RESEARCH PAPER

Inguinal Hernia as a Systemic Enzyme Dysfunction Disorder: A Prospective Comparative Study on the Role of Matrix Metalloproteinase-9 in The Transversalis Fascia

Dr. Varun Venkatesh[1] Dr. Ashwin Vinod[2] Dr. George Mathew John[3]

[1]Junior Resident, Department of General Surgery, Amrita Institute of Medical Sciences, Amrita Vishwa Vidhyapeetham, Kochi, Kerala.
Email: varunvenkatesh33@gmail.com
[2]Junior Resident, Department of General Surgery, Amrita Institute of Medical Sciences, Amrita Vishwa Vidhyapeetham, Kochi, Kerala.
Email: ashwinvinod04@gmail.com
[3]Professor, Department of General Surgery, Amrita Institute of Medical Sciences, Amrita Vishwa Vidhyapeetham, Kochi, Kerala.
Email: gmjohn07@gmail.com

Corresponding Author- Dr George Mathew John
Professor, Department of General Surgery, Amrita Institute of Medical Sciences, Amrita Vishwa Vidhyapeetham, Kochi, Kerala

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ABSTRACT

Background: Inguinal hernia is increasingly regarded as the local manifestation of a systemic disorder of collagen metabolism rather than a purely mechanical defect. Matrix metalloproteinases (MMPs) mediate extracellular matrix degradation, but evidence concerning MMP-9 is limited, drawn largely from serum rather than tissue, and rarely distinguishes hernia subtypes. This study measured MMP-9 in the transversalis fascia and examined its variation across subtypes.

Methods: This prospective comparative study was conducted from October 2019 to September 2021 at a tertiary care teaching hospital. Adults undergoing surgery for inguinal hernia formed the hernia group; adults undergoing abdominal surgery for other conditions formed the non-hernia group. A 1 cm x 1 cm specimen of transversalis fascia was obtained intraoperatively from each participant and MMP-9 quantified in tissue homogenates by enzyme-linked immunosorbent assay.

Results: Of 83 patients, 44 had an inguinal hernia and 39 did not. Mean tissue MMP-9 was higher in the hernia group (2088.99±345.69 ng/l) than in the non-hernia group (1990.16±276.37 ng/l), but the difference was not significant (p=0.158). MMP-9 was significantly higher in direct (2194.66±376.36 ng/l) than in indirect hernia (1949.95±246.37 ng/l; p=0.013), and higher in bilateral (2181.51±348.61 ng/l) than in unilateral hernia (1977.97±315.50 ng/l; p=0.051). No association was demonstrated with chronic cough, constipation, lower urinary tract symptoms, comorbidities or body mass index.

Conclusions: Fascial MMP-9 was significantly higher in direct than in indirect hernia and borderline higher in bilateral than in unilateral hernia, whereas the overall hernia versus non-hernia difference was not significant, suggesting more extensive matrix degradation in these subtypes.

Keywords: Inguinal hernia, Matrix metalloproteinase-9, Transversalis fascia, Extracellular matrix, Collagen metabolism, Hernia pathogenesis

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INTRODUCTION

A hernia is the abnormal protrusion of an organ, a viscus, or part of it through a natural or acquired defect in its containing wall.[1] Inguinal hernia is the most prevalent of all abdominal wall hernias, and its surgical correction is among the most frequently performed operations across the globe.[1] The origin of inguinal herniation continues to be a conundrum. It was long believed that herniation was a direct

**Author for Correspondence: gmjohn07@gmail.com*

consequence of raised intra-abdominal pressure resulting from chronic cough, or from straining in patients with constipation or obstructive urinary symptoms.[1] Over the years, several investigators have attempted to define the pathogenesis of hernia formation and to explore hernia as a disease of collagen.

The transversalis fascia constitutes the posterior-most defence of the inguinal canal against herniation.[2] Any structural modification of this fascia that reduces its resistance and strength can result in a hernia. Collagen is the most abundant protein in the human body and accounts for the greater part of the protein content of fascial tissue, so alterations in collagen metabolism have been implicated in hernia pathogenesis.[2] This theory is supported by the increased risk of inguinal herniation observed in connective tissue disorders characterised by collagen dysfunction, such as abdominal aortic aneurysm, Ehlers-Danlos syndrome and Marfan syndrome. The mechanical stability of connective tissue is largely governed by the ratio of type I to type III collagen. A reduced ratio has been demonstrated in the connective tissue of patients with hernia and is more marked in those with direct hernia than in those with the indirect variety.

