

Case-Control Study



Sacroiliac Joint Ligaments and Sacroiliac Pain: A Case–Control Study on Micro- and Ultrastructural Findings on Morphologic Alterations

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Background: The sacroiliac joint (SIJ) is a common source of low back pain. SIJ pain has shown to have negative impact on patients' quality of life. Although clinically there is an increasing interest to treat SIJ-related pain both conservatively and surgically, the underlying mechanisms related to pathology in that region are poorly understood. One hypothesis is that the SIJ ligaments are structurally altered in SIJ pain.

Objectives: The given study investigated patient cases with different pain durations undergoing posterior distraction arthrodesis of the SIJ, with subsequent micro- and ultrastructural assessment of the interosseous and posterior SIJ ligaments compared with autopsy controls without known history of low back pain.

Study Design: Case–control study. Morphologic-pathological analysis of tissue samples obtained during surgery with controls from legal medicine.

Setting: Rural hospital setting in Halberstadt, Germany.

Methods: SIJ ligaments were removed from 6 patients undergoing SIJ arthrodesis for histological and ultrastructural assessment in scanning and transmission electron microscopy, and compared with 6 controls without known history of SIJ pathology.

Results: A number of alterations were observed in the ligaments of patients with SIJ, namely ligament disruption, collagen loosening and coiling, vascularization, and hemorrhage. In some areas, these changes were observed in proximity to healthy (structurally unaltered and intact tissues), indicative of a potential disease progression. Comparison to controls yielded a significant correlation between SIJ pathology and the level of collagen degeneration ($\phi \geq 0.82$; $P < 0.001$).

Limitations: Small sample size, method of tissue removal from patients may have influenced tissue integrity.

Conclusions: The combined clinical, histological, and ultrastructural analysis provided, to our knowledge, first-time evidence of morphologic SIJ ligament alteration of a nontraumatic and noninflammatory cause. Further research is necessary to elucidate these structural changes and to substantiate pain duration and patient-history-dependent changes at the ligaments of the posterior pelvis.

Key words: Collagen, electron microscopy, histological and ultrastructural assessment, interosseous sacroiliac ligament, low back pain, sacroiliac joint

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The sacroiliac joint (SIJ) is a common source of low back pain (1-5). A variety of novel treatment strategies have emerged over the last few decades, especially for surgical fusion (6-10) or denervation (11-14) of the SIJ. To date, despite the joint being appreciated as an important site of assumed pathology (15), little is known about the potential mechanisms of pain generation. Four potential mechanisms leading to SIJ pain have been hypothesized for the joint, namely traumatic bone and ligament injury, inflammation, alterations in muscle function and morphology, and neuropathy of the supplying nerves (15,16).

An identification of such alterations on a morphologic basis has, to date, been unsuccessful with the exception of seronegative spondyloarthropathy (17-21) and traumatic bone or ligament disruption (22-24). Existing studies have so far failed to identify morphologic alterations directly related to chronic SIJ pain (25). Age- and posture-related changes in the joint have repeatedly been shown to be physiological adaptations to enhance form and force closure (26-31), being mediated via the bony ridges and grooves (32-35), the dense ligaments, and also the muscles stabilizing the joint actively (30,31,36,37).

One hypothesis related to SIJ pathology is that its ligaments are altered regarding morphology or composition, to the effect that load distribution throughout the joint becomes altered with pain being causative or an effect. Given the introduction of new surgical techniques aiming to stabilize or even fully fuse the SIJ (6-10), further research becomes necessary to clearly identify any pathology. To date, only one surgical technique uses a posterior approach to the SIJ and the interosseous and posterior ligaments (8,38), making it possible to assess their morphology following operative ligament removal to place an implant at the side, called distraction interference arthrodesis.

Tissues obtained from patients undergoing SIJ fusion with this technique allow for the unique chance to assess the SIJ ligaments of patients with chronic SIJ pain histologically and ultrastructurally. The aim of this given case-control study was to show specific changes present in the SIJ ligaments in cases of patients with chronic low back pain. It could be shown that in patients with SIJ pain ligament failure is observed, accompanied by hemorrhage and collagen disarrangement.

METHODS

SIJ ligament tissue samples were obtained from 6 patients undergoing SIJ fusion using the posterior distraction arthrodesis technique in the time frame 2016 to 2018 at a rural hospital setting in Halberstadt, Germany (all women, mean age 57.8 ± 9.5 years). All of these patients were diagnostically confirmed cases of SIJ-related pain. For comparison, age-matched SIJ ligament tissue samples were obtained bilaterally from 6 cadavers from legal medicine during autopsy with no previous history or autoptic signs of musculoskeletal disease (bilateral samples of 3 women and 3 men, mean age 57.3 ± 10.4 years). Ethical approval was obtained from the ethics committee of the University of Leipzig (301/18-ek).

