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Sonographic Measurements of Subsynovial Connective Tissue Thickness in Patients With Carpal Tunnel Syndrome

Margriet H. M. van Doesburg, MD, Aeele Mink van der Molen, MD, PhD, Jacqueline Henderson, PhD, Stephen S. Cha, MS, Kai Nan An, PhD, and Peter C. Amadio, MD

Department of Plastic, Reconstructive, and Hand Surgery, University Medical Center, Utrecht, the Netherlands (M.H.M.v.D., A.M.v.d.M.); and Orthopedic Biomechanics Laboratory, Division of Orthopedic Research (J.H., K.N.A., P.C.A.), and Division of Biomedical Statistics and Informatics (S.S.C.), MayoClinic, Rochester, Minnesota USA

Abstract

Objectives—A major pathologic finding in patients with idiopathic carpal tunnel syndrome is noninflammatory fibrosis and thickening of the subsynovial connective tissue. The objective of this study was to determine the ability of sonography to depict this thickening by comparing subsynovial connective tissue thickness in patients with carpal tunnel syndrome and healthy control participants.

Methods—Longitudinal sonograms of the middle finger superficial flexor tendon and subsynovial connective tissue were obtained at 3 levels: at the wrist crease (proximal tunnel), at the hook of the hamate (mid tunnel), and at the distal edge of the transverse carpal ligament (distal tunnel). The thickness of the subsynovial connective tissue perpendicular to the direction of the tendon and the diameter of the flexor digitorum superficialis tendon at the same level were measured. Then, a thickness ratio was created.

Results—At all 3 levels, the subsynovial connective tissue was thicker in patients than in controls ($P < .0001$) with a thickness ranging from 0.60 to 0.63 mm in patients and 0.46 to 0.50 mm in controls. The thickness ratio was significantly greater in patients at the hamate and distal levels ($P = .018$ and $.013$, respectively).

Conclusions—With this study, we have shown that it is possible to measure subsynovial connective tissue thickness with sonography, and the tissue is thicker in patients with carpal tunnel syndrome than in healthy controls.

Keywords

carpal tunnel syndrome; sonography; subsynovial connective tissue; tendon

Within the carpal tunnel, the subsynovial connective tissue is the lining around tendons that allows movement between the flexor tendons and median nerve, and it plays a fundamental role in terms of nutrition of the structures embedded in it.¹ Although the precise etiology of carpal tunnel syndrome has remained elusive, it is known that one major pathologic finding in idiopathic carpal tunnel syndrome is noninflammatory fibrosis and thickening of the subsynovial connective tissue.^{2–5} Some investigators have suggested that the pathologic

changes of the subsynovial connective tissue maybe a cause rather than a consequence of carpal tunnel syndrome.⁵

The use of diagnostic sonography has greatly enhanced the ability to diagnose injuries of tendons and tendon sheaths. Recently, steps have been made to image the subsynovial connective tissue with sonography as well.^{6–8} The principal advantages of sonography are its low cost, short study time, availability, and the possibility of dynamic imaging. In addition, the utility of sonography in the evaluation of carpal tunnel syndrome has been favorably compared to electromyography because of its noninvasiveness.⁴ The usefulness of sonography in monitoring carpal tunnel syndrome has been investigated by many authors. Static sonography has been described to depict conditions such as restricted median nerve sliding in the carpal tunnel,^{2,3,8} tendinous and ligamentous injuries and swelling of the median nerve in the proximal part of the carpal tunnel, and flattening of the median nerve in the distal part of the carpal tunnel.^{6,7,9} These approaches, however, are only able to capture late changes. A method that could identify earlier anatomic differences in, for example, patients who have symptoms but normal electromyographic results could potentially help identify novel therapies to prevent transition into a permanent neuropathy. We believe a promising opportunity is presented in imaging the subsynovial connective tissue by sonography because the ability to image changes in this structure not only would be a possible aid in understanding carpal tunnel syndrome but also could be used for further investigation of carpal tunnel evolution and treatment.

Therefore, the objective of this study was to investigate the subsynovial connective tissue thickness on sonography in patients with carpal tunnel syndrome and compare these results with those of healthy control participants.

