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Levator Ani avulsion: The histological composition of this site. A cadaveric study

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Introduction: The sonographic appearance of a levator muscle "avulsion" representing the literal detachment of the pubovisceral muscle (PVM) enthesis has been contested. The nature of the levator ani "avulsion" is still not fully understood. It is known, that the tensile strength of a tendon is dependent on collagen with increased synthesis of collagen occurring in tissue with increased mechanical load levels. This study aims to perform a quantitative histological evaluation of the PVM enthesis with or without the imaging finding of levator ani "avulsion" to determine if there is a difference in the proportion of muscle and collagen.

Method: Three-dimensional translabial ultrasound for PVM "avulsion" was performed on cadavers using a GE Voluson I with a 5-9 MHz electronic probe. Cadavers were meticulously dissected to identify the presence or absence of an anatomical avulsion. The PVM enthesis was excised for further histopathological processing and treated with three different colorations. Quantitative analysis using ImageJ software was conducted to compare tissue composition in samples with or without sonographic "avulsion." All stages were performed by two separate investigators blinded to each other's results. The results were analyzed using SPSS v24, IBM.

Results: Twenty-three PVM enthesis with histological staining were procured. Ultrasonographic "avulsions" were seen in 5/23 PVM enthesis. No anatomical avulsions were seen. There was no difference in the overall muscle or collagen content (Kruskal-Wallis, $P = 0.864$). The mean organized skeletal muscle content was 23% in the sonographic "avulsion" group versus 62% in the no "avulsion" group (Kruskall-Walis, $P = 0.02$). "Avulsions" were associated with a disorganized appearance at histology.

Conclusion: The tissue composition relating to the proportion of muscle and collagen was not significantly different in specimens with or without sonographic "avulsions." However, morphological differences were observed in the organization of the muscle fibres, which requires further evaluation.

KEYWORDS
avulsion, levator ani, pelvic floor, pubovisceral muscle

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1 | INTRODUCTION

An enthesis is the area where a ligament, tendon, or fascia inserts into bone. It functions to balance the differing tensile load by dissipating stress from tendon into bone, avoiding local peaks in tension.[1–3] The puboviseralis (puborectalis/pubococcygeus) enthesis is the insertion of the pubviseralis muscle (PVM) into the pubic bone. The term levator ani "avulsion" has been used to describe the sonographic imaging finding of hypoechogenicity at the PVM enthesis.[4] Since the first study to report the appearance of an "avulsion" on three- and four-dimensional translabial USS, the PVM enthesis has enthralled dozens of recent publications, yet the true nature of this defect is not fully understood.

The term, "avulsion," has been assigned by some authors, as it was assumed to represent the literal traumatic dislodgement of the PVM enthesis from its bony insertion on the posterior surface of the pubic bone.[5–8] The appearance of this lesion on ultrasound has been described in 20-50% of parous women.[4,9–12] It is associated with pelvic organ prolapse (POP) symptoms[13] and failure of pelvic floor repair surgery.[14] Counterintuitively, previous studies have observed the spontaneous resolution of this imagining finding[15,16] and an anatomical study failed to identify a correlation between sonographic "avulsions" and anatomical avulsions with not a single anatomical avulsion seen[17]; suggesting the term of "avulsion" may be a misnomer. It is therefore, unsurprising that surgical attempts at repairing this defect have been unsuccessful.[18]

This imaging finding is thought to be the sequalae of trauma sustained during vaginal birth and is rarely seen in nulliparous women.[19,20] During vaginal delivery, striated muscle, the main constituent of the PVM, may need to stretch to three times its original length to enable the passage of the fetus. In a non-gravid individual, striated muscle cannot withstand stretching to twice its length without being injured.[21,22] The necessary distension of the levator ani muscles and the resulting effects varies significantly with some women remarkably, having no appreciable morphological alterations in the pelvic floor.[23,24] It is known, that the tensile strength of a tendon is dependent on collagen with increased synthesis of collagen occurring in tissue with increased mechanical load levels.[21,22,25] We therefore, hypothesized that there may be a different proportion of collagen to muscle in sonographic "avulsions." The aim of this study was to perform a quantitative histological evaluation of the pubovisceral muscle (PVM) enthesis with or without the imaging finding of levator ani "avulsion" to determine if there is a difference in the proportion of muscle and collagen.