Excessive degradation of the extracellular matrix within the transversalis fascia was subsequently proposed as the mechanism of herniation, and among the enzymes investigated, matrix metalloproteinases (MMPs) were found to be the most important mediators of extracellular matrix degradation.[3] Twenty-three isoforms of MMP with endopeptidase activity are currently recognised, and several studies have shown that over-expression of MMPs in the transversalis fascia is critical to herniation.

Although associations have been postulated between MMP-1, MMP-2, MMP-9 and herniation, few studies have established them.[4] The evidence for MMP-2 is now reasonably consistent, whereas that for MMP-9 remains limited and contradictory: most reports have measured circulating rather than fascial enzyme, few have used a quantitative assay on the transversalis fascia itself, and fewer still have examined whether enzyme levels differ between the anatomical subtypes of inguinal hernia. The present study was therefore designed to quantify MMP-9 in the transversalis fascia of participants with inguinal hernia in comparison with individuals without hernia, and to examine the variation in enzyme levels between direct and indirect hernia and between unilateral and bilateral hernia.

MATERIAL AND METHODS

Study design and setting

A prospective comparative study was conducted between 1 October 2019 and 30 September 2021 in the departments of general surgery and gastrointestinal surgery at Amrita Institute of Medical Sciences, Kochi, Kerala, India. The study was conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments. Data were collected after obtaining clearance from the Institutional Review Board and Ethics Committee, Amrita School of Medicine (IRB-AIMS-2020-235), and the study was registered with the Clinical Trials Registry of India (REF/2022/06/055349). The manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Participants

Participants were stratified into two groups. The hernia group comprised patients older than 18 years with an inguinal hernia who were undergoing surgery for the same. The non-hernia group comprised patients in the same age stratum who were undergoing abdominal surgery for pathologies other than inguinal hernia. Patients with Marfan syndrome or Ehlers-Danlos syndrome, bowel obstruction or strangulation, gross ascites, a diagnosed aortic aneurysm, or a history of steroid therapy were excluded.

Before enrolment, written informed consent was obtained from every participant after the purpose of the study had been explained in their vernacular language. Demographic and clinical data, including body mass index, systemic hypertension, diabetes mellitus, coronary artery disease, chronic cough, chronic constipation and obstructive lower urinary tract symptoms, were recorded.

Sample size

The sample size was calculated from the mean and standard deviation of tissue MMP-9 levels reported in an earlier study (group 1: 163.03±66.24; group 2: 110.02±42.91).[5] With 80% power and 95% confidence, the minimum requirement was 17 patients in each group. A minimum of 30 patients per group was planned in order to improve precision, and all eligible patients presenting during the study period were recruited.

Tissue sampling and enzyme assay

A specimen of transversalis fascia measuring 1 cm x 1 cm was collected intraoperatively from each participant, washed in normal saline and stored at -80 degrees C until further assay. Once recruitment was complete, the specimens were thawed, minced and homogenised with an appropriate buffer. The homogenate was centrifuged at 2000 rpm, and quantitative analysis of MMP-9 was performed on the supernatant by enzyme-linked immunosorbent assay (ELISA) using a commercially available human MMP-9 kit ([manufacturer, city, country]) in accordance with the manufacturer's instructions (Figure 1). Results are expressed in ng/l.

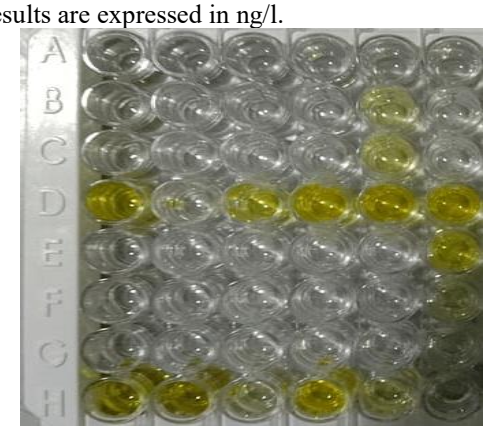

Figure 1: Microplate enzyme-linked immunosorbent assay used for the measurement of matrix metalloproteinase-9 in transversalis fascia homogenates

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, New York, United States). Continuous variables are presented as mean±standard deviation. The independent samples t test was used for comparisons between two groups, and one-way analysis of variance was used to compare MMP-9 levels across body mass index categories. The Karl Pearson correlation coefficient and linear regression were applied to assess correlation. A p value of less than 0.05 was considered statistically significant

RESULTS

A total of 83 patients were enrolled. The hernia group included 44 patients with an inguinal hernia who underwent surgery for the same. The non-hernia group included 39 patients diagnosed with pathologies other than inguinal hernia who underwent appropriate abdominal surgery.