Materials and Methods

Data Acquisition

To analyze the local anatomy and assess the subsynovial connective tissue thickness, longitudinal sonograms of the middle finger superficial flexor tendon and subsynovial connective tissue were obtained at 3 levels: at the wrist crease (proximal tunnel), at the hook of the hamate (mid tunnel), and at the distal edge of the transverse carpal ligament (distal tunnel). The middle finger flexor digitorum superficialis tendon was selected for measurement because it is the most palmar tendon and thus moves directly against the carpal flexor retinaculum during finger motion and because it is adjacent to the median nerve within the carpal tunnel. This study was approved by our Institutional Review Board.

We recruited 34 healthy volunteers (17 men and 17 women, mean age, 34.3 years; range, 22–67 years) in whom bilateral images were taken and 31 patients with carpal tunnel syndrome (11 men and 20 women; mean age, 51.0 years; range, 26–70 years) of whom 4 had unilateral and the other 27 had bilateral images taken. Patients were selected from among those undergoing diagnostic workup for carpal tunnel syndrome in the pretreatment period. Carpal tunnel syndrome diagnosis was confirmed both clinically and by electrodiagnostic studies in all patients. Clinical evaluations included sensibility (2-point discrimination) in the median nerve distribution of the hand, the Phalen test, the Tinel sign, manual muscle testing of the abductor pollicis brevis, and notation of the presence and extent of thenar muscle atrophy. Patients with any history of upper extremity surgery as well as any disorder associated with a higher incidence of carpal tunnel syndrome were excluded.

After getting informed consent, the sonographic measurements were performed. All sonographic studies were done by the same examiner, who was not blinded to whether the participant was a patient or a control. Each participant was imaged lying supine with the

shoulder abducted to 45°, with the elbow fully extended and the forearm in supination. The forearm of the examinee was fastened on a custom-made table with the wrist in the neutral position. An ultrasound scanner (Acuson Sequoia C512; Siemens Medical Solutions, Malvern, PA) equipped with an 15L8 linear array transducer was set to a 15-MHz acquisition frequency. The transducer was placed on the palmar wrist surface to make it parallel to the long axis of the middle finger flexor digitorum superficialis tendon (Figure 1). Positioning of the transducer was ensured by identification of anatomic structures: while flexing and extending the middle finger, the third flexor digitorum superficialis tendon was identified as a moving striated structure. More palmarly, the subsynovial connective tissue was recognized as a nonmoving hypoechoic layer. To minimize compression of the subsynovial connective tissue, the transducer was applied to the skin without additional pressure. The scanning was optimized for depth, focus, gain, and dynamic range and maintained throughout the examination for consistency. Then, 3 still images at the 3 different levels were taken.

Data Analysis

The still images were uploaded into ImageJ software (National Institutes of Health, Bethesda, MD; Figure 2). Using the Analyze menu, we measured the thickness of the subsynovial connective tissue, drawing a line perpendicular to the direction of the tendon, after which the software calculated the thickness. The diameter of the flexor digitorum superficialis tendon at the same level was also measured the same way as a reference for data analysis. The subsynovial connective tissue was defined as the thin echogenic layer at the border of the tendon, between the median nerve and the flexor digitorum superficialis tendon, as first described by Ettema et al.¹⁰ To compensate for differences in hand size, especially between men and women, the subsynovial connective tissue thickness was normalized to the flexor digitorum superficialis tendon diameter at the same level, using the thickness ratio, calculated as subsynovial connective tissue thickness/tendon thickness = thickness ratio. To calculate the correlation between the subsynovial connective tissue thickness and the electrodiagnostic results, we divided the electrodiagnostic results into mild, moderate, and severe according to the grading scheme for carpal tunnel syndrome severity described by Stevens.¹¹

The results were summarized by descriptive statistics (mean, standard deviation, median, and range) and by participant groups. A mixed model with repeated measures adjustment from individuals was used to compare the thickness measurements between patients with carpal tunnel syndrome and healthy controls. Individuals were repeated factors; left and right hands were random effects and patients with carpal tunnel syndrome and controls; and the 3 different locations were taken as fixed effects. The Pearson correlation coefficient and its *P* value were used to describe relationship between two factors. *P* < .05 was considered statistically significant. All statistical analyses were performed with SAS version 9.3 software (SAS Institute Inc, Cary, NC).

Results

Results are shown in Table 1 and Figure 3. At all 3 levels, the subsynovial connective tissue was thicker in patients than in controls (*P* < .0001) with a thickness ranging from 0.60 to 0.63 mm in patients and 0.46 to 0.50 mm in controls. The thickness ratio was significantly greater in patients at the hamate and distal levels (*P* = .018 and .013, respectively).

