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ORIGINAL RESEARCH

Diagnosis of Carpal Tunnel Syndrome in Patients Without Diabetes With Hemodialysis Using Ultrasonography: Is It a Useful Adjunctive Tool?

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Abstract

Objective: (1) To examine the ultrasonography (US) characteristics in patients with hemodialysis-related carpal tunnel syndrome (H-CTS) and (2) to evaluate the accuracy of a proposed US parameter-dynamic ratio of median nerve-to-hamate hook distance (RMHD) in diagnosis of H-CTS.

Design: A case-control study.

Setting: A tertiary medical center and a secondary hospital from November 2017 to March 2021.

Participants: Consecutive patients (N=207) without diabetes under hemodialysis were recruited and divided into a hemodialysis without carpel tunnel syndrome (CTS) (H-Control) group and an H-CTS group. Age-matched volunteers (N=89) without diabetes or upper extremity disorders were enrolled as the control group.

Intervention: US examinations by 2 operators blinded to the patient's clinical information.

Main Outcome Measures: US parameters including cross-sectional area of the median nerve at the carpal tunnel inlet (CSA-I) and outlet (CSA-O), the flattening ratio of the median nerve at the inlet (FR-I) and outlet (FR-O), and RMHD.

Results: Handedness and arteriovenous fistula showed no associations with CSA-I/O and FR-I/O. Compared with the control group (n=69), the CSA-I was significantly larger in the H-Control group (n=63) and H-CTS group (n=76) (P<.001, both). There were no significant differences in the FR-I/-O among the 3 groups. For the second aim, in the H-CTS group (n=38), there was a significantly lower RMHD compared with both the control (n=20) and H-Control groups (n=30) (0.1%±2.2% vs 3.5±2.3% and 3.8±1.7%, P<.001, both). An RMHD cutoff value of <2.7% yielded a specificity of 80.0%, a sensitivity of 94.7%, and an overall accuracy of 88.2% in the diagnosis of H-CTS.

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Conclusions: Neither CSA-I/-O or FR-I/-O have a role in the diagnosis of H-CTS. RMHD might be a useful US parameter in the diagnosis of CTS in patients without diabetes undergoing hemodialysis.

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Carpal tunnel syndrome (CTS) is one of the most common nerve entrapment syndromes.[1] To date, a thorough clinical assessment, including history and a physical examination, is regarded as the criterion standard for the diagnosis of CTS.[1,2] Generally, a nerve conduction study (NCS) is used for confirming the diagnosis[3,4] and is very sensitive.[5] Recently, mounting evidence suggests that ultrasonography (US) can be used as an effective tool to reconfirm the clinically diagnosed CTS,[3,6] with advantages including low cost, shorter examination time, and high availability. Cross-sectional area (CSA) of the median nerve at the inlet of the carpal tunnel is the most commonly used parameter in US examination.[3,7]

Hemodialysis is a well-known risk factor for CTS incidence,[8] where the duration of hemodialysis positively correlates with the prevalence of CTS.[9,10] Clinically, the possible concomitant polyneuropathy, from either uremia or diabetes, makes the diagnosis of CTS more difficult or unreliable in patients under hemodialysis, even when using a clinical diagnosis[11,12] or NCS.[13,14] An adjunctive and readily available diagnostic tool, such as US, might be a useful alternative. However, the US parameters most relevant to hemodialysis-related CTS (H-CTS) are still unclear. The reduced movement of the median nerve during finger flexion and extension has been reported in patients with CTS.[15-20] In our daily practice, less transverse sliding movement of the median nerve during finger motion was observed in the patient with H-CTS. Therefore, the aims of this study include (1) examining the US characteristics in patients with H-CTS and (2) evaluating the accuracy of a proposed US parameter-dynamic ratio of the median nerve-to-hamate hook distance (RMHD) in the diagnosis of H-CTS.