The ages of the study population ranged from 25 to 79 years. The mean age was 58.3±13.6 years in the hernia group and 52.2±14.5 years in the non-hernia group. Of the 44 patients in the hernia group, 42 (95.5%) were male and two (4.5%) were female. Among the 39 patients in the non-hernia group, 18 (46.2%) were male and 21 (53.8%) were female. The male preponderance among patients with inguinal hernia was statistically significant ($p<0.001$).

MMP-9 was assayed in the transversalis fascia of all enrolled patients. The mean MMP-9 level was higher among patients with inguinal hernia than in the non-hernia group, although the difference did not reach statistical significance (Table 1).

On the basis of clinical and operative findings, patients in the hernia group were further classified into those with a direct hernia and those with an indirect hernia. A statistically significant increase in MMP-9 levels was observed in participants with a direct hernia in comparison with those with an indirect inguinal hernia (Table 1). Patients in the hernia group were also classified as having a unilateral or a bilateral inguinal hernia on the basis of their clinical presentation. Higher MMP-9 levels were found in participants with bilateral inguinal hernia, with borderline statistical significance (Table 1).

Table 1: Comparison of tissue matrix metalloproteinase-9 levels according to the presence and type of inguinal hernia.

Group	N	Mean MMP-9 level (ng/l)	SD	P value*
Inguinal hernia group	44	2088.99	345.69	0.158
Non-hernia group	39	1990.16	276.37	
Direct inguinal hernia	25	2194.66	376.36	0.013
Indirect inguinal hernia	19	1949.95	246.37	
Unilateral inguinal hernia	20	1977.97	315.50	0.051
Bilateral inguinal hernia	24	2181.51	348.61	

*P values were derived from the independent samples t test and refer to the paired comparisons of hernia versus non-hernia group, direct versus indirect hernia, and unilateral versus bilateral hernia. MMP-9: matrix metalloproteinase-9; SD: standard deviation.

Within the hernia group, the conditions traditionally held to raise intra-abdominal pressure, namely chronic cough, chronic constipation and obstructive lower urinary tract symptoms, were examined for an association with tissue MMP-9. None of these factors had a significant effect on enzyme levels (Table 2).

Table 2: Tissue matrix metalloproteinase-9 levels in relation to conditions associated with raised intra-abdominal pressure, within the hernia group (n=44).

Predisposing condition	Yes/no	N	Mean MMP-9 level (ng/l)	SD	P value*
Chronic cough	Yes	4	2088.05	446.49	0.996
	No	40	2089.09	341.21	
Constipation	Yes	4	2135.73	212.96	0.780
	No	40	2084.32	357.80	
Lower urinary tract symptoms	Yes	7	2268.97	351.69	0.135
	No	37	2054.94	338.57	

*P values were derived from the independent samples t test. MMP-9: matrix metalloproteinase-9; SD: standard deviation.

The comorbid conditions of the entire study cohort, namely systemic hypertension, diabetes mellitus and coronary artery disease, were analysed in the same way. None of these conditions was associated with a significant variation in MMP-9 levels (Table 3).

Table 3: Tissue matrix metalloproteinase-9 levels in relation to comorbid conditions across the entire study cohort (n=83).

Comorbidity	Yes/no	N	Mean MMP-9 level (ng/l)	SD	P value*
Systemic hypertension	Yes	30	2095.47	327.54	0.264
	No	53	2012.60	310.10	
Diabetes mellitus	Yes	21	2129.37	322.21	0.148
	No	62	2013.15	322.21	
Coronary artery disease	Yes	11	2044.85	369.21	0.980
	No	72	2042.20	311.28	

*P values were derived from the independent samples t test. MMP-9: matrix metalloproteinase-9; SD: standard deviation.

Body mass index was calculated for every participant and classified as underweight, normal, overweight or obese in accordance with the Asia-Pacific guidelines, and the mean MMP-9 level in each category was analysed. No significant association or correlation was found between MMP-9 levels and body mass index (p=0.372; Table 4).

Table 4: Tissue matrix metalloproteinase-9 levels according to body mass index category in the entire study cohort (n=83).

