Reproducibility of ultrasonographic subsynovial connective tissue thickness measurements in the carpal tunnel

Masterthesis

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“Ondergetekende, Yara van Kooij, bevestigt hierbij dat de onderhavige verhandeling mag worden geraadpleegd en vrij gefotokopieerd. Bij het citeren moet steeds de titel en de auteur van de verhandeling worden vermeld.”

ABSTRACT

Objective: The cause of carpal tunnel syndrome (CTS) is frequently idiopathic. Recent research concluded that thickening of the subsynovial connective tissue (SSCT) may lead to compression of the median nerve in patients with idiopathic CTS. It is possible to measure this thickness with ultrasound (US). However, the reproducibility of this technique has not been investigated before. The primary purpose of this study was therefore to determine the intra-rater reproducibility and the inter-rater reliability of SSCT thickness measurements with US in patients with idiopathic CTS, and in healthy controls. To compensate for differences in hand size, the secondary purpose was to determine the measurement properties for the thickness ratio of the SSCT to the third flexor tendon digitorum superficialis (FDS).

Methods: US images of patients with idiopathic CTS and healthy controls were collected in a previous study through convenience sampling. The US images were taken longitudinally at the wrist crease (proximal tunnel), hamate level (mid-tunnel) and the distal edge (distal tunnel) of the carpal tunnel. Three examiners calculated the thickness of the SSCT and the third FDS tendon at two different moments. The intra-rater and inter-rater reliability were calculated using the intraclass correlation coefficient (ICC) (2,1). The smallest detectable change (SDC) was determined for the agreement.

Results: Three examiners evaluated US images of 29 patients with idiopathic CTS and 34 healthy controls. ICC values for the intra-rater reliability of the SSCT measurement ranged from 0.151 to 0.676 for patients and from -0.24 to 0.680 for healthy controls. ICC values for the TR measurement varied from 0.187 to 0.616 for patients and 0.011 to 0.574 for healthy controls. ICC values for the inter-rater reliability of the SSCT measurement ranged from -0.129 to 0.442. For the TR measurement the ICC scores varied from -0.24 to 0.254. The SDC varied from 50% to 156% of the mean thickness measurements.

Conclusion: The reproducibility of the SSCT thickness measurements in the carpal tunnel with US is low. However, there seems to be a trend for a fair to good reliability at the proximal carpal tunnel level.

Key words: Carpal tunnel syndrome; median nerve, reliability, agreement, ultrasound.

SAMENVATTING

Doelstelling: De oorzaak van het carpaal tunnel syndroom (CTS) is in de meeste gevallen idiopathisch. Uit recent onderzoek blijkt dat het subsynoviale bindweefsel in de carpale tunnel verdikt is bij patiënten met idiopathisch CTS. Deze verdikking kan mogelijk een compressie van de nervus medianus veroorzaken. Met echografie kan de dikte van het subsynoviale bindweefsel worden opgemeten. Echter, de reproduceerbaarheid van deze techniek is nog niet onderzocht. De hoofddoelstelling van dit onderzoek was het berekenen van de intra- beoordelaars reproduceerbaarheid en inter-beoordelaars betrouwbaarheid van diktemetingen van het subsynoviale bindweefsel, met behulp van echografie, bij patiënten met CTS en bij gezonde proefpersonen. Ter compensatie voor verschillen in handgrootte was de tweede doelstelling het berekenen van deze klinimetrische eigenschappen voor de dikteratio metingen; de dikte van het subynoviale bindweefsel ten opzichte van de derde flexor digitorum superficialis pees.

Methoden: Echografische beelden van patiënten met idiopathisch CTS en gezonde proefpersonen zijn in een eerder onderzoek verzameld middels een gelegenheidssteekproef. De echografische beelden zijn longitudinaal gemaakt ter hoogte van de proximale polsplooi, (proximale tunnel), hamatum level (midden-tunnel) en de distale carpale tunnel. Drie beoordelaars hebben de echografische beelden beoordeeld op twee verschillende meetmomenten. De inter- en intra- beoordelaars betrouwbaarheid is berekend met de intraclass correlation coëfficiënt (ICC) (2,1). De smallest detectable change (SDC) is berekend om de overeenstemming te evalueren.