List of abbreviations:

ANOVA	**analysis of variance**
AVF	**arteriovenous fistula**
CSA	**cross-sectional area**
CSA-I	**cross-sectional area of the median nerve at the inlet of the carpal tunnel**
CSA-O	**cross-sectional area of the median nerve at the outlet of the carpal tunnel**
CTS	**carpal tunnel syndrome**
FR-I	**flattening ratio of the median nerve at the inlet of the carpal tunnel**
FR-O	**flattening ratio of the median nerve at the outlet of the carpal tunnel**
gMHD	**hamate hook-to-median nerve distance in the gripping position**
H-Control	**patients under hemodialysis without carpal tunnel syndrome**
H-CTS	**hemodialysis-related carpal tunnel syndrome**
ICC	**intraclass correlation coefficient**
NCS	**nerve conduction study**
rMHD	**hamate hook-to-median nerve distance in the resting position**
RMHD	**dynamic ratio of the median nerve-to-hamate hook distance**
US	**ultrasonography**

Methods

Ethics statement

The study was approved by the institutional review board of the author's hospital (No.: B-ER-109-162), and all methods were performed in accordance with the approved guidelines.

Participants

This is a case-control study. For our first aim, to examine the US characteristics in patients with H-CTS, the patients under hemodialysis were consecutively enrolled from November 2017 to December 2019. The inclusion criterion was that patients must have been under hemodialysis >6 months. The exclusion criteria included prior history of diabetes, peripheral neuropathy, cervical radiculopathy, and operations in the upper extremities; inflammatory joint disease; or previous carpal tunnel release. The CTS of patients undergoing hemodialysis was mainly determined according to clinical symptoms (pain, numbness, tingling, waking at night) and signs (Tinel sign or Phalen test)[21] and then reconfirmed by the NCS. Then, the enrolled patients were divided into a hemodialysis without CTS (H-Control) group and an H-CTS group. We also enrolled aged-match volunteers as the control group, who were free from diabetes, any upper extremity disease, or CTS symptoms. The proposed US parameter, the RMHD, was examined in patients enrolled from January 2020 to March 2021.

US parameters

The US examination was done using a Logiq-e R7scanner[a] with an L4-12t-RS (4.2-13.0 MHz) linear array transducer. The majority of all enrolled patients underwent the US examination the next day after hemodialysis when they visited in the outpatient clinic. The examinee was seated in a comfortable position with the forearm resting on a table, wrist in full supination, and fingers semi-flexed. Axial and transverse images were obtained at the proximal and distal carpal tunnel. No additional force was applied other than the weight of the transducer to avoid any artificial deformity of the soft tissue. The examination protocol was similar to that discussed in previous studies.[22,23] For the median nerve, CAS at the inlet of the carpal tunnel (CSA-I) and the outlet (CSA-O) as well as the flattening ratio (FR) at the inlet (FR-I) and outlet (FR-O) were measured and recorded. The CSA was measured using the trace function by tracing inside the hypoechoic rim of the nerve. The FR was defined as the ratio of the major to minor axes of the median nerve.[24] The proposed US parameter, the RMHD, was evaluated using dynamic transverse US imaging at the outlet (at the level of the hamate hook). The distance between the tip of the hamate hook and the ulnar edge of the median nerve in the resting position (rMHD) was measured and recorded. Then, the examinee was asked to gently make a fist. The median nerve-to-hamate hook distance in the gripping position (gMHD) was also measured and recorded (fig 1). To minimize dismiliarity in basedline median nerve-to-hamate hook distance among individuals, the transverse

