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MRI Inflammation of the Hand Interosseous Tendons occurs in anti-CCP positive at-risk individuals and may precede the development of clinical synovitis

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Abstract

Interosseous tendon inflammation (ITI) has been described in rheumatoid arthritis (RA). Whether ITI occurs in at-risk individuals before the onset of clinical synovitis is unknown.

Objectives: To investigate, by magnetic resonance imaging (MRI), ITI in anti-cyclic citrullinated peptide positive at-risk individuals (CCP+ at-risk) and to describe the anatomy, prevalence and clinical associations across the RA continuum.

Methods: Hand MRI was performed in 93 CCP+ at-risk, 47 early RA (ERA), 28 established 'late' RA (LRA) and 20 healthy controls (HC) and scored for ITI, flexor tenosynovitis (TSV) and RA MRI score (RAMRIS) at the metacarpophalangeal joints (MCPJs). Cadaveric and histological studies were performed to explore the anatomical basis for MRI ITI.

Results: The proportion of subjects with ITI and the number of inflamed ITs increased along the disease continuum ($p<0.001$): 19% of CCP+ at-risk, 49% of ERA and 57% of LRA had ≥1 IT inflamed . ITI was not found in any HC. ITI was more frequently identified in tender MCPJs compared with non-tender MCPJs (28% vs 12% respectively). No IT tenosynovial sheath was identified in cadavers on dissection or histological studies suggesting MRI findings represent peri-tendonitis. Dye studies indicated no communication between the IT and the joint.

Conclusions: ITI occurs in CCP+ at-risk individuals and can precede the onset of clinical synovitis. The interosseous tendons may be important non-synovial extra-capsular targets in the development and progression of RA.

Introduction

Rheumatoid arthritis (RA) is conventionally considered as a disease of the synovial joints. However, individuals at-risk of RA (including those with anti-citrullinated protein antibodies (ACPA)) often develop musculoskeletal symptoms before the onset of clinical synovitis (i.e. synovitis determined on physical examination) or subclinical synovitis (i.e. synovitis determined on high resolution imaging but not physical examination) (1-3). Extra-capsular structures may be important early targets of RA-related inflammation. This may involve the tenosynovium or potentially even tendons without a tenosynovial sheath (i.e. peri-tendonitis). Indeed tenosynovitis appears to be an early and prevalent magnetic resonance imaging (MRI) lesion in at-risk individuals, both in clinically suspect arthralgia (CSA) patients (4) and ACPA-positive at-risk individuals (5). Tenosynovitis of the wrist and finger flexor tendons is also the strongest predictor of progression to arthritis in CSA patients (4). Furthermore, tenosynovitis is a frequent presentation of RA, causes significant disability and occurs in remission, where it is predictive of flares (6).

Unlike tenosynovitis of the wrist and finger flexor tendons, the involvement of other extra-capsular structures critical to hand function has not been completely elucidated. For example, the interosseous muscles of the hands are regarded as the cornerstone of hand function (7) and their tendons run adjacent to the metacarpophalangeal (MCP) joints. Occupation-related overuse injuries of these muscles and their tendons have been described (8). A recent study identified a high frequency of inflammation of the interosseous tendons in patients with RA (9). Whether these tendons become inflamed in at-risk individuals and whether they may be responsible for symptoms in these subjects is unknown. We therefore sought to comprehensively investigate interosseous tendon

inflammation (ITI) across the RA continuum by describing the anatomy, histology, prevalence and clinical associations in both anti- cyclic citrullinated peptide positive at-risk (CCP+ at-risk) individuals and RA patients.

The main aim of this study was to assess whether MRI ITI is present in CCP+ at-risk individuals without clinical synovitis. As we hypothesised MRI ITI would be present in CCP+ at-risk, the secondary aim of the study was to determine whether MRI ITI is associated with clinical features in CCP+ at-risk individuals

Methods

Design

A retrospective analysis of MRI and clinical data of CCP+ at-risk individuals, RA patients and healthy controls was undertaken.

In order to understand whether ITI should be considered a tenosynovitis or a peri-tendonitis, cadaveric and histological studies were performed to explore the anatomical basis for MRI ITI.