Body mass index category	N	Mean MMP-9 level (ng/l)	SD
Underweight	2	1844.30	369.25
Normal	25	2116.72	284.50
Overweight	23	1975.95	389.35
Obese	33	2044.80	280.10

Body mass index was classified in accordance with the Asia-Pacific guidelines. One-way analysis of variance, p=0.372. MMP-9: matrix metalloproteinase-9; SD: standard deviation.

DISCUSSION

Demographic profile of the study cohort

Most participants with a diagnosis of inguinal hernia presented after the sixth decade of life, and these patients constituted about 77.3% of the hernia group. This finding is similar to that of other studies from India, in which the peak prevalence of inguinal hernia was seen after 40 years of age, with a rising prevalence in each subsequent decade.[6] A nationwide register-based study from Denmark showed a bimodal prevalence of inguinal hernia that peaked first in the first decade of life.[7] Since the present study excluded the paediatric population, this bimodal distribution was not appreciated and only the second peak was observed. It is well established that increasing age is accompanied by a progressive increase in the destruction of the extracellular matrix and by weakening of the local anatomy of the inguinal region.[8]

The hernia group showed a male preponderance, with 95.5% men and 4.5% women. This sex-based variation is attributed to the intrinsic weakening of the inguinal canal in males as a consequence of testicular descent during embryological development, and the finding of a male-dominated disease is confirmed throughout the world literature. A study conducted in southern India also showed a similar male preponderance among patients with an inguinal hernia, with a ratio of 7:1.[6] The lifetime risk of developing inguinal herniation is 25% in men compared with 5% in women.[6,7]

An indirect hernia is about five times more common than a direct hernia and is the most prevalent type irrespective of sex.[1] In the present study, 56.82% of the patients had a direct hernia and 43.18% had an indirect hernia. This disparity is probably attributable to the modest sample size of our study in comparison with large epidemiological series, and to the exclusion of the paediatric population, in which indirect hernia predominates.

Evolution of the evidence linking matrix metallo-proteinases to inguinal hernia

The proposition that inguinal hernia represents a disorder of connective tissue rather than a purely mechanical failure has been assembled over nearly three decades. Bellon et al examined the biochemical substrate of the transversalis fascia in 1997 and found no difference in MMP-1 expression between patients with hernia and controls, with no detectable MMP-9 in either group.[9] The same group returned to the question in 2001 using fibroblasts cultured from the transversalis fascia and demonstrated constitutive

over-expression of MMP-2 in young patients with direct hernia, again without detectable MMP-9.[10] Because the abnormality persisted in cells removed from the mechanical environment of the groin, these findings were interpreted as evidence of an intrinsic, possibly genetically determined, defect of fibroblast function rather than a secondary consequence of raised intra-abdominal pressure.

Subsequent work extended the observation beyond the inguinal region. Pascual et al demonstrated up-regulation of active MMP-2 in the abdominal skin of patients with direct inguinal hernia, at a site remote from the hernial defect, which argues for a generalised rather than a purely local abnormality of matrix turnover.[11] Studies of circulating enzyme pointed in the same direction. Jain et al, working in northern India, reported significantly raised serum MMP-2 in patients with inguinal hernia, with the greatest elevation in the direct variety, although MMP-2 was undetectable in their fascial specimens.[12] Smigielski et al and, more recently, Wang et al described elevated serum MMP-2 with reciprocal changes in tissue inhibitor of metalloproteinases (TIMP)-2 in patients with inguinal hernia.[13,14] A systematic review by Bracale et al, which analysed 17 studies, concluded that MMP-1, MMP-2, MMP-9, MMP-12 and MMP-13 are all raised in the serum and fascia of patients with inguinal hernia, and that the association between MMP-2 and direct hernia remains the most firmly established relationship in this field.[15]

Evidence specific to matrix metalloproteinase-9

The evidence relating to MMP-9 is considerably thinner and less consistent than that for MMP-2. After the negative findings of Bellon et al, the enzyme attracted little attention until Antoniou et al reviewed the field in 2009 and concluded that the data on MMP-1, MMP-9 and MMP-13 in abdominal wall hernia were insufficient or frankly contradictory.[4,9,10] The same group subsequently measured MMP-2, MMP-9, TIMP-1 and TIMP-2 in fascial explants and in preoperative plasma, and found significantly higher tissue MMP-9 and MMP-2 together with reduced TIMP-1 and TIMP-2 in patients with hernia compared with controls.[5] Aren et al studied the transversalis fascia of 60 patients with inguinal hernia and 30 controls by immunohistochemistry and reported significantly higher MMP-1, MMP-2 and MMP-9 in the hernia group.[16] Isik et al measured serum enzymes and their inhibitors and found raised MMP-1, MMP-2, MMP-9 and MMP-13 with reduced TIMP-1, TIMP-2 and TIMP-3, an imbalance that was most pronounced in patients with bilateral hernia.[17] Serra et al, examining tissue and plasma from patients with varicocele, inguinal hernia and chronic venous disease, found MMP-9 to be highest in individuals in whom two or more of these conditions coexisted and proposed the enzyme as a common denominator of a generalised disorder of collagen metabolism.[18]