Resultaten: De beoordelaars hebben 29 echografiebeelden geëvalueerd van patiënten met idiopathisch CTS en 34 van gezonde proefpersonen. ICC scores voor de intra-beoordelaars betrouwbaarheid van subsynoviale bindweefsel metingen variëren van 0.151 tot 0.676 bij patiënten en van -0.24 tot 0.680 bij gezonde personen. Voor de dikteratio varieert de ICC tussen 0.187 tot 0.616 bij patiënten en van 0.011 tot 0.574 bij gezonde personen. De ICC scores voor de inter-beoordelaars betrouwbaarheid van het subsynoviale bindweefsel is -0.129 tot 0.442. Voor de dikteratio zijn deze ICC scores -0.24 tot 0.254. De SDC varieert van 50% tot 156% ten opzichte van de gemiddelde

gemeten diktes.

Conclusie: De reproduceerbaarheid van de diktemetingen van het subsynoviale bindweefsel metingen en de dikteratio is laag. Er is een trend waarneembaar voor een redelijke tot goede betrouwbaarheid ter hoogte van het proximale level van de carpale tunnel.

Sleutelwoorden: Carpaal tunnel syndroom; nervus medianus, betrouwbaarheid, overeenstemming, echografie.

Introduction

Carpal tunnel syndrome (CTS) is an entrapment neuropathy that affects the median nerve in the carpal tunnel. Between 1981 and 2005, the incidence of CTS in the United States of America (USA) was 491 per 100,000 for women and 258 per 100,000 for men (1). The prevalence of CTS was 7.8% in a pooled analysis of six prospective studies in the USA (2). The carpal tunnel contains nine flexor tendons and the median nerve which are surrounded by the subsynovial connective tissue (SSCT). The SSCT provides nutrition for all the structures in the carpal tunnel and is a sliding surface for the flexor tendons and median nerve (4,5). Patients with CTS have pain with or without paresthesias in the thumb, index and middle finger. Prolonged compression in the carpal tunnel can result in atrophy of the muscles innervated by the median nerve (3).

CTS can be caused by several factors and disorders. Anatomical abnormalities such as a ganglion can compress the median nerve in the carpal tunnel. Systemic disorders as rheumatoid arthritis can cause oedema in the carpal tunnel, which could result in compression of the median nerve (3,6). However, in most cases the specific cause remains unclear, these patients belong to the group with idiopathic CTS (7). The underlying histopathology of idiopathic CTS is investigated by Ettema et. al (8). They concluded that SSCT fibrosis or thickening may lead to compression of the median nerve and could change the tendon excursion (8).

Studies have shown that it is possible to measure this SSCT thickening with ultrasound (US) (9,10). Van Doesburg et al. (10) performed a pilot study in which measurements of the SSCT thickness at three different levels in the carpal tunnel (proximal, mid and distal) were performed. The SSCT thickness ranged from 0.60 to 0.63 millimetres (mm) in patients with idiopathic CTS, compared to 0.46 to 0.50 mm in healthy controls (10). The thickness ratio (TR), calculated as SSCT thickness divided by the third flexor digitorum superficialis (FDS) tendon thickness, was used in this study to compensate for differences in hand size, and was also greater in patients than in healthy controls (10). This are important findings for different reasons. Firstly, measuring SSCT thickness with US could be helpful to identify the precise aetiology of idiopathic CTS. Secondly,

because there is no gold standard for diagnosing CTS (11), measuring the SSCT thickness with US could be helpful to diagnose CTS in the future (10).

However, before the thickness measurement of the SSCT can be used clinically, the reproducibility must be established. It is known that the reproducibility of US is highly influenced by rater variance (12,13), therefore, it is important to investigate the intra-rater as well as the inter-rater reliability. To be able to discriminate between patients with CTS and healthy persons the reliability must be appropriate, and for evaluative purposes the agreement should be established (14). In the previous pilot study, the evaluation of the US images was performed by only one investigator (10). Therefore, it would be useful to re-examine these results by different examiners to verify the study outcome and to investigate the measurement properties of this relatively new technique.

The primary purpose of this study was to assess the intra-rater reproducibility and the inter-rater reliability of US measurements of the SSCT thickness in the carpal tunnel in patients with idiopathic CTS and in healthy controls. The secondary purpose was to assess the intra-rater reproducibility and the inter-rater reliability of the thickness ratio in both groups.