2 | METHOD

Female cadaveric material was ethically obtained and utilized according to the Human Tissue Act of 2004. Nine cadavers were fixed using a modified solution of 7% formalin, 7% phenol, 25% isopropyl alcohol, and 61% water. A further six cadavers were soft fixed with the Thiel preservation method using glycol, boric acids, chlorocresol, formaldehyde, and alcohol.

The pelvic floor was imaged using a Voluson I portable ultrasound machine (GE Healthcare, UK). The RIC 5-9 MHz transvaginal probe was employed due to its smaller head and superior contact with the cadaveric tissue; the probe was not advanced into the vagina. Tomographic ultrasound images were acquired by authors (VK) and (AD). The best quality images were used for analysis. The presence or absence of an "avulsion" injury was confirmed according to standard methodology.[26] Only complete "avulsions" were considered to ensure a definitive finding was being assessed. Slices were scored as normal or abnormal, separately for the left and right insertion sites. If the image quality was poor then the USS was repeated until the experienced sonographers were happy with the image quality in all planes. Particular care was taken to assess the constructed image in the axial plane to ensure no artefacts were present due to poor contact or technique.

The cadavers were meticulously dissected via the retropubic space to reveal the PVM enthesis on the pubic bone, good views were obtained. The integrity of the PVM enthesis on the pubic bone was examined by visual inspection, with the use of magnification if necessary, to determine the presence or absence of an anatomical PVM avulsion. The integrity of the PVM insertion was examined by authors (VK) and (AD), whom were blinded to each other's findings.

At the site of the PVM insertion, samples were excised parallel to the PVM fibre direction for further histopathological analysis. Samples were immediately fixed in 10% neutral buffered formalin. Following fixation, the specimens were washed and dehydrated in a series of alcohol solutions of ascending concentration. The samples were then cleared of organic solvents before embedding the specimens with paraffin. Once the paraffin blocks were cooled and hardened they were sectioned with a microtome and mounted on a glass slide using mounting medium. The paraffin specimens were then dissolved out with xylene and rehydrated in a series of solutions of descending alcohol concentration prior to staining with Hematoxylin and Eosin (H&E), Masson's Trichrome and van Gieson stains according to standard procedures.[27]

Hematoxylin and Eosin (H&E) is the standard histological staining method and is primarily used to display the structural features of a specimen. The Verhoeff-Van Gieson color allows selective demonstration of collagen fibres, muscle, fibrin, and erythrocytes with muscle staining yellow and collagen red.[27] Van Gieson stain can also detect fibrosis between individual muscle fibres and the location of nuclei.[27] Masson's trichrome uses a three-color system staining protocol and is very effective at distinguishing muscle fibres (stain red), from surrounding connective tissue (stain blue); elastic fibres colour black.[27] These colorations were chosen as they best distinguish between muscle and collagen to enable quantitative analysis.

Slides were digitalized using Hamamatsu NanoZoomer Digital slide scanner and viewed on NDP.view2 software. Whole slide images were produced for quantitative analysis with the open source software, ImageJ.[28] Masson's Trichrome specimens three-color system staining protocol enabled very effective distinction between muscle fibres (stain red), from surrounding connective tissue (stain blue).[27] Images were calibrated to pixels to ensure standardization between specimens. Color threshold analysis was achieved using Hue, Saturation, Brightness tool to distinguish and measure red from blue. Muscle and connective tissue percentage ratio was obtained for each specimen. The entire specimen was analyzed. All images were analyzed using ImageJ by two independent investigators, blinded to the sonographic findings and each other's measurements. ImageJ methodology is depicted in Figures 1A–E.