Surgical Technique

With the patient in prone position, a midline approach was used at the level of the upper border of the sacrum followed by a lengthwise incision of the thoracolumbar fascia close to the posterior superior iliac spine. The posterior and interosseous SIJ ligaments were subsequently exposed at the S1-S2 level, as described elsewhere (8). As part of the surgical procedure, these ligaments were removed within the recess formed between the posterolateral aspect of the sacrum and the corresponding cortical surface of the ilium. The tissue samples used for histology and electron microscopy were removed sharply to rule out any damage induced by blunt manipulation, resulting in collagen disintegration. The required DIANA implant (Signus Medizintechnik, Alzenau, Germany) was then inserted over a guidewire positioned along the weight-bearing axis of the ilium. The recess and the implant were subsequently filled completely with homologous cancellous bone. Samples were obtained from the controls in a similar manner and by the same team of experienced SIJ interventionists during back and pelvis preparation at forensic autopsies to guarantee for comparability, and all tissues were removed with extreme care not to cause iatrogenic injury.

Histology and Electron Microscopy

Representative samples of the removed ligaments were immediately fixed in 3% glutaraldehyde/0.1 M phosphate buffer (pH = 7.4). Tissues for histology were postfixed in 3% paraformaldehyde, paraffin-embedded and sectioned at 10 μ m. Hematoxylin-eosin (HE) and Giemsa staining was carried out as routine staining meth-

ods. Further subsamples for electron microscopy were washed in distilled water and dehydrated, followed by the critical point drying process (CPD-030, Bal-Tec AG, Liechtenstein). Scanning electron microscopy (SEM) was conducted using a JSM-6700F field emission microscope (JEOL Ltd., Tokyo, Japan) at magnifications ranging from 2,500x to 33,000x. Transmission electron microscopy (TEM) samples were processed as shown previously (39). A Philips CM100 BioTWIN (Philips/FEI Corporation, Eindhoven, the Netherlands) equipped with a Mega-View III digital camera (Olympus Soft Imaging Solutions GmbH, Münster, Germany) was used to obtain TEM images at magnifications between 9,700x and 33,000x. All tissues were assessed in a blinded manner to minimize the bias of the rater.

Statistical Evaluation

The statistical comparisons between both groups (SIJ patients vs. control group, and women only in both groups) were performed using Microsoft Excel (Microsoft Corporation, Redmond, WA) and SPSS Version 24 (IBM Corporation, Armonk, NY). Cramér's ϕ correlations were determined following the chi-square test to compare the collagen matrix integrity in SEM between the samples from patients with SIJ and controls. For this purpose, 5 fields of vision were assessed at magnifications of 2,500x and 20,000x for a semiquantitative classification of collagen integrity. Fields with no collagen damage were classified as "fully intact," fields with damaged fibers as "partial rupture," and fields with fiber bundle or multiple fiber damage as "fully disrupted" according to the classification shown elsewhere (40). *P* values of ≤ 0.05 were considered as statistically significant.

RESULTS

In the patient cohort with SIJ pain presented here, none had any major trauma related to their SIJ pathology. One of the 6 women in the SIJ pain group was nulliparous, one uni-, and 4 multiparous. Two of the 3 women in the control group were multiparous and one

nulliparous. The diagnostic algorithm included at least 3 positive tests for SIJ pain included Mennell sign, FABER test, distraction test, compression test, thigh thrust test, sacral thrust test, and sitting intolerance. None of the patients suffered from neurologic deficits prior to the surgery. Visual analog scale ratings on pain averaged 6.8 ± 1.0 prior to the surgery at rest, and 9.1 ± 1.3 when physically active. Preoperative magnetic resonance imaging (MRI) and computed tomography (CT) typically showed no signs of traumatic injury, as depicted in Fig. 1. However, arthritis of the SIJ with vacuum phenomenon, joint narrowing, and subchondral sclerosis were observed commonly as radiologic changes. Surgical fusion of the SIJ was conducted using a 17-mm implant in one case and 19-mm implants in 4 cases, respectively. Postoperative x-ray and CT showed an exact positioning of the implant in all cases, as exemplified in Fig. 1.

Histological and Ultrastructural Findings

Both intact and undisturbed and altered regions were observed in the samples removed during surgery. Figure 2 illustrates microscopically intact ligaments of the SIJ obtained from healthy controls. The typical characteristics were parallel-aligned collagen bundles and intact tenocytes throughout these samples from the controls (Fig. 2A). Quantities of proteoglycan-rich regions were further observed, indicative of slight chondrification (Fig. 2B). The ultrastructural workup by SEM confirmed the parallel alignment of collagen bundles (Fig. 2C) and intact D-periods at further magnification, shown by the striated appearance (Fig. 2D).