Patients and methods

This reproducibility study is based on a previous cross sectional pilot study which was performed in 2009 at the Mayo Clinic in Rochester, MN (USA) and published in 2012 (10). There were no extra procedures for the participants in this current study, since only the existing ultrasound images were investigated. Informed consent was given in the previous study by all the participants, according to the principals of the Mayo Clinic. Permission for this reproducibility study was given by the Mayo Clinic.

Participants

The patients of the previous study were selected through convenience sampling among patients undergoing diagnostic tests during the pre-treatment period in the Mayo Clinic. Patients were eligible to participate if they were above 18 years of age, diagnosed with

idiopathic CTS, and when the diagnosis was confirmed clinically and electro-diagnostically. The control group consisted of healthy adult volunteers without any history of CTS. Participants were excluded if they had a history of upper extremity surgery, trauma, or any disorder related with a higher incidence of CTS (10). For this reproducibility study, we evaluated the right hand ultrasound images of all participants.

Examiners

The examiners have various levels of experience with US, which was considered representative for the Dutch population working with US in daily practice. Examiner 1 (MvD), researcher of the previous study and plastic surgery resident at the University Medical Centre Utrecht (UMCU), has four years of experience with US of the carpal tunnel and the SSCT. Examiner 2 (NV), physical therapist and teacher in US techniques, has two years of experience with US of the upper extremity. Examiner 3 (YvK), physical therapist, has six months of experience with US of the hand and wrist. Before the start of this study, the examiners underwent a two-hour training session. In this training, the background of the previous study, the computer program and precise measurement technique were clarified and practiced.

Measurement procedure

The US images of the SSCT were taken longitudinally at three different levels of the carpal tunnel; the wrist crease (proximal tunnel), hamate level (mid-tunnel) and the distal edge (distal tunnel) of the carpal tunnel, using a Siemens Sequoia C512 ultrasound system with a linear array transducer, while the hand was fixed in a custom made fixator. Details of this study protocol are described by van Doesburg et al.(10). For this reproducibility study, the thickness of the structures was determined and calculated in mm with ImageJ software (version 1.32J, National Institutes of Health, USA). Both SSCT and FDS tendon thickness were measured (Figure 1).

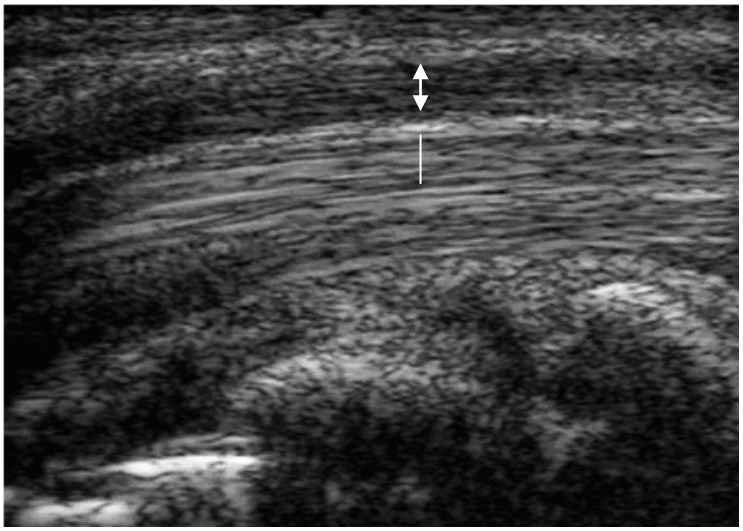

Figure 1. Longitudinal ultrasound image at the proximal level of the carpal tunnel.
Arrow: median nerve. Straight line: flexor superficialis tendon. Between the median nerve and flexor tendon the subsynovial connective tissue is located. On the right side the radius and on the left side the lunate and capitate bone are pictured.

SSCT thickness was calculated perpendicular to the direction of the third FDS tendon. The TR was calculated as SSCT thickness in mm divided to the third FDS tendon thickness. The first assessment of all US images was conducted by NV and YvK in March 2013. Data of the previous pilot study (10) (collected in 2009), were used as first evaluation by MvD. With an interval of three weeks, the second round of evaluation was performed by examiners NV, YvK and MvD (April 2013). Examiners were blinded to each other's as well as to their previous measurements results.