Clinical Subjects

Anti- CCP positive at-risk individuals with musculoskeletal (MSK) symptoms but no clinical synovitis (CCP+ at-risk), disease-modifying anti-rheumatic drug (DMARD)-naïve early RA patients (ERA), established 'late' RA patients (LRA) and asymptomatic healthy controls (HC)

were recruited at Chapel Allerton Hospital, Leeds, UK. Informed consent was received from all subjects.

The Leeds CCP+ at-risk cohort has been previously described (3, 10). Patients aged >18 years presenting to their GPs or other health professionals with new-onset MSK symptoms (e.g. arthralgia, epicondylitis, subacromial bursitis) but no clinical synovitis were invited to participate. Primary care recruitment was adopted by the UK Primary Care Clinical Research Network. Anti-CCP testing was performed centrally using the commercially available anti-CCP2 (immunocap method; Phadia, Sweden). Those with a positive test were invited to attend a dedicated research clinic in Leeds where recruitment for the current MRI study was undertaken. Patients from the Leeds early arthritis clinic who were anti-CCP positive but did not have clinical synovitis were also recruited.

ERA patients had not received DMARDs at the time of imaging. LRA patients had ≥ 1 year disease duration (total duration of reported symptoms), were anti-CCP and/or rheumatoid factor (RF) positive and had active disease (DAS 28 ≥3.2). These patients had received ≥ 1 DMARD and underwent MRI prior to receiving rituximab as part of a separate study (11).

Healthy controls included staff members from the University of Leeds and members of the local community. None of the controls had any MSK symptoms at the time of recruitment.

Demographic and clinical details were recorded at the time of imaging assessments. All subjects (except HC) underwent MSK examination by a rheumatologist prior to the imaging assessments and swollen and tender MCP joint counts were recorded. Blood testing for C-reactive protein (CRP) was performed at the clinical visit.

MRI

All subjects underwent MRI of the most symptomatic or dominant hand and wrist (see supplementary materials for full details). All CCP+ at-risk, ERA patients and HC MRI scans were performed on a 3T Siemans Verio system (Erlangen, Germany). Due to logistical issues all LRA patients were scanned on a 1.5T Siemans Avanto (see supplementary materials for further details of MRI systems). All MRI scans were independently scored for the presence or absence of ITI by two musculoskeletal radiologists (AG, ER). The radiologists were blinded to all patient details and studies were presented to them in a random order with respect to disease status. Any discrepancies in scoring between the two radiologists were reviewed at the end of the reporting exercise and a consensus score was agreed. The consensus score was then used in the analysis. ITI was defined as the presence of enhancing tissue surrounding the tendon which was evident in two planes (9). Eight tendons were assessed in each hand (i.e. each MRI study): the tendons of the dorsal interossei (1-4), the palmar interossei (1-3) and the abductor digiti minimi (ADM).

In addition to IT scoring, all MRI studies were scored for the presence of synovitis, bone marrow oedema (BME) and erosions at MCP joints 2-5 according to the Outcome Measures in Rheumatology (OMERACT) RA MRI scoring system (RAMRIS) (12). Tenosynovitis of the flexor digitorum tendons was scored dichotomously as ‘present’ or ‘absent’ in keeping with the dichotomous scoring of ITI. In the majority of studies (including all CCP+ at-risk studies) RAMRIS and tenosynovitis scoring was performed by the same radiologists that scored ITI (AG, ER), and a consensus score was used in the analysis. However, in a small number of cases only scores from a single radiologist were available and these were therefore used in

the analysis. In all cases, the radiologists were blinded to all patient details and studies were presented to them in a random order according to disease status.

Anatomical Study

To assess the relationship between the interosseous tendons and the adjacent MCP joint, twenty fresh hand specimens from anonymous donors were obtained (Anatomy Department, Universitat de Barcelona). The first dorsal interosseous muscle and tendon were identified by ultrasound (US) from the myotendinous junction to the capsular insertion. The adjacent second MCP joint was also identified on US. Using US-guidance, a green dye (green acrylic paint mixed 50:50 with water) was injected along the interosseous tendon proximal to its capsular insertion. Similarly, a blue dye (blue acrylic paint mixed 50:50 with water) was injected into the second MCP joint space using US-guidance. Specimens were then frozen and transverse sections were made. Ethical approval for this study was obtained by the Universitat de Barcelona, Spain**.**