Descriptive data was obtained to describe demographics on fixation method, age at death and cause of death. The frequencies and percentages of "avulsion" injuries were compared between ultrasound scans and anatomical dissection for each side. The percentage of collagen and muscle was calculated for each sample using ImageJ. Kruskal-Wallis test by ranks was used to determine a link between muscle and connective tissue proportion with sonographic PVM "avulsion." To ensure assessor agreement and validity of the study, assessments were conducted twice in at least 10 specimens by two separate investigators whom were blinded to each other's assessment for each stage. Measurements of agreement were then calculated using Cohen's kappa co-efficient. Statistical analysis was performed with the statistical package for the social sciences (SPSS) v24, IBM.

3 | RESULTS

3.1 | Sample selection and demographics

Cadaveric specimens ranged in age from 65 to 97 years (mean 82.3 years). Cause of death varied and included cardiovascular accident, fragility of old age, and pneumonia.

Fifteen cadavers were procured, of these, two cadavers were excluded, one due to missing ultrasound data and the second due to death from pelvic neoplasia. Ultrasound data was therefore available for 13 cadavers. Ultrasonographic "avulsions" were seen in 4/13 (30.1%) cadavers. The defect was bilateral in 1/13 (7.7%) and unilateral in 3/13 (23.1%).

Each enthesis, left and right, were considered its own variable for histopathological analysis. Thirteen cadavers were imaged, resulting in 26 (13 left and 13 right) individual enthesis. Histological images were missing for three enthesis resulting in a total of 23 enthesis for image J analysis. All sonographic "avulsions" had histological samples available.

3.2 | Image J analysis

ImageJ quantification of muscle and collagen within the Masson's Trichrome coloration is depicted in Table 1. The proportion of muscle in the ultrasound "avulsion" group to no "avulsion" group was 38.8 and 37.7%, respectively. The proportion of collagen was 61.2% for the ultrasound "avulsion" group and 62.2% for the no "avulsion" group. There was no difference in the overall muscle or collagen content (Kruskal-Wallis, $P = 0.864$).

3.3 | Intra-observer and inter-observer reproducibility

The Cohen's K and standard error for intra- and inter-observer agreement between ultrasound was 1.0+/−0.00 and 0.85 +/−0.142, respectively, representing perfect and good agreement. Agreement on anatomical findings was perfect for both intra- and inter-observer ($K = 1.0$). Intra-observer and inter-observer variability for Image J analysis was $K = 0.73$.

3.4 | Morphological evaluation

The two groups had distinct morphological differences in the histological arrangement of the tissues. In the no "avulsion" group, the muscle fibres appeared organized in a linear arrangement, in contrast within the "avulsion" group the muscle fibres appeared disorganized. The mean organized skeletal muscle content was 23% in the "avulsion" group versus 62% in the no "avulsion" group (Kruskall-Walis, $P = 0.02$). The damaged fibres appear tortous, with loss of striations in these areas. See Figures 2A–D.

In the no "avulsion" group, the elastic fibres are seen to have a fine reticular pattern with elastin fibre deposition lying within the intermuscular planes. In the "avulsion" specimens, elastin fibres appear chaotic with elastin fibres appearing not only within intermuscular space but also within the muscular tissue with evidence of variability in fibre size.

4 | DISCUSSION

This is the first study to look at the histology of the PVM enthesis in relation to the sonographic "avulsion" injury. The PVM enthesis was continuous with the pubic bone in all cadavers with not a single anatomical "avulsion" seen on dissection; this is consistent with other anatomical studies.[17,29] There were no quantitative differences between muscle and