Data analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS), version 20.0 (SPSS Corp, Chicago, Ill, USA). Baseline characteristics are presented as mean ± standard deviation (SD) or in number (n) and percentage (%). An independent samples T-test was used to compare differences in age in patients and healthy controls. Data were checked for normality with the Shapiro-Wilk test. An alpha of $p<0.05$ was considered as statistically significant. Log transformation was applied in case of a positive skewness. The intraclass correlation coefficient (ICC) was used to calculate reliability. To take the systematic difference between examiners into account, the ICC agreement (model 2,1), calculated with the two way random ANOVA, was used in this study. In general, ICC values above 0.75 are considered as excellent, values

between 0.40–0.74 are fair to good and values below 0.40 are considered as poor (15,16). Agreement was determined with the smallest detectable change (SDC). The SEM agreement ($\sqrt{(\sigma^2_{pt} + \sigma^2_{residual})}$) was calculated from the ICC formula, described by de Vet et al. (14). The SDC was calculated as 1,96 * $\sqrt{2}$ * SEM. The intra-rater reproducibility was calculated for all examiners separately. The inter-rater reliability was calculated between MvD and NV, MvD and YvK, and NV and YvK, using the second evaluation round (April 2013).

Results

Twenty-nine patients with right handed idiopathic CTS and thirty-four healthy controls participated in the previous study (10). The mean age of the patients was significant higher compared to the healthy controls. Demographic and baseline characteristics of the participants are described in table 1.

Table 1. Demographic and baseline characteristics of the participants (n=63).

Characteristic	Patients (n=29)	Controls (n=34)	P- value
Age (years), mean ± SD	50.8 ± 11.9	34.3 ± 9.7	0.000
Female, n (%)	18 (62)	17 (50)	
Bilateral CTS, n (%)	27 (93)	-	

SD, standard deviation; n, number; CTS, carpal tunnel syndrome

The mean thickness measurements of the SSCT and TR are presented in table 2. Normal distribution was not reached after (log)transformation for the second SSCT and TR measurement on the mid and distal level by YvK. There were no missing values in this study.

Table 2. Mean SSCT thickness and TR in patients and healthy controls.

TR ratio (mm)						
	NV		MvD		YvK	
Location CT	**Patients**	**Controls**	**Patients**	**Controls**	**Patients**	**Controls**
Proximal, mean ± SD	0.32 ± 0.08	0.25 ± 0.05	0.29 ± 0.09	0.28 ± 0.09	0.18 ± 0.07	0.17 ± 0.08
(range)	(0.18 – 0.46)	(0.11 – 0.38)	(0.16 – 0.50)	(0.11 – 0.50)	(0.07 – 0.48)	(0.07 – 0.36)
Mid, mean ± SD	0.27 ± 0.08	0.21 ± 0.05	0.26 ± 0.06	0.25 ± 0.06	0.15 ± 0.05	0.13 ± 0.05
(range)	(0.16 - 0.52)	(0.13 – 0.32)	(0.16 – 0.41)	(0.17 – 0.40)	(0.06 – 0.27)	(0.05 – 0.24)
Distal, mean ± SD	0.28 ± 0.09	0.21 ± 0.04	0.25 ± 0.06	0.22 ± 0.05	0.15 ± 0.06	0.14 ± 0.04
(range)	(0.14 – 0.52)	(0.13 – 0.34)	(0.16 – 0.38)	(0.11 - 0.31)	(0.10 – 0.45)	(0.06 – 0.22)
SSCT thickness (mm)						
Proximal, mean ± SD	0.79 ± 0.21	0.60 ± 0.16	0.66 ± 0.19	0.53 ± 0.19	0.41 ± 0.18	0.36 ± 0.18
(range)	(0.46 – 1.18)	(0.26 - 1.15)	(0.35 – 1.12)	(0.30 - 1.18)	(0.17 - 1.05)	(0.12 - 0.84)
Mid, mean ± SD	0.78 ± 0.23	0.59 ± 0.14	0.59 ± 0.15	0.50 ± 0.10	0.37 ± 0.13	0.32 ± 0.11
(range)	(0.46 – 1.39)	(0.35 - 0.95)	(0.35 – 1.04)	(0.31 - 0.72)	(0.17 - 0.53)	(0.12 - 0.52)
Distal, mean ± SD	0.75 ± 0.19	0.60 ± 0.12	0.58 ± 0.12	0.48 ± 0.11	0.41 ± 0.20	0.34 ± 0.11
(range)	(0.41 – 1.24)	(0.39 - 0.86)	(0.37 – 0.79)	(0.30 - 0.70)	(0.24 - 1.37)	(0.17 – 0.60)