The samples obtained from patients with SIJ pain showed a different picture compared with the healthy controls. Here, a variety of morphologic alterations were seen, indicative of disruptions in the ligament tissue (Figs. 3 and 4). Figure 3A gives an overview from one patient sample and includes cartilage as well as SIJ ligaments and a hematoma. The magnification of the HE-stained sample (Fig. 3B) shows intact collagens

Table 1. Evaluation of collagen integrity from SEM regarding collagen integrity. The total of 100.1% is the result of rounding.

Sample Type	Collagen Integrity			Cramér's ϕ
	Fully Intact	Partially Disrupted	Fully Disrupted	
Control 2,500x (n = 60)	71.7%	26.7%	1.7%	$\phi = 0.82$ $P < 0.001$
SIJ pain 2,500x (n = 30)	0.0%	53.3%	46.7%	
Control 20,000x (n = 60)	46.7%	51.7%	1.7%	$\phi = 0.83$ $P < 0.001$
SIJ pain 20,000x (n = 30)	0.0%	33.3%	66.7%	

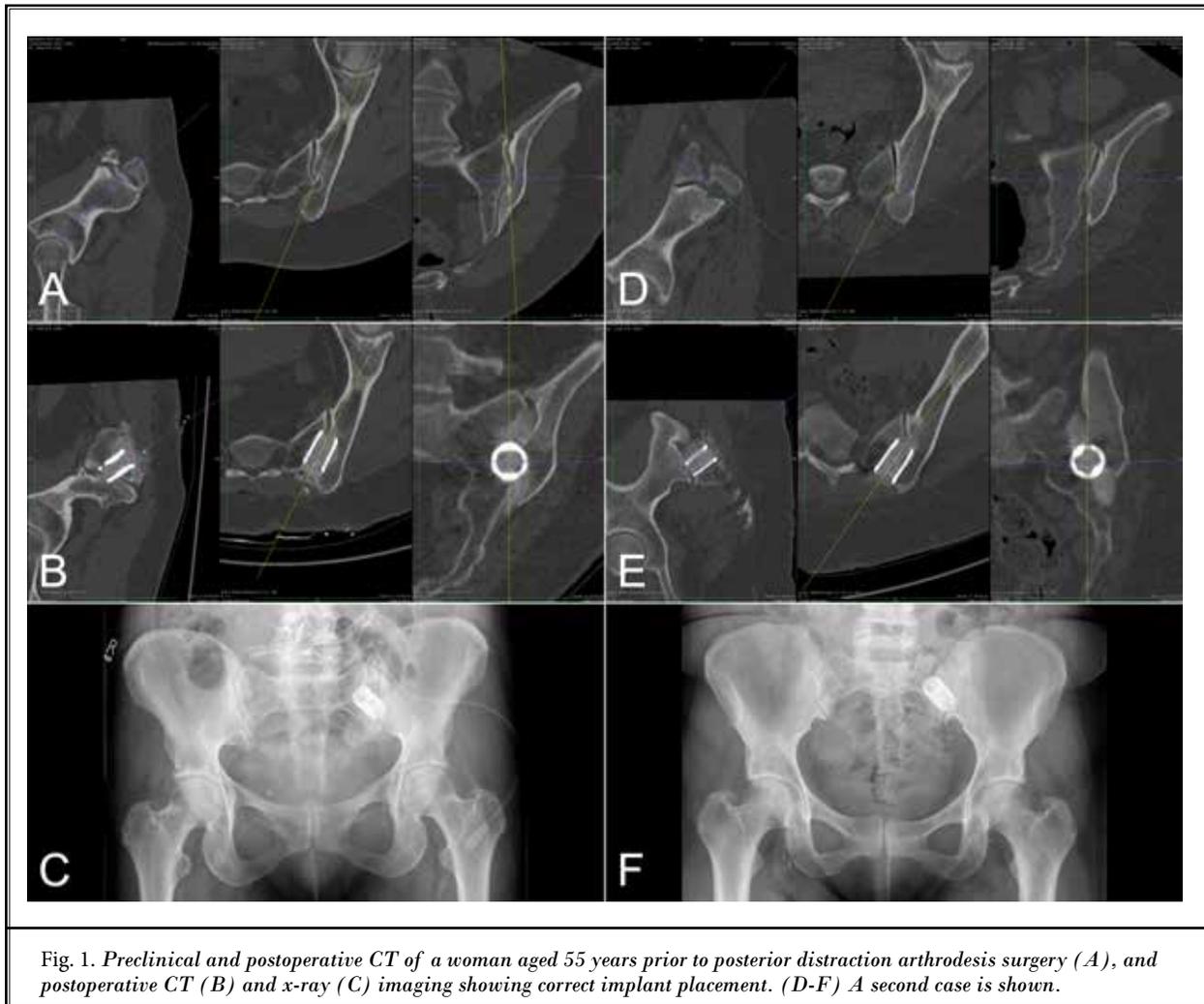


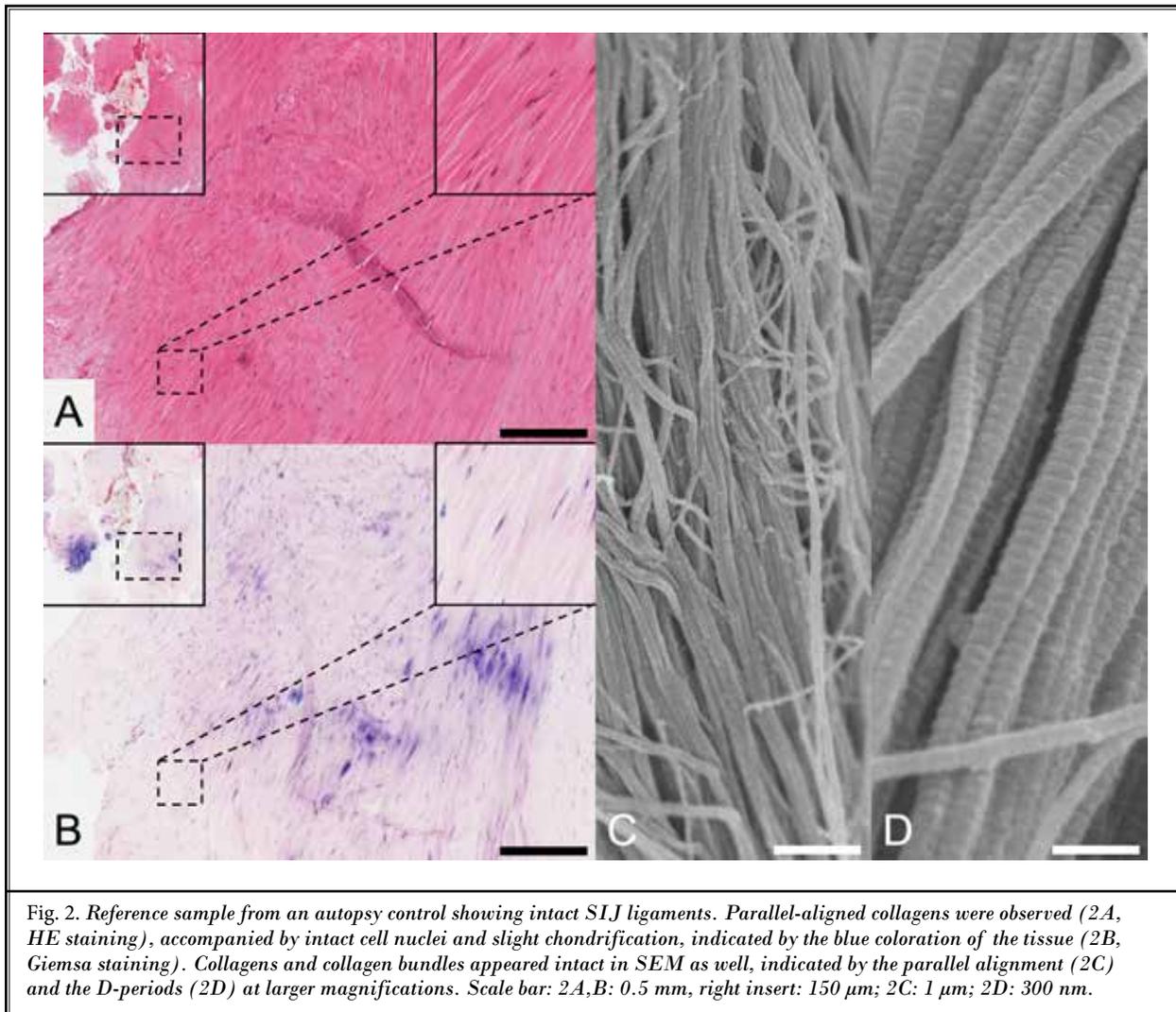
Fig. 1. Preclinical and postoperative CT of a woman aged 55 years prior to posterior distraction arthrodesis surgery (A), and postoperative CT (B) and x-ray (C) imaging showing correct implant placement. (D-F) A second case is shown.