To further confirm the absence of a tendon sheath around the interosseous tendons, two embalmed adult human cadaver hands were dissected. The distal attachment of the first dorsal interosseous tendon was identified by dissection and processed for histological analysis (Department of Anatomy and Embryology, Complutense University of Madrid). The specimens were fixed in 10% formalin and embedded in paraffin. Each specimen was sliced as a whole on a single plane. 7µm sections were cut and stained with haematoxylin-eosin and Mallory's trichrome dye. Additionally, the first dorsal interosseous tendon insertion was investigated in two human foetuses age 14 weeks (greatest length 115 mm in both). The specimens belong to the collection kept at the Department of Anatomy and Embryology at

UCM. 12µm sections were cut and stained with haematoxylin-eosin. Digital photomicrographs were taken with a Nikon DXM 1200 labour microscope (Nikon Corp., Tokyo, Japan) and edited using Act One and Adobe Photoshop CS6 software. Ethical approval for this study was obtained by Complutense University of Madrid.

Statistical analysis

The number of inflamed interosseous tendons was compared between subject groups using a Jonckheere-Terpstra test in order to assess whether the median number of sites increased according to disease along the RA continuum. In all analyses where MRI-detected synovitis, BME and erosions are reported at joint level, only those joints where inflammation scores were over and above that seen in the same anatomical location in symptom-free controls of the same age range were included (i.e. true subclinical inflammation) (14). Adjustment for symptom-free controls was performed in order to account for the observation that MRI-detected inflammation is prevalent in the general population, especially in older people and at certain anatomical sites e.g. MCP 2 and 3 (14). True subclinical inflammation was considered to be present if that joint or bone was i) scored positive for inflammation and ii) the score obtained at that joint or bone was present in <5% of age-matched symptom free persons (14). Tenosynovitis could not be adjusted for in this way as this was scored dichotomously (i.e. present or absent) rather than semi-quantitatively in this study.

Results

Clinical Study

Baseline characteristics

Ninety-three CCP+ at-risk, 47 ERA, 28 LRA and 20 HC were included. The frequency of tender and swollen MCP joints and CRP level increased along the RA-continuum with increasing disease duration (table 1). Overall MRI inflammation (synovitis, tenosynovitis, BME, erosions) at the MCP joints also increased in a similar fashion (see supplementary materials).

MRI Interosseous tendon inflammation

MRI ITI was observed as enhancing tissue around the mid portion of the tendon, proximal to the enthesis (figure 1). The proportion of patients with ITI increased along the RA continuum (table 2); 18/93 (19%) CCP+ at-risk, 23/47 (49%) ERA and 16/28 (57%) LRA patients had inflammation of at least one IT. Of note, no ITI was identified in any HC. The number of inflamed IT per patient also increased along the RA-continuum (Jonckheere-Terpstra J=5.90, $p<0.001$). In all patient groups, ITs associated with MCPJ2 and MCPJ5 were most frequently affected (table 2), although trends with respect to increasing ITI prevalence across the groups were similar in all locations. Of note, ITI was identified in both anti-CCP positive and anti-CCP negative ERA patients: 17/34 (50%) of anti-CCP positive ERA patients had ITI compared with 6/13 (46%) of anti-CCP negative ERA patients. The two radiologists showed an excellent level of agreement for the identification of ITI in this study: kappa (k) = 0.893

(standard error = 0.025), comparable to that demonstrated in the original description of MRI ITI [kappa (k) = 0.91 (standard error = 0.03)] (9).

Association between interosseous tendon inflammation and clinical features

The prevalence of MCPJ tenderness increased with disease duration (table 1 and 3). ITI was more frequently identified in tender MCPJs compared with non-tender MCPJs; twenty-eight percent of all tender MCPJs had an associated ITI, whereas only 12% of non-tender MCPJs had an associated ITI (table 3). Synovitis, BME, erosions and tenosynovitis were also more frequently identified in tender MCPJs compared with non-tender MCPJs (table 3).

Early morning stiffness (EMS) duration (minutes) was not markedly different in CCP+ at-risk with ITI (i.e. at least one inflamed IT at any site) compared to those without ITI (median (IQR) 10 (0, 60) vs 5 (0, 10)). Similarly, the presence of synovitis, BME, tenosynovitis or erosions at ≥ 1 MCPJ did not appear to be associated with EMS duration (supplementary materials). The number of affected MCPJs was not associated with EMS duration for any of the MRI features.