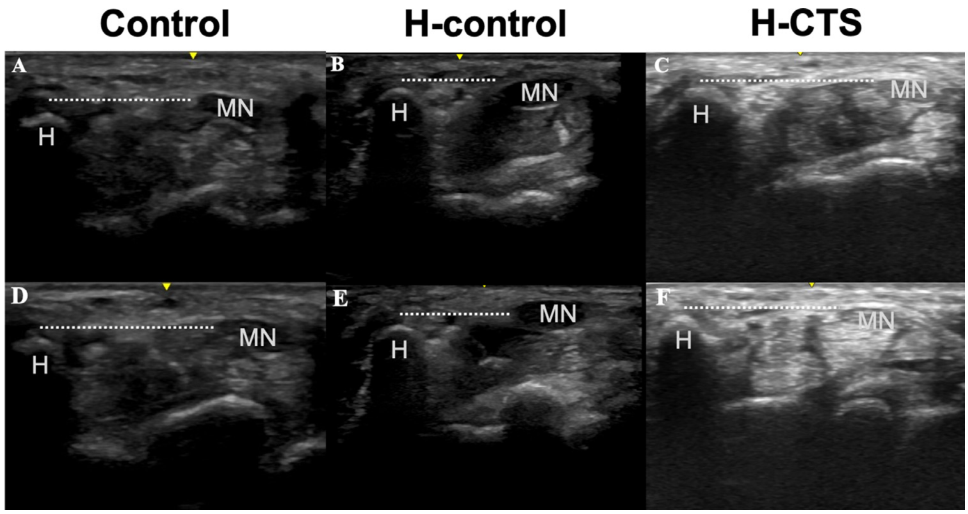

Fig 1 Ultrasonography evaluation of the distance between the tip of the hamate hook and the ulnar edge of the rMHD (A-C) and the gMHD (D-F) in control, H-Control, and H-CTS groups, respectively. The RMHD is defined as gMHD−rMHD/rMHD. Abbreviations: H, hamate hook; MN, median nerve.

mobility of the median nerve is defined as a ratio rather than an absolute value. The RMHD was defined as (gMHD − rMHD)/rMHD. All the US parameters (the CSA, FR, and RMHD) were measured twice, and the mean value was determined. To assess the interobserver reliability, the US examination was done on the same day by 2 operators who were blinded to the patients' clinical information. Half of the examinees (randomly chosen) received the second examination within 1 week after the first examination to assess intraobserver reliability. The inter- and intraobserver reliability were evaluated using the intraclass correlation coefficient (ICC).[25] The final figure of each US parameter was averaged from the measurements made by the 2 operators.

Statistical analysis

Mean values and SDs were calculated for the continuous variables. Differences in the CSA, FR, and demographic data were assessed using the analysis of variance test and the Scheffe test as the post hoc tests for the continuous variables, and the chi-square test was used for the categorical variables. For the difference in the RMHD, the Kruskal-Wallis H test and the Mann-Whitney *U* test were used as the post hoc tests because of the relatively small sample size. The receiver operating characteristic curves were used to evaluate the performance of the RMHD in the diagnosis of H-CTS, as well as to obtain the optimal cutoff value for determining H-CTS. To account for the small sample, we calculated the exact 95% CI using the Clopper-Pearson method[26] for sensitivity, specificity, and overall accuracy; *P* values <.05 were considered statistically significant. Data were analyzed using SAS ver. 9.4.[b]

Results

Demographic data

For the first aim, we enrolled 69 volunteers in the control group, 63 patients in the H-Control group, and 76 patients in the H-CTS group. None of the enrolled participants had a history of diabetes. There were no significant differences in age, sex, handedness, and history of hyperuricemia among the 3 groups (table 1). There were more patients with trigger digit and hypertension in both the H-Control and H-CTS groups than the control group. There were no significant between-group differences in duration of hemodialysis for the H-Control and H-CTS groups. After January 2020, the RMHD was examined in the enrolled patients: 20 volunteers in the control group, 30 patients in the H-Control group, and 38 patients in the H-CTS group. There were no significant differences in age, sex, and handedness among the 3 groups. The demographic data are shown in supplemental table S1 (available online only at

