a difference of 5 nm in fibril diameter may also have been too small and created a type II error.

Normal ageing, as well as a prolonged period of symptoms, might also produce a reduction in tendon fibril diameter and symptoms. The uninfected patients were slightly older than the infected ones, which is regarded as unfavourable in terms of tendon degeneration.[31] Further, the time from the index operation was significantly longer among the uninfected patients, which may also influence the results.

Previously presented poor PROM results after THA revisions due to infection are supported by the histological results in the present study.[2,3] Tendons have very little regenerative capacity of their own, and there is no scientific evidence of regeneration to normal tendon tissue.[32] Bacteria may stimulate inflammation by inducing the tenocytes to fibroblast activation, which can cause subsequent fibrosis.[33] The material in the present study is too sparse to enable an analysis of whether certain bacteria are more disadvantageous in terms of tendon degeneration. Only one patient in the present study had a significant polymicrobial infection. This has been shown to correlate with inferior treatment outcomes due to bacteriological synergy,[34] but the effect on tendon degeneration is unknown. Regarding the effect of different bacteria and other toxic agents, the complicated molecular

mechanisms and interactions of inflammation and tendon regeneration require further study.[35]

PJIs are a challenge to the orthopaedic society. Progress regarding bacteriological culturing and antibiotic treatment, together with close co-operation between specialized arthroplasty surgeons and specialists in infectious diseases, has been prosperous. The present study demonstrates a connection between PJIs and tendon degeneration. It is known that tendon repair results in the formation of a fibrovascular scar that never attains the gross, histological, or mechanical characteristics of a normal tendon.[32]

A further understanding of the mechanisms of regeneration may promote adjuvant medical treatment and tailored physiotherapy. However, it appears that a previous lateral approach.[16] Repeated revisions and two-stage procedures are also disadvantageous to patient rehabilitation.[36]

One major limitation of this study is the small number of infected patients, putting it at risk of being underpowered. In addition, it was not known how long the infection had been active. The occurrence and duration of nutritional and endocrine diseases were not exhibited. Even if the patients did not have medical treatment, hyperglycaemia and hypothyroidism may have existed, and possibly affected tendon tissue and collagen fibrils. Furthermore, no PROM assessments were made over time, and no follow-up of the histological and ultrastructural appearance was obtained.

Taken together, biopsies from living patients in a clinical context with an infected THA present a histological GMED tendon degeneration. The poor regenerative capacity of tendons may explain the inferior results in PROMs regarding hip function seen in other studies of patients with a previous PJI.[2] This may induce falls or fear of falling, which is a well-established cause of morbidity and mortality in elderly people.[37,38]

In conclusion, more histological degeneration in the GMED was found in patients undergoing THA revision surgery due to PJI than in patients undergoing THA revision surgery for other reasons.

Take home message

- Periprosthetic joint infection in the hip causes histological degeneration of the gluteus medius tendon. Poor regenerative capacitity of this tendon may cause gait deficiency and poor patient reported outcomes.
- This should be considered both in surgical treatment and the rehabilitation process.

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