CT, carpal tunnel; SD, standard deviation; mm, millimetre; SSCT, subsynovial connective tissue; TR, thickness ratio

Reliability

The intra-rater reliability scores for each level and each examiner are provided in table 3. ICC scores of the SSCT measurement ranged from 0.151 to 0.676 for patients and from -0.24 to 0.680 for healthy controls. For the TR measurement the ICC values varied from 0.187 to 0.616 for patients and 0.011 to 0.574 for healthy controls. As shown in table 4, poor to fair inter-rater reliability scores were found for the SSCT measurement, while poor reliability scores were found for the TR measurement.

Table 3. Intra-rater reliability of the TR and SSCT measurements.

	ICC (95% CI)		
	TR		
Location/ Examiner	**NV**	**MvD**	**YvK**
- Controls			
Proximal	0.296 (-0.023 - 0.567)	0.011 (-0.279 – 0.319)	**0.574** (0.304 - 0,760)
Mid	0.235 (-1.06 – 0.527)	0.024 (-0.182 – 0.276)	0.300 (-0.07 - 0.566)
Distal	0.286 (-0.065 – 0.55)	0.015 (-0.274 - 0.322)	0.320 (0.011 - 0.581)
- Patients			
Proximal	0.302 (-0.054 – 0.594)	0.324 (-0.008 - 0.603)	**0.616** (0.220 - 0.811)
Mid	0.187 (-0.149 – 0.499)	0.328 (-0.006 - 0.607)	**0.475** (0.076 - 0.730) ~
Distal	**0.419** (0.065 – 0.678)	0.296 (-0.064 - 0.580)	**0.489** (0.056 – 0.746) ~
	SSCT		
- Controls			
Proximal	**0.523** (0.229 – 0.729)	0.250 (-0.077 - 0.534)	**0.680** (0.451 - 0.826)
Mid	0.199 (-0.153 - 0.503)	-0.24 (-0.354 - 0.312)	0.314 (-0.004 - 0.580)
Distal	0.239 (-0.108 - 0.532)	0.251 (-0.098 - 0.542)	0.279 (-0.35 - 0.551)
- Patients			
Proximal	**0.429** (0.099 – 0.680)	**0.507** (0.183 - 0.733)	**0.659** (0.192 - 0.853)
Mid	0.151 (-0.236 – 0.491)	0.265 (-0.118 – 0.575)	**0.605** (0.216 – 0. 811) ~
Distal	0.327 (-0.049 – 0.618)	**0.484** (0.149 - 0.720)	**0.676** (0.283 – 0.853) ~

ICC, intraclass correlation coefficient; CI, confidence interval; mm, millimetre; SSCT, subsynovial connective tissue; TR, thickness ratio; ~ not normally distributed. In bold ICC values above 0.40

Table 4. Inter-rater reliability of the TR and SSCT measurements.

	ICC (95% CI)		
	TR		
Location / Examiner	**NV- MvD**	**NV- YvK**	**MvD- YvK**
- Controls			
Proximal	0.152 (-0.159 - 0.449)	0.082 (-0.110 - 0.317)	0.254 (-0.101 - 0.578)
Mid	-0.24 (-0.278 - 0.268)	0.084 (-0.085 - 0.304)	0.025 (-0.059 - 0.159)
Distal	0.127 (-0.219 - 0.444)	-0.17 (-0.128 - 0.151)	0.175 (-0.087 - 0.484)
- Patients			
Proximal	0.040 (-0.320 – 0.393)	0.181 (-0.091 – 0.501)	0.138 (-0.095 - 0.413)
Mid	-0.080 (-0.446 – 0.299)	0.080 (-0.079 – 0.303)	-0.11 (-0.111 - 0.151)
Distal	0.000 (-0.336 – 0.348)	0.153 (-0.091 – 0.446) ~	0.070 (-0.097 – 0.298) ~
	SSCT		
- Controls			
Proximal	**0.415** (0.106 - 0.654)	0.184 (-0.95 - 0.479)	**0.442** (-0.102 - 0.763)
Mid	-0.129 (-0.389 - 0.179)	0.030 (-0.067 - 0.179)	0.049 (-0.085 - 0.237)
Distal	0.085 (-0.127 - 0.336)	0.006 (-0.070 - 0.129)	0.226 (-0.095 - 0.528)
- Patients			
Proximal	0.144 (-0.161 – 0.451)	0.200 (-0.077 – 0.545)	0.290 (-0.105 - 0.633)
Mid	0.126 (-0.125 – 0.407)	0.029 (-0.065 – 0.183) ~	0.013 (-0.118 – 0.210) ~
Distal	0.006 (-0.207 – 0.278)	0.152 (-0.092 – 0.444) ~	0.191 (-0.094 – 0.480) ~