We did not find any correlation between subsynovial connective tissue thickness and electrodiagnostic results, with Pearson *r* values ranging from −0.17 to 0.21.

Discussion

With this study, we have shown that it is possible to assess subsynovial connective tissue thickness with sonography, and on average the tissue is thicker in patients with carpal tunnel syndrome than in healthy controls. The importance of this study is 2-fold. First, thickening of the subsynovial connective tissue might be an early indicator/predictor of carpal tunnel syndrome, supporting a clinical diagnosis when electrodiagnostic study results are normal. Of course, this possibility would need much further study. Second, these results are potentially a first step in developing a new noninvasive method that may help in the care of patients with carpal tunnel syndrome in the future.

Several studies have already shown that fibrosis and thickening of the subsynovial connective tissue are present in patients with carpal tunnel syndrome but not in individuals without this diagnosis. Donato et al¹² and Jinrok et al¹³ showed pathologic vascular proliferation, vascular hypertrophy, and vascular obstruction with wall thickening in the subsynovial connective tissue of patients. Ettema et al¹⁴ showed that patients with carpal tunnel syndrome had thicker fibrous bundles between the layers of subsynovial connective tissue than did healthy controls. Of note, the healthy controls used in the study by Ettema et al¹⁴ were cadaver specimens with no antemortem history of carpal tunnel syndrome, whereas the patients were middle-aged adults, suggesting that the fibrosis is not a function of age but of disease.

Of course, it is unclear at this point whether the subsynovial connective tissue fibrosis causes the neuropathy, or whether both the fibrosis and neuropathy are caused by some other, as yet unidentified, factor. Regardless, measurement of subsynovial connective tissue thickness could be clinically useful for several reasons. It could be used to support a clinical diagnosis of carpal tunnel syndrome when clinical signs are abnormal but electrodiagnostic study results are normal. Studies of subsynovial connective tissue thickness might also be helpful in patient care. It is possible, for example, that thicker subsynovial connective tissue might be associated with a poorer response to interventions such as steroid injection, splinting, and simple decompression. We plan to look for these correlations in future studies. We found a wide variation of normal results in this study. However, this study was meant as a first step toward potentially using subsynovial connective tissue thickness measurements in diagnosing carpal tunnel syndrome. To our knowledge, these measurements have never been done in patients before, and we want to give a general idea of this method and its potential (future) applications. Now we have shown that it is possible to measure the subsynovial connective tissue using sonography and that there is a difference between controls and patients, we can focus on the specifics such as reliability and diagnostic performance in future studies. Even though we tried to base our sonographic settings on other studies with similar purposes, we will need to improve this process in the future to get less variable and better clinically applicable results.

In this study, we only measured subsynovial connective tissue thickness at one time point. It would be more ideal to study the tissue thickening over time and to compare the progression of tissue thickening and clinical neuropathy. Such data will help clarify whether subsynovial connective tissue thickening is an early, concomitant, or late finding in patients with clinically diagnosed carpal tunnel syndrome.

Several parameters that might be potentially clinically useful were measured in this study. Ettema et al¹⁰ showed that no significant differences were noted between the thickness of the subsynovial connective tissue measured by sonography and that measured during cadaver dissection. They found a tissue thickness in healthy controls ranging from 0.62 mm at the wrist crease level to 0.66 mm at the hamate and distal edge levels. Our results in

healthy controls were slightly lower, but this difference might have been due to the use of color Doppler imaging by Ettema et al,¹⁰ in which angle dependency might alter measurements. In both their study and ours, the tissue was thicker at the hamate and distal edge levels. This finding could be due to the fact that within the carpal tunnel, pressure and shear are higher at the proximal level, which is the entrance of the carpal tunnel. The thickness of both tendons and the subsynovial connective tissue could be dependent on hand size and sex, and to rule these factors out, we created the thickness ratio. Therefore, this parameter would be most reliable and clinically most useful.