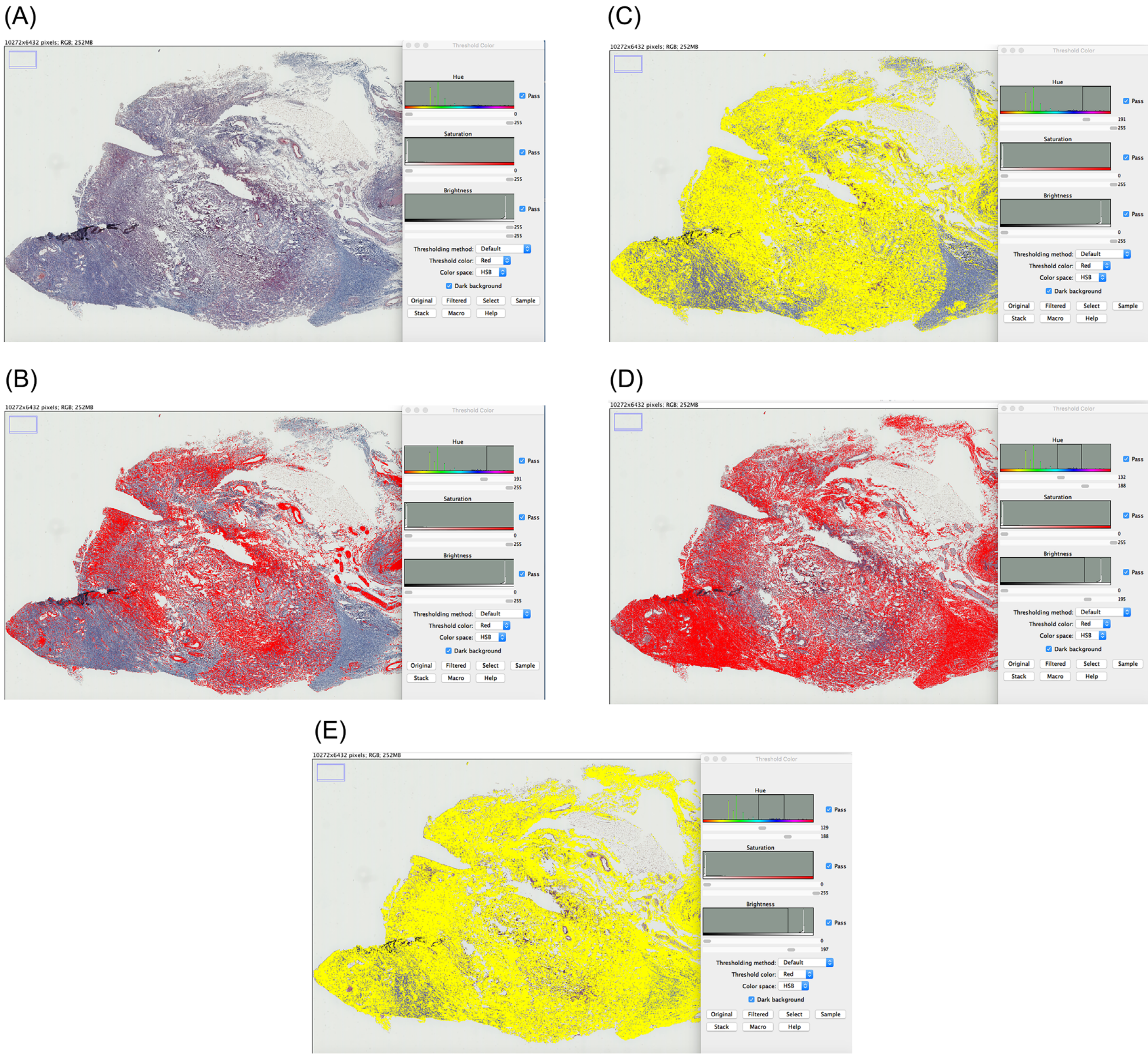

FIGURE 1 Pictographic method of the steps undertaken to perform quantitative analysis using the Hue, Saturation, Brightness tool on ImageJ to distinguish between muscle fibres (stain red) from surrounding collagen (stain blue). A, Whole slide overview with no filter. B, Whole slide highlighted for color red. C, Whole slide selected for color red. D, Whole slide highlighted for color blue. E, Whole slide selected for color blue

collagen within the PVM enthesis of cadavers with and without sonographic "avulsions."