(note the bands in the tissue appearance in the top right corner), as well as disrupted collagens in the central part of the image, intermitted by a blood vessel. The Giemsa staining showed the extent of the collagen bundle disruption more visibly (Fig. 3C and D). In SEM (Fig. 3E and F), signs of collagen disruption were observed, showing both intact and unraveled collagens, partially with collagen bundle breakage. Figure 4 gives further examples of pathological alteration within the ligament tissue. The collagens of the sacroiliac ligaments were disrupted (note the loss of overall collagen orientation in the sample in Fig. 4A and B), and blood extravasation was seen outside of the vessels (perivascular) in the tissue. Giemsa staining (Fig. 4C and D) confirmed an undirected chondrification interspersing the collagens. The ultrastructural workup by SEM in Fig. 4E-G showed further signs of degeneration, with an

overall lumpy appearance (Fig. 4E and F), loss of collagen periodicity (Fig. 4F), and collagen balls indicative of mechanical failure of the collagens (Fig. 4G).

Further imaging provided by TEM is shown in Fig. 5, resembling the findings from SEM. Regions with regular and dense collagen alignment and visible D-periods were observed in the controls (Fig. 5A and B), and in the samples from patients with SIJ pain, areas with loosened collagens and reduced collagen diameter (Fig. 5C and D) and regions with kinked collagens (Fig. 5E and F).

Quantification of the findings from SEM revealed that a majority of collagens were fully or partially intact in the controls in both the 2,500x and 20,000x magnification (Table 1). In the samples from the patients with SIJ pain, a majority were partially or fully disrupted especially in higher magnifications. Full collagen damage



was observed more often in higher magnifications. Statistical comparison revealed that collagen integrity was significantly higher in controls than in patients with SIJ pain, with a strong association toward collagen damage in patients with SIJ ($\phi \geq 0.82$). On a qualitative level, similar histological and ultrastructural findings were observed when comparing the findings in the SIJ pain group with the female controls separately. No relation was observed between numbers of pregnancies and ligament integrity.

DISCUSSION

To our knowledge, this study for the first time provided morphologic evidence on the pathological changes that occur in the SIJ ligaments in patients with

chronic SIJ pain. Although changes have previously been hypothesized as a cause or consequence for the SIJ, no histological or ultrastructural changes have, to date, been reported for the ligamentous soft tissues of the posterior pelvis as a consequence of nontraumatic and noninflammatory cause.

A variety of surgical techniques have evolved for treating the SIJ surgically in recent years (6-9,41), complementing existent nonsurgical treatments (25,42-44), fluoroscopy-or CT-guided injections (45-48), peripheral nerve stimulation (49,50), and radiofrequency ablation (11-14). Although the efficacy of these surgical techniques is presently under discussion, but not in the scope of this research, one of these surgical techniques, the posterior distraction arthrodesis method, now al-