Anatomical Study

Detailed dissection of fresh hand specimens revealed no identifiable synovial tendon sheath around the IT of the cadaveric specimens. Identification of the blue and green dye on transverse sections was achieved in 13/20 (65%) specimens (figure 1b). Blue dye was localised in the intra-articular space and was not seen outside the joint capsule. In contrast, green dye was localised around the ITs and interosseous muscle and was not seen within

the joint capsule. These findings suggest an absence of communication between intra-capsular synovial membrane and the adjacent IT.

Cadaveric dissection revealing the first dorsal interosseous tendon and its attachment is shown in supplementary figure 1. Histological examination of the first dorsal interosseous tendon from a foetal hand (figure 2A and B) and adult hand (figure 2C – G) confirmed presence of an epitendon, but no synovial sheath surrounding the tendon could be identified.

		HC n=20	CCP+ at-risk n=93	ERA n=47	LRA n=28
Age: mean (SD)		47.9 (10.3)	48.1 (12.3)	55.6 (15.3)	51.5 (13.3)
Female		75%	69%	74%	93%
Symptom duration, months: median (IQR)		NA	14 (6, 40)	7 (3, 14)	96 (42, 216)
Tender joint count	0	100%	83%	43%	25%
	1	-	6%	26%	4%
	2	-	4%	17%	32%
	3	-	3%	9%	4%
	4	-	3%	6%	36%
Swollen joint count	0	100%	100%	43%	21%
	1	-	-	23%	14%
	2	-	-	28%	25%
	3	-	-	4%	21%
	4	-	-	2%	18%
Anti-CCP+: n(%)		NA	93 (100)	35 (74)	26/27 (96)
Rheumatoid factor +: n(%)		NA	44/92 (48)	28/46 (61)	19/24 (79)
EMS (mins): median (IQR)		NA	10 (0, 30)	120 (30, 180)	60 (30, 150)
CRP (mg/L): median (IQR)		NA	<5 (<5, <5)	8 (<5, 19)	11 (5, 27)

Table 1: Baseline characteristics of all participants. The frequency of tender and swollen joints and CRP level increased along the RA continuum with increasing disease duration. HC, healthy controls; CCP+ at-risk, anti-CCP positive at-risk individuals; ERA, early RA patients; LRA, late RA patients. Joint counts refer to 2^{nd}-5^{th} metacarpophalangeal joints (MCPJs). EMS, early morning stiffness duration (minutes); CRP, C-reactive protein (mg/dL).

Interosseous tendon inflammation present at:	HC n=20	CCP+ at-risk n=93	ERA n=47	LRA n=28
MCP2	- (0)	11% (10)	34% (16)	39% (11)
MCP3	- (0)	4% (4)	23% (11)	21% (6)
MCP4	- (0)	1% (1)	15% (7)	25% (7)
MCP5	- (0)	9% (8)	28% (13)	32% (9)
Dorsal tendons	- (0)	12% (11)	45% (21)	50% (14)
Palmar tendons	- (0)	10% (9)	32% (15)	32% (9)
Any site (patient-level)	- (0)	19% (18)	49% (23)	57% (16)
Any site (site-level)	- (0)	3% (24/744)	15% (55/376)	18% (40/224)
Number of sites per patient (n/8)				
0	100% (20)	81% (85)	51% (24)	43% (12)
1	-	14% (13)	17% (8)	21% (6)
2	-	4% (4)	15% (7)	18% (5)
3	-	1% (1)	6% (3)	-
4	-	-	2% (1)	11% (3)
≥5	-	-	9% (4)	7% (2)

Table 2: Interosseous tendon inflammation according to RA status. HC, healthy controls; CCP+ at-risk, anti-CCP positive at-risk individuals; ERA, early RA patients; LRA, late RA patients. Dorsal tendons refers to 1^{st} – 4^{th} dorsal interosseous tendons and abductor digiti minimi. Palmar tendons refers to 1^{st} – 3^{rd} palmar interosseous tendons.