ICC, intraclass correlation coefficient; CI, confidence interval; mm, millimetre; SSCT, subsynovial connective tissue; TR, thickness ratio; ~ not normal distributed. In bold ICC values above 0.40

Agreement

In table 5 SDC values of SSCT and TR measurements are given as percentage of the mean thickness measurement by the three examiners. The SDC scores varied from 50% to 156% of the mean thickness measurements.

Table 5. Agreement of the TR and SSCT measurements.

TR ratio									
Location / Examiner	**NV**			**MvD**			**YvK**		
	Mean (mm)	SDC (mm)	%	Mean (mm)	SDC (mm)	%	Mean (mm)	SDC (mm)	%
- Controls									
Proximal	0,25	0,20	80	0,28	0,21	75	0,17	0,23	135
Mid	0,21	0,18	86	0,25	0,15	60	0,13	0,12	92
Distal	0,21	0,18	86	0,22	0,12	55	0,14	0,15	107
- Patients									
Proximal	0,32	0,23	72	0,29	0,21	72	0,18	0,20	111
Mid	0,27	0,21	78	0,26	0,15	58	0,15	0,15	100
Distal	0,28	0,26	93	0,25	0,15	60	0,15	0,23	153
SSCT									
- Controls									
Proximal	0,60	0,46	77	0,53	0,45	85	0,36	0,50	139
Mid	0,59	0,36	61	0,50	0,25	50	0,32	0,29	91
Distal	0,60	0,43	72	0,48	0,3	63	0,34	0,32	94
- Patients									
Proximal	0,79	0,54	68	0,66	0,46	70	0,41	0,48	117
Mid	0,78	0,53	68	0,59	0,38	64	0,37	0,35	95
Distal	0,75	0,63	84	0,58	0,34	59	0,41	0,64	156

SDC; smallest detectable change; mm, millimetre; SSCT, subsynovial connective tissue; TR, thickness ratio

Discussion

The purpose of this study was to determine the intra-rater reproducibility and the inter-rater reliability of SSCT thickness and TR measurements with US in patients with idiopathic CTS and in healthy controls. The SDC values for agreement are relatively large (50% to 156%) in comparison with the TR and the mean thickness of the SSCT. Therefore it was concluded that this measurement technique is not appropriate for evaluative use yet. Despite the general poor reproducibility values in this study, there seems to be a trend for a fair to good reliability of SSCT measurement on the proximal level of the carpal tunnel. No structural reproducibility differences were found between patients with CTS and healthy controls.

The low reliability on the mid and distal level of the carpal tunnel could be caused by the poor quality of some US images. This made the identification of the SSCT, median nerve and flexor tendon more complex. The transducer position should be accurate during the measurement procedure to obtain US images of high quality. Due to the anatomical curve in the palm of the hand, the positioning of the transducer is more complicated in the distal part of the carpal tunnel, which could be an explanation for the poor reliability of the mid and distal level. These findings are confirmed by other studies, describing that the proximal tunnel position allowed the best control between the US beam and the underlying structures (9,17,18).

The inter-rater reliability in this study was poor. Discrepancy between examiners has been described in other studies as well, where US is reported to be an examiner dependent tool (12,13,19). The reliability gained by MvD was structurally lower compared to the other two examiners. The explanation for this fact can be twofold. First, during the first evaluation round, MvD measured the thickness of the structures directly after the dynamic recording of the carpal tunnel structures. It is easier to identify the non-moving SCCT layer and the moving flexor tendon during motion recording, therefore this could have influenced the outcome of MvD. Second, one could argue that the time interval between the two evaluation rounds might play a role. The interval between the two evaluation rounds by MvD was four years. Examiners YvK and NV evaluated the images with an interval of three weeks and produced higher reliability values. This could be explained by recall bias. However, it was considered that, in view of the large number of US images, an interval of three weeks should be long enough for evaluation without remembering the previous measurement details.