Overall, there was a significantly smaller proportion of organized muscle fibres within the "avulsion" group. These findings are in keeping with MRI studies, which identified anatomical disorganized appearance at the site of a damaged enthesis, and thinning of the PVM on that side.[30,31] Furthermore, this disorganized and tortuous appearance of damaged muscle fibres have been observed following stretch injuries in skeletal muscle of rats.[32] This may suggest stretch injury has occurred within the "avulsion" cohort. This would support the link between this imaging finding and vaginal

TABLE 1 Histological composition of the enthesis tissue using a Masson Trichrome stain in cadavers with and without ultrasonographic avulsion

	Stain type	Mean	SD	min	max
Ultrasound avulsion Absent ($n = 18$)	Muscle (%)	37.7	13.3	15.3	68.0
	Collagen (%)	62.2	13.3	32.0	84.7
Ultrasound avulsion Present ($n = 5$)	Muscle (%)	38.8	11.1	25.1	53.2
	Collagen (%)	61.2	11.1	46.8	75.0

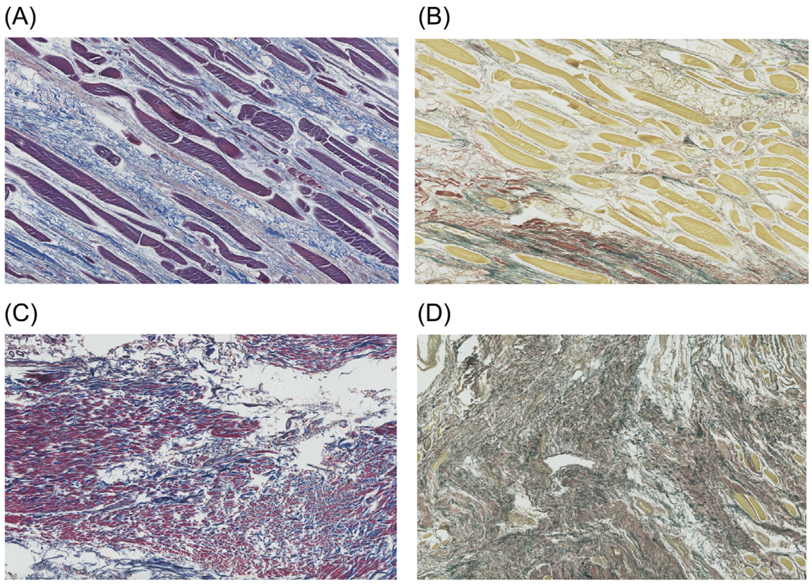

FIGURE 2 PVM enthesis muscle in cadavers. A, Masson Trichrome stain in normal enthesis. B, Van Gieson stain in intact enthesis. C, Masson Trichrome in cadavers with appearance of avulsion on ultrasound. D, Van Gieson stain in cadavers with appearance of avulsion on ultrasound

delivery,[33] where the PVM is thought to stretch more than three times its original length and double the maximum stretch capacity expected to cause injury in muscle of a non-gravid individual.[22,23]

The accuracy and the ability to image tissue is dependent on the direction of the ultrasound wave in relation to the tissue of interest.[34] The appearance of increased disorganized muscle fibers within the sonographic "avulsion" group would affect the acoustic impedance of the tissues, generating a different image on ultrasound. Linearly organized tissues lead to specular reflection of the ultrasound waves back into the probe, this generates an echogenic image (whiteness) on ultrasound. Disorganized tissues scatter the ultrasound waves in all directions, leading to a hypoechogenic image (black) in ultrasound.[34,35] See Figures 3A,B.