In the future, further research needs to be done to make thickness measurements more clinically applicable. The ability of this method to discriminate between pathologically thick and normal subsynovial connective tissue needs to be investigated, as well as the cutoff values. We did not find any correlation between tissue thickness and electromyographic severity in this study; however, it would be useful to repeat these measurements with a greater sample size. Interestingly, a recent publication did show a correlation between a different measure of subsynovial connective tissue abnormality (neovascularization) and outcomes. As in our study, there was no correlation of electrodiagnostic severity with subsynovial connective tissue abnormality, preoperative symptoms, or clinical outcomes.¹⁵

Finally, the presented method is laborious and should be modified for clinical use. One possible disadvantage of the thickness ratio is that if both the tendon and the subsynovial connective tissue thicken by an equal percentage, then the ratio would remain unchanged. An option to identify and correct for this possibility would be to also measure the total thickness of the tendon and tissue together, a possibility that remains for future studies.

The tightness of the carpal tunnel is probably best represented at the hook of the hamate level because it is right in the middle of the carpal tunnel. The proximal level is measured at the wrist crease, which is just at the entrance of the carpal tunnel.

We encountered some difficulties during this study. During image acquisition, we noticed that flexor digitorum superficialis tendon and subsynovial connective tissue imaging are much easier at the proximal part of the carpal tunnel. Imaging at the middle and distal parts of the carpal tunnel required applying some pressure to the transducer because of the thicker subcutaneous tissues of the palm. Even though we tried to avoid applying pressure, this factor may have affected the analysis. Another limitation of this study was that we did not use a reference standard for our measurements, nor did we do electrophysiologic testing in the volunteers to rule out carpal tunnel syndrome. For ethical reasons, however, we were not able to directly measure the subsynovial connective tissue and tendon thickness of the healthy volunteers in vivo because it would have required a surgical intervention. However, Ettema et al¹⁰ used cadaveric subsynovial connective tissue measurements as controls and showed that no significant differences were noted between the tissue thickness measured by sonography and that measured during cadaver dissection. Also, we did not test the reproducibility of the technique, even though sonography is known for high inter-rater variation. That analysis remains for future studies. However, others have shown that a very similar method is valid.¹⁶

In conclusion, we have presented a method for measuring subsynovial connective tissue thickness using sonography and showed that the tissue is significantly thicker in patients with carpal tunnel syndrome than in healthy controls. These findings suggest that thickening of the subsynovial connective tissue due to fibrosis is a pathologic finding in patients with carpal tunnel syndrome, and sonography might be useful as a diagnostic aid for early detection of carpal tunnel syndrome in the future.

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Figure 1.
Graphic representation of the study setup with the examinee's hand on the custom-madetable and the ultrasound transducer longitudinally placed on the wrist.

Figure 2. Longitudinal sonograms at 3 levels within the carpal tunnel. Arrows indicate flexor tendon diameter measurement; arrowheads, subsynovial connective tissue diameter measurement; and MN, median nerve.

Figure 3.

Mean tendon and subsynovial connective tissue (SSCT) thickness and thickness ratio with standard deviation in patients with carpal tunnel syndrome and controls. * $P < .05$.

Table 1**Tendon and Subsynovial Connective Tissue Thickness and Thickness Ratio**

Level	Tendon Thickness, mm (95% CI) Range	P	SSCT Thickness, mm (95% CI) Range	P	Thickness Ratio (95% CI) Range	P
Wrist crease						
Control	2.06 (1.56–3.10)		0.46 (0.23–0.70)		0.24 (0.10–0.38)	
	1.27–3.85		0.21–0.91		0.11–0.40	
Patient	2.36 (1.42–3.32)	.002	0.63 (0.20–1.06)	<.0001	0.27 (0.09–0.45)	.234
	1.39–3.46		0.23–1.62		0.13–0.74	
Hamate						
Control	2.40 (1.36–3.44)		0.48 (0.30–0.81)		0.21 (0.11–0.31)	
	1.52–3.92		0.31–0.80		0.11–0.35	
Patient	2.58 (1.80–3.36)	.009	0.60 (0.29–0.91)	<.0001	0.24 (0.12–0.36)	.018
	1.68–3.51		0.29–1.27		0.13–0.44	
Distal edge						
Control	2.49 (0.91–3.55)		0.50 (0.29–0.72)		0.20 (0.10–0.30)	
	1.42–4.70		0.22–0.78		0.10–0.31	
Patient	2.63 (1.69–3.59)	.099	0.61 (0.40–0.83)	<.0001	0.23 (0.13–0.33)	.013
	1.64–3.74		0.29–1.04		0.12–0.34	

CI indicates confidence interval and SSCT, subsynovial connective tissue. *P* values show significance between patients and controls.