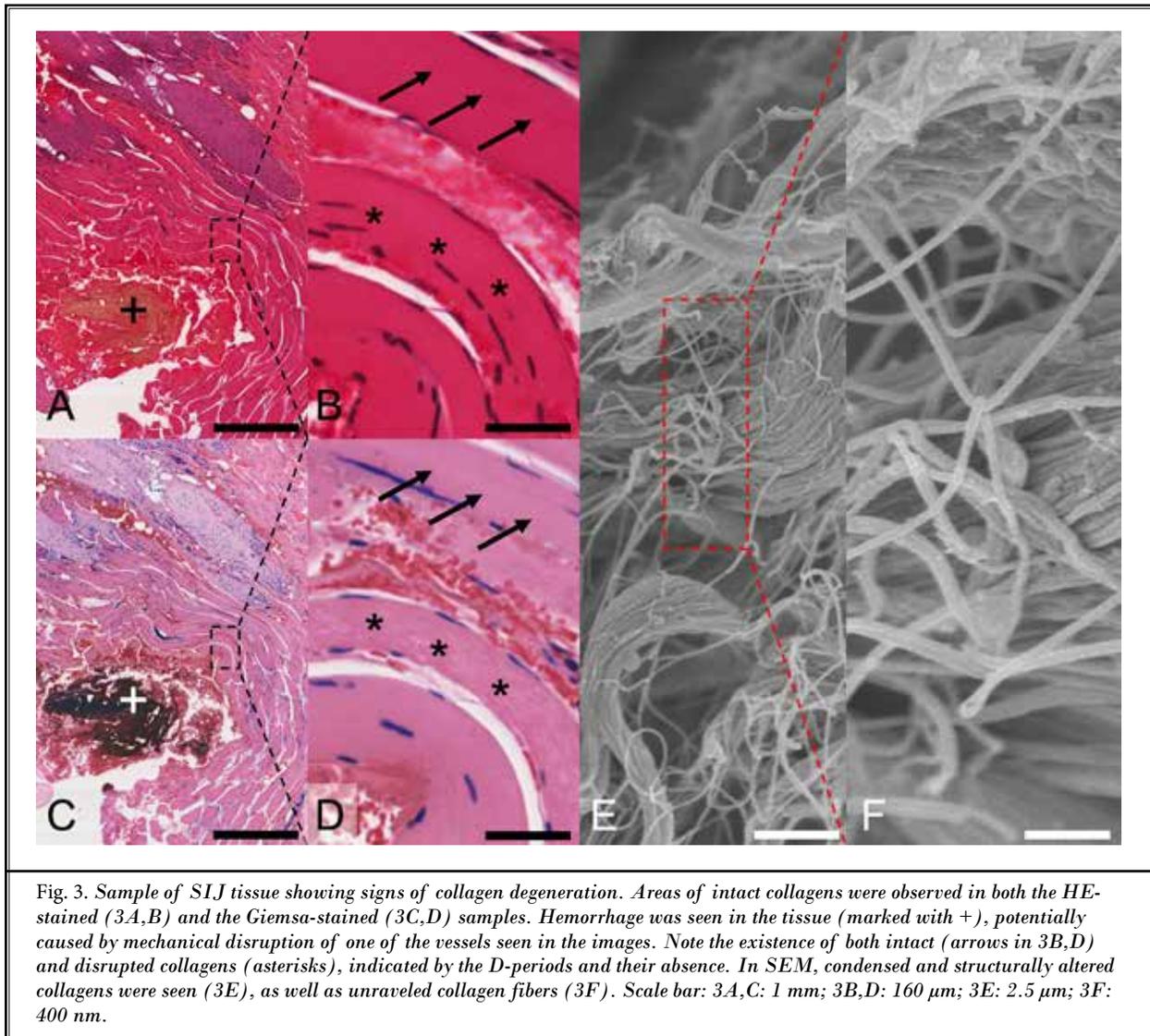
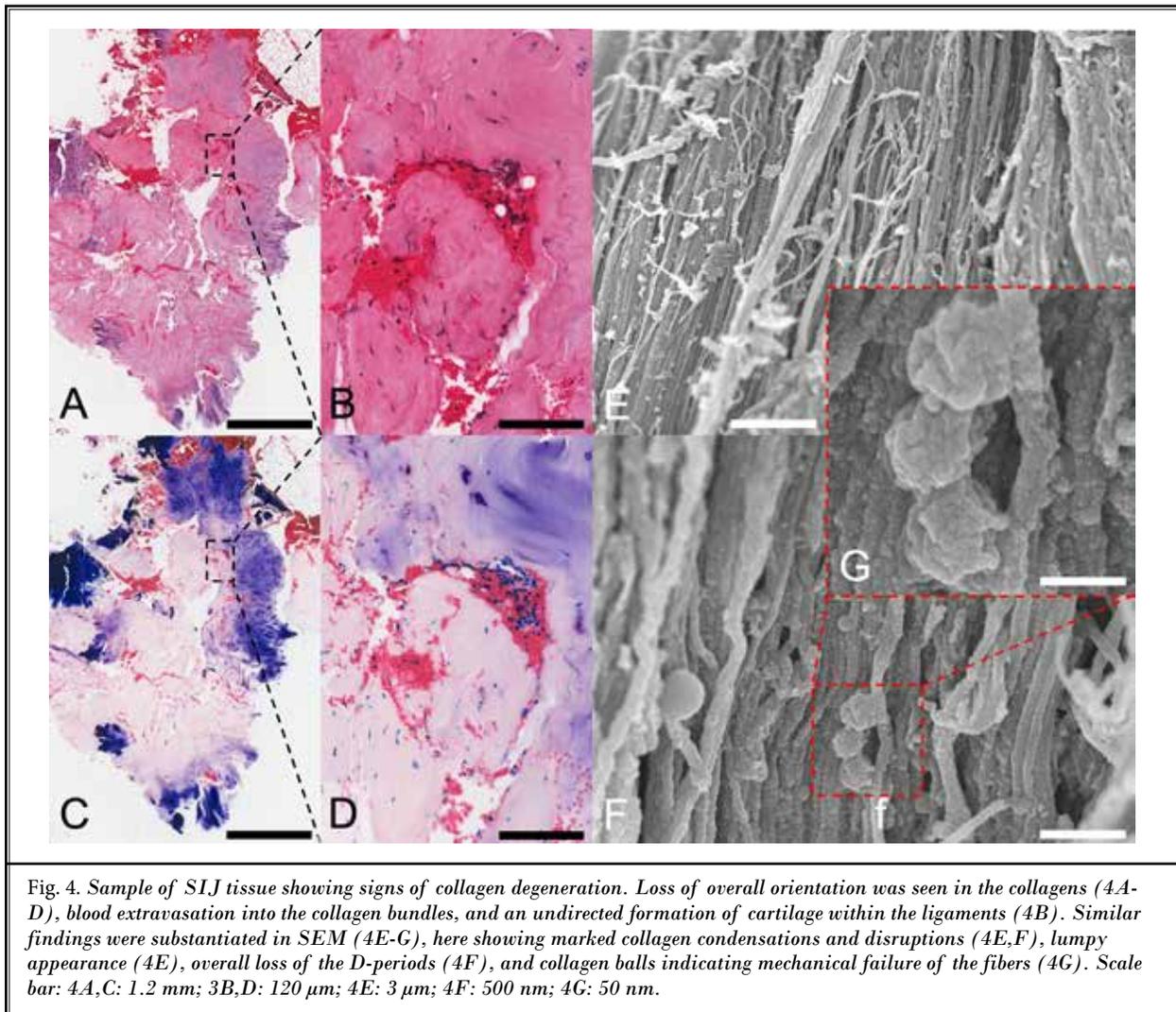