	Non-tender MCPJs n=507	Tender MCPJs n=141
Age: mean (SD)	50.6 (13.7)	52.2 (13.9)
Female	71% (358)	84% (118)
Group CCP+ at-risk	66% (337)	18% (25)
ERA	26% (132)	37% (52)
LRA	7% (38)	38% (54)
Synovitis > 0	20% (101)	37% (52)
Synovitis > 1	6% (30)	19% (27)
BME > 0	4% (21)	14% (20)
Tenosynovitis > 0	30% (153)	49% (69)
Erosions > 0	3% (17)	13% (18)
ITI	12% (59)	28% (40)

Table 3: Clinical and MRI features according to clinical tenderness at MCP joints (MCPJs 2-5) for CCP+ and RA subjects (n=162). MCPJS, metacarpophalangeal joints; CCP+ at-risk, anti-CCP positive at-risk individuals; ERA, early RA patients; LRA, late RA patients; BME, bone marrow oedema; ITI, interosseous tendon inflammation.

Discussion

Individuals at-risk of RA often experience a prodrome of joint pain and stiffness before the onset of clinical synovitis. This may reflect the earliest phase of RA inflammation, which in many cases will progress to full-blown disease. However, the cause of these symptoms and their relevance to disease progression is not clear. Understanding this phase of disease is likely to deliver important insights into pathogenesis and also inform future preventative strategies.

This study is the first to demonstrate that the IT of the hands are inflamed in anti-CCP positive at-risk individuals and may represent an extra-capsular cause for early symptoms in the absence of clinical synovitis. We have also demonstrated that, on cadaveric dissection and histological examination, these tendons do not have a tenosynovial sheath and do not directly communicate with the joint capsule. This, alongside the observation that fluid is not seen around these tendons on MRI (9), suggests MRI ITI represents an additional non-synovial target of inflammation in the RA continuum (i.e. peri-tendonitis rather than a true tenosynovitis).

ITI was identified in 19% of CCP+ at-risk individuals with increasing prevalence with RA disease progression. The number of inflamed tendons in each patient also increased with disease progression. Of note, we did not identify any ITI in the healthy controls. This is in keeping with the observation that MRI tendon inflammation is rarely seen in healthy subjects (14).

The association between specific clinical features (EMS duration, MCPJ tenderness) and MRI inflammation in anti-CCP positive at-risk individuals has not previously been reported. However, Van Steenbergen et al have previously reported no association between EMS

duration and MRI inflammation in individuals with CSA (15). While we found no association between ITI and EMS duration, there was an increased frequency of ITI in tender MCPJs compared with non-tender MCPJs. This is an interesting finding, particularly as small joint tenderness is predictive of arthritis development in CCP+ at-risk subjects (10). The potential association between clinical features and ITI should be further explored in a prospective study, where IT tenderness and flexor tendon tenderness at the MCPJs could be specifically assessed by clinical examination.

In line with our findings, others have demonstrated that tendon inflammation is prevalent in the hands of early arthritis patients (16) and at-risk individuals (4, 5). In these studies tendon inflammation was mainly characterised by tenosynovitis, although isolated peri-tendinous inflammation of the digital extensor tendons was described in patients with early RA (16); our current data extend the concept of early extra-capsular inflammation and suggest non-synovial tendon inflammation, i.e. peri-tendonitis, may also be an important disease target in at-risk individuals who do not have clinical synovitis.

While the dye injections in our cadaveric study revealed no communication between the interosseous tendon and adjacent MCPJ, the specimens used were from anonymous donors who did not appear to have RA. It is not known if this would be different in the setting of established RA-related MCP joint inflammation.

Although we have identified ITI as an early feature in the RA disease continuum, it is not clear how specific this lesion is for anti-CCP –related inflammation (or autoimmune-related inflammation). Indeed we identified a similar prevalence of ITI in anti-CCP positive ERA patients compared with anti-CCP negative ERA patients, suggesting ITI is unlikely to be an ACPA-specific phenomenon. Furthermore, although MRI peri-tendinous inflammation has

been reported in established RA, this finding is not necessarily disease-specific. It is also possible that ITI may occur due to mechanical factors in some patients with hand arthralgia. Future work should, therefore, investigate whether ITI also occurs in symptomatic anti-CCP negative patients with arthralgia and also in other rheumatic diseases.

In conclusion, this study has identified MRI inflammation of the hand ITs in CCP+ at-risk individuals who do not have clinical synovitis. This lesion was more frequently seen in tender MCPJs compared with non-tender MCPJs. These data suggest the ITs may be an early non-synovial extra-capsular target of RA inflammation. Further longitudinal data are needed to investigate whether ITI predicts the development of clinical and subclinical synovitis in individuals at-risk of RA.