Table 1 Demographic data by study groups

	Control (n=69)	H-Control (n=63)	H-CTS (n=76)	*P* Value
Age (y), mean ± SD	57.9±9.4	57.7±7.7	60.0±8.8	.642
Duration of hemodialysis (y), mean ± SD	NA	4.6±2.5	4.8±2.5	.624
Sex (male/female), n	22/47	36/27	43/33	.292
Handedness (right/left), n	66/3	62/1	72/4	.515
Hypertension	19	37*	43†	.001
History of hyperuricemia	0	4	3	.163
Trigger digit	0	5*	9†	.016

The *P* value is based on the ANOVA for the global test of difference among the 3 study groups.
Abbreviations: Control, age-matched volunteers; H-CTS, patients under hemodialysis with carpal tunnel syndrome; NA, not applicable.
* Between-group differences for H-Control and control groups using the post hoc test.
† Between-group differences for H-CTS and control groups using the post hoc test.

http://www.archives-pmr.org/). In this study, all patients in the H-CTS group underwent carpal tunnel release surgery later, and their CTS symptoms all improved.

Interobserver agreement and intraobserver reliability

The ICCs for the interobserver agreement were 0.86 for CSA-I, 0.84 for CSA-O, 0.88 for FR-I, 0.87 for FR-O, 0.88 for rHMD, 0.86 for gMHD, and 0.83 for RMHD (supplemental table S2, available online only at http://www.archives-pmr.org/). The ICCs for intraobserver reliability are listed in supplementary table S2. All agreements and reliability on US parameters measurements were considered good.

Association of handedness and arteriovenous fistula with US parameters

Considering possible confounding factors such as handedness in all patients and arteriovenous fistula (AVF) in patients under hemodialysis, we evaluated the differences in the US parameters in the subgroups. There were no significant between-group differences in CSA-I, CSA-O, FR-I, and FR-O between dominant hands and nondominant hands for the control group and H-Control group (supplemental tables S3 and S4, available online only at http://www.archives-pmr.org/). In the H-Control group, there were no significant differences in CSA-I/-O and FR-I/-O between hands with and without AVFs (supplemental table S5, available online only at http://www.archives-pmr.org/). According to the findings, handedness and AVF have no association with either CSA-I/-O or FR-I/-O. Therefore, the data from right hands in the control group and H-Control group, and from the symptomatic hands in the H-CTS group were used for the further analyses.

US parameters

Compared with the control group, the CSA-I was significantly larger in the H-Control and H-CTS groups (10.0±1.6 and 10.1±1.5 mm^2, respectively, vs 8.9±1.4 mm^2, P<.001, both), and CSA-O was larger in the H-Control group (10.7±3.1 vs 9.0±1.8 mm^2, P=0.002). There was no significant difference in the FR-I/-O among the 3 groups. Between the H-Control and H-CTS groups, there were no significant differences in either the CSA-I/-O or the FR-I/-O (table 2).

Table 2 Ultrasonography parameters by study groups

Group	CSA-I (mm^2)	CSA-O (mm^2)	FR-I	FR-O
Control (n=69)	8.9±1.4	9.0±1.8	2.4±0.9	2.6±1.0
H-control (n=63)	10.0±1.6*	10.7±3.1*	2.7±1.0	2.8±0.9
H-CTS (n=76)	10.1±1.5†	10.4±3.0	2.8±1.0	2.7±0.9
P value	< .001	.001	.090	.738

NOTE. Values are presented as mean ± SD. The P value is based on the ANOVA for the global test of difference among the 3 study groups.
Abbreviations: Control, age-matched volunteers; H-CTS, patients under hemodialysis with carpal tunnel syndrome.
* Significant between-group differences in H-control and control groups using the post hoc test.
† Significant between-group differences in H-CTS and control groups using the post hoc test.