Fig. 3. Sample of SIJ tissue showing signs of collagen degeneration. Areas of intact collagens were observed in both the HE-stained (3A,B) and the Giemsa-stained (3C,D) samples. Hemorrhage was seen in the tissue (marked with +), potentially caused by mechanical disruption of one of the vessels seen in the images. Note the existence of both intact (arrows in 3B,D) and disrupted collagens (asterisks), indicated by the D-periods and their absence. In SEM, condensed and structurally altered collagens were seen (3E), as well as unraveled collagen fibers (3F). Scale bar: 3A,C: 1 mm; 3B,D: 160 μm; 3E: 2.5 μm; 3F: 400 nm.

lows for the removal of parts of the SIJ ligaments as part of a SIJ fusion procedure. These tissues can be evaluated as part of a morphologic and pathological assessment. However, the SIJ ligaments thus far appear to be neglected regarding histological routine assessment.

Previous research indicated that alterations in joint morphology occur in the SIJ quite early in life as a consequence of upright posture to increase friction in the joint and to enhance load distribution from the spine and trunk to the pelvis and lower extremities (26,28,29,33,51-53). Different subtypes of cartilage have been reported for the sacral and iliac joint surfaces with hyaline and fibrillary cartilage, with the latter

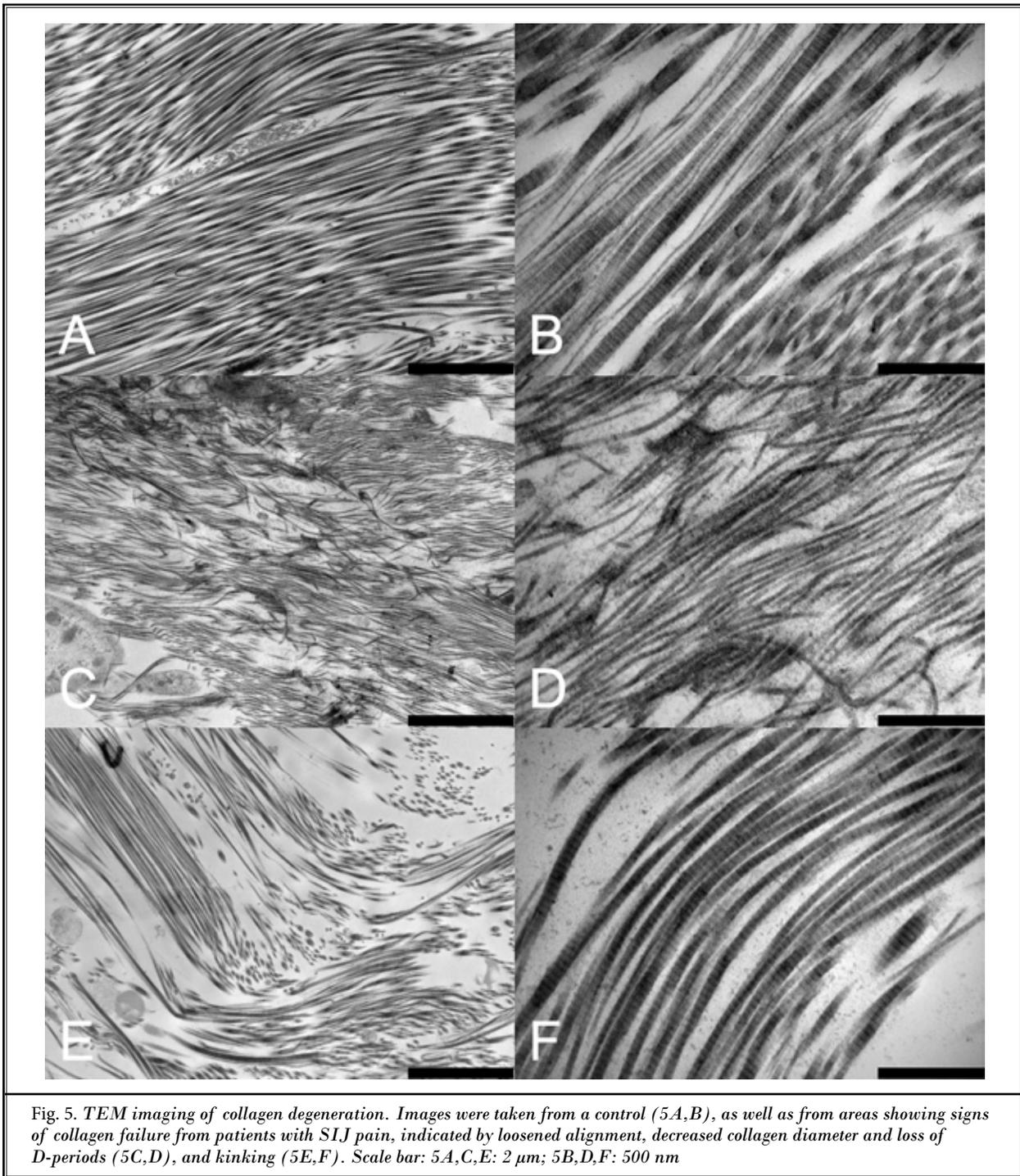
showing an irregular network of thickened collagens, inhomogeneous appearance as a result of shearing forces (33). Furthermore, subchondral bone plates penetrated with blood vessels (33,35,54) and diminished type 2 collagen immunoreactivity, as well as type 1 collagens at the joint surface (33), have been found at the SIJ surface, all indicators of osteoarthritis. In particular, type 1 cartilage does not normally exist in other healthy hyaline joints (33). It has been stated that such changes involve not only the cartilage but also the bone interface, namely with osteophytes, subchondral sclerosis, cartilage loosening, and the formation of grooves and ridges (32-35,51). There is controversy if bony erosions,