In contrast to the current study, other studies which investigated the reproducibility of US in the carpal tunnel found high reliability values (20-22). However, in these studies the diameter of the median nerve and flexor tendons were investigated. The reproducibility of SSCT measurements with US has not been investigated before and measuring the SSCT with US is more challenging compared to a nerve or tendon evaluation (9).

The current study has several limitations. Firstly, this study did not investigate the total ultrasonographic procedure, because only existing US images were evaluated by the examiners. Therefore, the results of this study are not valid in clinical practice, where the examiner usually performs the total scanning procedure. Secondly, the examiners were not blinded for patient characteristics and could therefore be biased. Thirdly, data of the second SSCT and TR measurement on the mid and distal level by YvK was even after (log)transformation not normally distributed. Therefore, no conclusion can be drawn from these ICC values. Lastly, some negative ICC values were found, which can occur when little variance exists between group means and more variance exists within groups (23). As stated by Giraudeau (24), negative values have no theoretical legitimacy. Despite these limitations, this study was a first step to investigate the reproducibility of SSCT measurement with US. Other studies investigated the thickness of the SSCT with US (9,10), or by obtaining a biopsy of the SSCT (25), but did not investigate the reproducibility. Knowledge about the reproducibility is essential for further research and the potential use of this US technique in clinical practice. In addition, an investigation was performed of both healthy persons and patients. Although it was hypothesized that the thickened SSCT of patients with CTS would be easier to visualize, it could not be confirmed with the current results.

The additional value of the SSCT and TR measurements with US could be twofold. Firstly, SSCT fibroses seems to play an important role in idiopathic CTS (10). Fibrosis or thickening may lead to compression of the median nerve and could change the tendon excursion (8). Indeed, recent studies confirmed a different motion pattern of the flexor tendons in the carpal tunnel in patients with idiopathic CTS compared with healthy persons (5,26,27). However, it is not clear in which order these processes take place. It is possible that fibrosis of the SSCT changes the tendon gliding system. On the other hand, changes in tendon gliding patterns may cause fibrosis of the SSCT (5,10). In a longitudinal study, for example, the process of SSCT thickening and changes in tendon gliding patterns could be further investigated with US. Secondly, measuring the SSCT thickness with US could be helpful for diagnosing CTS in the future (10). Currently, there is no gold standard for diagnosing CTS. A combination of patient history, symptoms,

provocation tests, sensory evaluation and electrophysiological tests is commonly used in clinical practice (11). Besides, an evaluation with US of the cross-sectional area of the median nerve and the presence of abnormal structures in the carpal tunnel is recommended by some authors (28). The US measurements of the SSCT thickness provide additional information and therefore could be valuable to diagnose CTS.

However, previously, more research is essential to optimize this US technique with a standardized measurement protocol. Succeeding studies should include the complete measurement procedure, and obtain the thickness measurement directly after the dynamic records, to approach the use of US in clinical practice. Also, it is important to define the precise definition of the SSCT, and the borders of the median nerve and flexor tendons. In addition, the SSCT is a connective tissue between all tendons and the median nerve in the carpal tunnel. In this study the SSCT layer between the median nerve and the third FDS was investigated. Previous studies evaluated the SSCT in different locations in the carpal tunnel (9,25). It would be valuable to investigate the other locations for SSCT thickening and its reliability in further studies. It might also be interesting to investigate the thickness of the SSCT with other modalities such as magnetic resonance imaging scanning.

Conclusion

The reproducibility of the thickness measurement of the subsynovial connective tissue and thickness ratio in the carpal tunnel with ultrasound is low. However, there is a trend for a positive reliability at the proximal carpal tunnel level. The authors believe that SSCT thickness measurements with US could be useful in the future, however the technique should be optimized before it is applicable for further research and useful in clinical practice. Since better results are found for SSCT thickness measurements at the proximal carpal tunnel level, the authors suggest that further research using ultrasound has to be focused on this area of the carpal tunnel.

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