Table 3 Values for rMHD and gMHD positions and the RMHD in ultrasonography examination

Group	rMHD (mm)	gMHD (mm)	RMHD (%) (min~max) (gMHD−rMHD)/rMHD
Control (n=20)	19.3±1.1	20.0±1.2	3.5±2.3 (0.5~9.2)
H-control (n=30)	19.1±1.1	19.9±1.0	3.8±1.7 (1.0~8.2)
H-CTS (n=38)	19.7±1.2	19.7±1.2	0.1±2.2*,† (−5.8~3.4)
P value	.149	.361	<.001

NOTE. Values are presented as the mean ± SD. The P value is based on the Kruskal-Wallis H for the global test of difference among the 3 study groups.
Abbreviations: Control, age-matched volunteers; H-CTS, patients under hemodialysis with carpal tunnel syndrome.
* Significant between-group differences for the H-CTS and control groups using the post hoc test.
† Significant between-group differences for the H-CTS and H-Control groups using the post hoc test.

Ratio of median nerve-to-hamate hook distance

For rMHD and gMHD, there were no significant differences among 3 groups. The H-CTS group had significantly lower RMHD than that in the control and H-CTS groups (P<.001, as shown in table 3). The receiver operating characteristic curve and area under the curve are presented in fig 2. The area under the curve was estimated at 0.94 (95% CI, 0.90-0.99). A cutoff value for the RMHD<2.7% for diagnosing H-CTS yielded a specificity of 80.0% (95% CI, 61.4%-92.3%), a sensitivity of 94.7% (95% CI, 82.3%-99.4%), and an overall accuracy of 88.2% (95% CI, 78.1%-94.8%) in the diagnosis of H-CTS (table 4).

Discussion

The present study evaluated the US characteristics in patients with uremia with and without CTS and the accuracy of a US parameter, the RMHD, proposed as a diagnostic tool for H-CTS. Handedness and AVF showed no associations with various US parameters, including the CSA-I/-O and FR-I/-O. The CSA-I was significantly larger in patients with uremia (H-Control and H-CTS groups), independent of the presence of CTS. Additionally, there were no significant differences in the FR-I/-O among 3 groups. We noted that the RMHD was significantly lower in the H-CTS group than the H-Control and control groups, but there were no significant differences in the RMHD between the control group and the H-Control group. A cutoff value of the RMHD<2.7% yielded an overall accuracy of 88.2% in diagnosing H-CTS, with a good sensitivity of 94.7% and a good specificity of 80.0%

CTS has been reported in approximately 10% of patients receiving long-term hemodialysis,[9] which is a higher prevalence than that in general population,[27] where a lengthier duration of hemodialysis has been found to lead to a higher prevalence of CTS.[9,10] Because of coexisting uremic or diabetic neuropathy, the diagnosis of CTS using clinical information is sometimes difficult in patients undergoing hemodialysis.[11,12] To date, in spite of the need for special devices, a NCS is still regarded as the criterion standard in adjunctive tools to confirm a CTS diagnosis. However, a routine NCS cannot diagnose CTS in cases with concomitant neuropathy or severe CTS.[14] Therefore, other adjunctive tools for diagnosis of H-CTS would be helpful. Recently, US, which is a