Set against these positive reports, Li et al measured circulating MMP-2 and MMP-9 in 110 patients with primary and recurrent inguinal hernia and 45 controls, and found a significant rise in MMP-2 in the direct and recurrent groups but no corresponding difference in MMP-9, and no variation in MMP-9 between direct and indirect hernia.[19] Evidence on the inhibitor side is similarly divided, with reduced fascial TIMP-2 and raised tissue TIMP-1 in direct hernia both having been described, and with Durukan et al reporting altered TIMP expression in the aetiology of inguinal and incisional hernia.[20] The overall position is therefore that MMP-9 is plausibly involved in herniation, but that its behaviour at the tissue level, and particularly across the anatomical subtypes of inguinal hernia, has not been settled.

Comparison of the present findings with the published literature

Our finding that mean tissue MMP-9 was higher in patients with inguinal hernia than in the comparison group, but did not reach statistical significance, sits between the positive tissue studies of Antoniou et al and Aren et al and the negative circulating study of Li et al.[5,16,19] Several factors may account for this intermediate result. The enzyme was quantified by ELISA in fascial homogenate, a technique that measures total MMP-9 protein rather than the active fraction, whereas zymographic and immunohistochemical methods weight active enzyme and cellular localisation differently. Our comparison group also consisted of patients undergoing abdominal surgery for other pathology rather than healthy volunteers, and several such conditions are themselves associated with matrix remodelling, which would tend to narrow the difference between the groups. Finally, the sample size was calculated to detect the large effect reported by Antoniou et al; the smaller separation actually observed between the hernia and non-hernia groups would require a substantially larger cohort to demonstrate.[5]

Where our findings depart most clearly from the published literature is in the comparison between anatomical subtypes. Tissue MMP-9 was significantly higher in direct than in indirect hernia. Li et al found no such difference in circulating enzyme, and Aren et al, who did study fascial tissue, analysed their results by hernia status rather than by subtype.[16,19] The direction of our result parallels the well-replicated association between MMP-2 and direct hernia and is biologically coherent, since direct herniation occurs through an intact but structurally weakened posterior wall and would be expected to reflect matrix degradation more faithfully than indirect herniation, which follows a pre-existing anatomical pathway.[10,11,15] Elevated tissue enzyme levels in participants with a direct hernia are consistent with inordinate degeneration of the extracellular matrix and reversal of the type I to type III collagen ratio, thereby weakening the local inguinal anatomy.

Our observation of higher MMP-9 in bilateral than in unilateral hernia, with borderline significance, is concordant with Isik et al, who found the MMP and TIMP imbalance to be most marked in bilateral disease, and with the report of Serra et al that MMP-9 rises as collagen-related conditions accumulate in the same individual.[17,18] The postulated explanation is that patients with bilateral herniation have a predisposition to more systemic destruction of the extracellular matrix by MMPs together with reduced regulation by the tissue inhibitors of metalloproteinases.[17] Bilaterality may therefore serve as a clinical marker of the systemic severity of matrix

degradation, which is of more than academic interest given the higher recurrence risk associated with bilateral disease. Data on comorbid conditions such as systemic hypertension, diabetes mellitus and ischaemic heart disease were evaluated for an association with MMP-9 levels, and these factors were not found to affect tissue MMP-9. Other studies have likewise found no association between these comorbidities and MMP levels.[17,18] This negative finding argues that the enzyme elevation observed in direct and bilateral hernia is not simply a reflection of the metabolic and vascular comorbidity that accompanies advancing age. Elevated body mass index has been considered contributory to the development of herniation, since obesity is associated with raised intra-abdominal pressure and therefore with a disequilibrium between that pressure and the resistance of the abdominal wall. Several long-term cohort studies have nevertheless shown that a raised body mass index is associated with a reduced risk of groin hernia.[21] Rosemar et al suggested that the increase in fat and in the thickness of the abdominal wall that accompanies a rising body mass index may itself impede herniation, and that greater deposition of fat in the omentum and mesentery renders them short and blunt and therefore less likely to protrude into the hernial orifices.[21] In contrast, a systematic review and meta-analysis of risk factors for recurrent inguinal hernia conducted by Burcharth et al showed a positive correlation between increasing body mass index and hernia recurrence.[22] The body mass indices of our patients were classified in accordance with the Asia-Pacific guidelines for the Indian population, and no significant association or correlation was found between body mass index and MMP-9 levels.