cartilage roughening, and fibrillation are perceived as normal in the SIJ in the course of ageing (32-35,51). Also, there is consensus that the characteristics of osteoarthritis for other synovial joints might not necessarily apply to the SIJ in light of the functional adaptations (15,28,34,51) this joint has, as the change in loading during the course of upright posture makes this joint unique.

However, to date, the given changes have largely been limited to the hard tissues, whereas the study on the morphology of the SIJ ligaments in patients with pain originating from this area was hampered by the limited surgical accessibility, and has been unproven as to whether any changes occur to the SIJ ligaments in this pathology. The ligaments are known to be densely

innervated from the L4 and L5 segments (16,55-61), with direct branches of the dorsal and ventral rami of the lumbosacral plexus (4,58,61-63), as well as the obturator (63) and the superior gluteal nerve (4,62). Predominantly, the S1 and S2 nerve roots appear to contribute, being situated between the interosseous and posterior SIJ ligaments (16,48). These nerve fibers are housed between the ligaments and the existence of substance P, calcitonin gene-related peptide, and tyrosine hydroxylase might be one potential source for sustained SIJ pain (56). This evident spatial and functional relationship further underlines the importance of elucidating the pathology of the SIJ ligaments. To our knowledge, this given report provides for the first time morphologic evidence into mechanical failure of



ligaments without making attempt to clarify the etiology of these observations; this is vastly limited to clinical studies and beyond the scope of this work.

Limitations

The given explorative study has a number of limitations: only a few samples were included, and because of this small number harvested from women with SIJ

pathology exclusively, no relations to pain duration, age, or gender could be described at a level allowing to correlate these findings. Further to this, no cartilage has been included in the assessment, although it has been described anecdotally that SIJ pathology might be related to cartilage degeneration. However, potential of this proposed postsurgical assessment lies in the evaluation of ligament degeneration, substantiating SIJ pathology and relating it to major load-bearing structures. Future studies will need to substantiate these findings and relate them to mid- and long-term patient outcomes. It would further be desirable that obtaining the tissues would always be carried out by the same surgeon. Although this has been done by experts here, it would help further standardize the given approach of tissue retrieval.

CONCLUSIONS

With the given surgical method of posterior distraction arthrodesis (8), it was, to our knowledge, for the first time possible to assess the morphology of the SIJ ligaments with diagnostically confirmed pain, and to investigate these tissues in detail with particular focus on the collagens being part of the formed matrix.

CT- and MRI-based methods have so far failed to give evidence on potential changes of the ligamentous apparatus (35,64), with the exceptions of traumatic disruption (22-24) and spondyloarthropathy (17-21). A similar study had used CT-guided aspirates from the SIJ, showing comparable high sensitivity and specificity for the diagnosis of SIJ-related pathology, but with clear focus on inflammation of the joint (65). In summary, compared with the structurally intact condition, a number of features were observed in ligament tissue samples from patients with chronic SIJ pain. Collagen degeneration with loss of collagen integrity and loss of orientation and chondrification is significantly different between patients with SIJ pathology and age-matched controls. These findings may serve as an indicator of mechanical failure of the ligaments in patients with SIJ pain.

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