Key messages

What is already known about this subject?

- Individuals at-risk of RA (including those with anti-citrullinated protein antibodies) often develop musculoskeletal symptoms before the onset of clinical or subclinical synovitis
- MRI tenosynovitis of the flexor tendons is a prevalent finding in at-risk individuals
- There is a high prevalence of interosseous tendon inflammation (ITI) in the hands of patients with established RA

What does this study add?

- ITI occurs in anti-CCP positive at-risk individuals without clinical synovitis

- Cadaveric and histological studies show the interosseous tendons do not have a tendon sheath and do not directly communicate with the joint capsule
- MRI ITI may be associated with clinical MCP joint tenderness and could explain symptoms in at-risk individuals who do not have clinical synovitis

Figure legends:

Figure 1:

Interosseous tendon inflammation in anti-CCP+ at-risk individuals. 1a) Inflammation of the 1st and 2nd dorsal interosseous tendons and 1st palmar interosseous tendon (arrows). Metacarpophalangeal joint (MCPJ) inflammation is present at the 2nd and 3rd MCPJs and flexor tenosynovitis of the 2nd finger is also observed (asterix). 1b) Transverse section of cadaveric 2nd MCPJ following ultrasound-guided dye injections. Green dye has accumulated around the superficial margin of the interosseous muscle but remains outside the MCPJ capsule. Blue dye injected into the joint remains within the joint capsule. 1c) Inflammation of the 3rd palmar interosseous tendon. Flexor tenosynovitis is also present (asterix). 1d) Inflammation of the 1st dorsal interosseous tendon (white arrow). There is no inflammation in the adjacent MCPJ or of the 2nd dorsal interosseous tendon (black arrow). 1e) Isolated inflammation of the 2nd dorsal interosseous tendon (arrow). No adjacent synovitis or tenosynovitis is seen. 1f) Illustration of the anatomy of the dorsal interosseous tendons of the hand. The interossei originate from the medial and lateral aspects of the metacarpals and attach into the extensor hood and proximal phalanx of each finger. 1g) Illustration of the anatomy of the palmar interosseous tendons. The three palmar interossei attach to the index, ring and little fingers.

Figure 2:

Histological examination of the first dorsal interosseous tendon. A) Frontal section of the metacarpophalangeal joint of a human fetus (14 weeks post-conception) with

Haematoxylin-eosin staining. B) High power magnification of black square in A: 1, superficial first dorsal interosseous tendon; 2, deep first interosseous tendon inserting into the base of the proximal phalanx; 3, insertion of the deep tendon of the first interosseous into the joint capsule. MT, second metatarsal head; PH, proximal phalanx; PS, synovial plica; V, blood vessel. C) Frontal section of the myotendinous junction of the first dorsal interosseous tendon in an adult cadaver with Mallory's trichrome stain. The tendon is formed by collagen fascicles (CF) arranged longitudinally. The epitendon (EPT) surrounds the tendon (illustrated by black line). D) High power magnification of the square in C shows muscle fascicles (MF) separated by endomysium (EM) and surrounded by perimysium (PM). PM is continuous with peritendon (PT) that surrounds CF. E) Frontal section of the distal insertion of the first dorsal interosseous tendon in an adult cadaver with Mallory's trichrome stain. 1, superficial first dorsal interosseous tendon; 2, deep first dorsal interosseous tendon. F) High power magnification of the black square in E shows the EPT containing blood vessels. There is no tendon sheath surrounding the EPT. G) High power magnification of the red square in E. Blood vessels are seen in the EPT with no surrounding tendon sheath.

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Competing Interests

No competing interests declared

Contributorship

KM recruited patients, collected and analysed the data and wrote the manuscript. MADA designed the study and helped prepare the manuscript. ER scored the MRI scans. EMAH led the statistical analysis. LH recruited patients and collected data. IM,MP, JRM, JM and EN performed the cadaveric and histological studies. JLN was one of the study clinicins. ALT and JEF recruited patients and collected clinical data. AJG and PE designed and led the study. All co-authors read and revised the manuscript.

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Ethics approval

NHS Health Research Authority National Research Ethics Service Committee Yorkshire & the Humber – Leeds West.

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