Contribution of the present study

Most studies of MMP-9 have measured circulating enzyme rather than enzyme within the structure that actually fails, and the discrepancy between circulating and fascial findings has been demonstrated repeatedly, most strikingly by Jain et al, in whose cohort serum MMP-2 was significantly raised while the same enzyme was undetectable in the fascia.[9,12] The present study measured MMP-9 directly in the transversalis fascia using a quantitative assay that yields an absolute concentration, rather than the semi-quantitative immunohistochemical score used in the one comparable tissue study.[16] Where fascial tissue has previously been examined, patients have usually been analysed as a single group of hernia cases against controls, so that the anatomical subtype has been treated as incidental. The present study stratified prospectively by direct versus indirect and by unilateral versus bilateral hernia, and the finding of significantly higher enzyme levels in direct hernia extends to MMP-9 a relationship that has so far been demonstrated convincingly only for MMP-2.[10,11,15] In addition, the Indian literature on this question is confined almost entirely to MMP-2 and to serum measurement, despite the considerable burden of inguinal hernia in this population; to our knowledge, quantitative tissue MMP-9 values from an Indian population have not previously been reported.[12] Finally, chronic cough, constipation, lower urinary tract symptoms, hypertension, diabetes mellitus, coronary artery disease and body mass index were assessed prospectively and none was associated with tissue MMP-9, which strengthens the interpretation of the observed subtype differences.

Clinical implications

If the association between fascial MMP-9 and direct or bilateral herniation is confirmed in larger cohorts, two applications become plausible. Enzyme assay might help to identify the patient whose groin is failing because of intrinsic matrix degradation rather than mechanical loading, and in whom a tissue-based repair is therefore likely to fail, favouring mesh reinforcement and, in bilateral or recurrent disease, a posterior approach. Enzyme measurement might also serve as an intermediate outcome in trials of pharmacological modulation of matrix turnover. These possibilities remain speculative on present evidence, and no clinical decision should currently rest on an MMP assay.

Limitations

Serum MMP-9 and the tissue inhibitors of metalloproteinases were not assayed, as only tissue levels of MMP-9 were considered; the balance between the enzyme and its inhibitors may be more informative than the enzyme concentration alone. The study was conducted at a single tertiary care centre with a modest sample size, and the comparison group consisted of patients undergoing abdominal surgery for other pathologies rather than healthy individuals, so that coexisting disease may itself have influenced enzyme expression. The two groups differed significantly in sex distribution and, to a lesser extent, in mean age, and the analyses were not adjusted for these variables. Multiple pairwise comparisons were performed without formal correction, so the subtype findings, and in particular the borderline result for bilateral hernia, should be regarded as hypothesis-generating rather than confirmatory. The assay measured total MMP-9 protein rather than enzyme activity, and the cross-sectional design cannot establish whether the enzyme elevation precedes herniation or follows it. Patients were not followed up, so no inference can be drawn about recurrence.

CONCLUSION

Tissue levels of MMP-9 in the transversalis fascia were significantly higher in patients with a direct inguinal hernia than in those with an indirect hernia, and were higher, with borderline significance, in patients with a bilateral hernia than in those with a unilateral hernia. The overall difference between patients with and without inguinal hernia did not reach statistical significance, and no association was demonstrated between enzyme levels and body mass index or the comorbidities studied. These findings are consistent with more extensive degradation of the extracellular matrix in the groin of patients with direct and bilateral hernia, and they support the view that inguinal herniation is not merely a local mechanical failure. By quantifying the enzyme within the fascia itself and by reporting values separately for each anatomical subtype, this study addresses a gap in a literature that has relied largely on circulating enzyme and has treated inguinal hernia as a single entity. Larger and adequately powered studies that measure serum as well as

tissue enzyme concentrations, that include the tissue inhibitors of metalloproteinases, and that follow patients for recurrence are required before enzyme assays can be used to identify patients at risk of herniation, or to inform the choice of repair in clinical practice.

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