We acknowledge several limitations in this research. As a cadaveric study, the donors were of advanced aged with the mean age of 82.3 years. The generally very elderly cohort, relatively small sample size, in addition to the lack of parity and previous pelvic surgical history limits the extrapolation of these results to younger women. Moreover, due to the difficulty of obtaining a young nulliparous cadaver, this study lacked a control. Notwithstanding, previous studies on nulliparous women identified that increasing age can lead to myopathic histomorphological changes, however, in parous women, increasing age resulted in no further increase in these changes.[36]

Cadavers are regularly used for ultrasound validation studies and have been shown to translate well to healthy subjects.[37,38] Nevertheless, we acknowledge that poor hydration of tissue can affect image quality and due to the nature of our subjects the ability to accurately interpret an

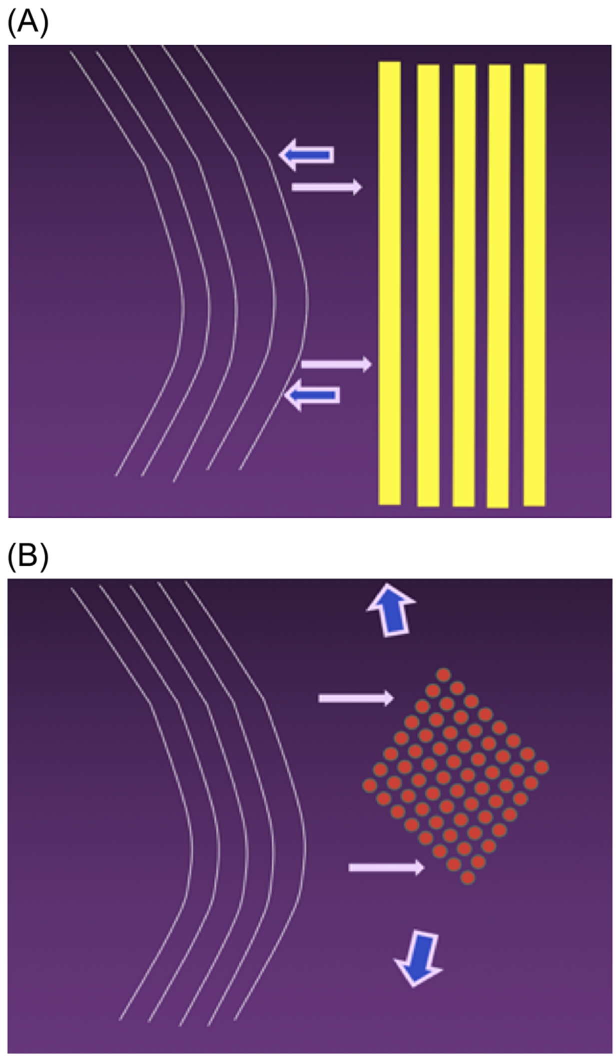

FIGURE 3 Acoustic impedance. A, Specular reflection. B, Scattered reflection

image may have been affected. That said, the display of perfect and good agreement between intra- and inter-observer analysis, validates our results. Furthermore, as the principle aim of the study was to compare the differences within the same fixed tissue the true impact is considered to be minor.

This study used only the traditional colorations, further studies using specialized staining methods focusing on differentiating between smooth and skeletal muscle and different collagen tissue types would be of interest. Further research into this topic is encouraged as increased understanding of this imaging finding will enable us to direct future studies toward prevention, detection, and treatments resulting from injuries sustained during childbirth.

5 | CONCLUSION

This is an important addition to the knowledge of pelvic floor morbidity resulting from childbirth. The PVM enthesis is continuous with pubic bone in the specimens with or without a sonographic "avulsion," reconfirming that this defect is not the literal detachment of the PVM enthesis from its insertion. The sonographic appearance of "avulsion" corresponds to the histological appearance of muscle injury, rather than a true separation of muscle from bone. It may be more accurate to refer to this ultrasonographic finding as a "levator ani injury" site rather than an "avulsion."

There was no quantitative difference in the proportion of muscle, collagen, and elastin. Histological tissue changes were however seen within the "avulsion" group suggesting tissue damage and an overall smaller proportion of organized muscle.

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