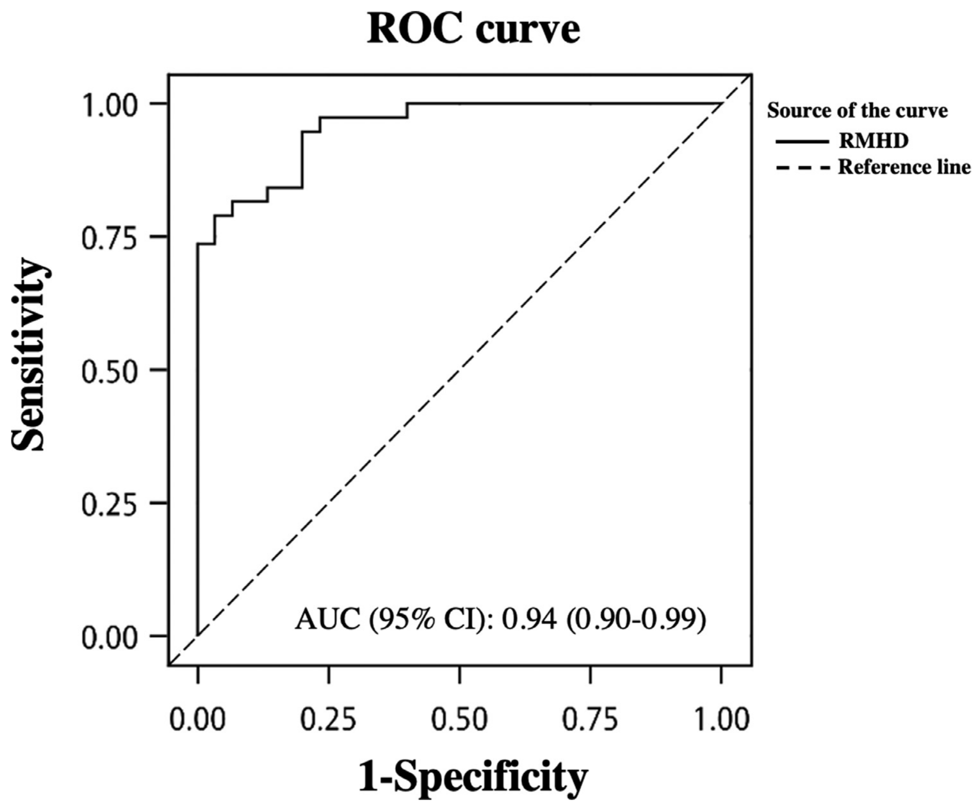

Fig 2 Receiver operating characteristic curve of the RMHD. 1. Cross-sectional area of median nerve has no diagnostic role in H-CTS. 2. RMHD was significantly less in patients without diabetes with H-CTS. 3. An RMHD cutoff value of <2.7% yielded an accuracy of 88.2% in H-CTS diagnosis without diabetes. Abbreviations: AUC, area under the curve; ROC, receiver operating characteristic.

painless, portable, and cost-effective examination, was proposed as the initial diagnostic test for CTS.[3] A CSA-I cutoff value of $\geq$10mm[2] in the median nerve is the most commonly used US parameter by which to diagnose CTS, with a sensitivity as high as 97.9% in the general population.[3] However, Ok et al[28] reported a significant difference in the CSA between dominant and nondominant hands in either right-handed or left-handed volunteers. Therefore, as our first step, we evaluated the effect of handedness and AVF on the US parameters. We found no significant differences in the CSA-I/-O or FR-I/-O between dominant and nondominant hands in either the control or H-Control group. The existence of AVF did not affect the 4 US parameters in the H-Control group. Carolus et al[29] also found there to be no significant difference in the CSA-I between right hands and left hands in patients with uremia without CTS and healthy volunteers without uremia.

Meanwhile, there is still no consensus about the US diagnostic criteria on H-CTS. Takahashi et al[12] found greater values in carpal tunnel width and palmar radiocarpal ligament thickness in patients with uremia with CTS history. Yamazaki et al[30] reported that the compression rate of the median nerve is significantly correlated with clinical symptoms, medical history, and serologic features associated with dialysis-related CTS. Xin et al[31] reported that both the CSA and the subcutaneous fat/median nerve strain ratio in an H-CTS group were higher than those in an H-Control. The measured CSA was the largest value in the carpal tunnel, usually slightly cranial to the pisiform. However, in our results, there were no significant differences in 4 US parameters, CSA-I/-O and FR-I/-O, between H-CTS and H-Control groups. The inconsistent results might result from dissimilarities in the duration of hemodialysis. Hemodialysis leads to an increased CSA of the median nerve both according to our results and a study by Carolus et al.[29] CSA of the median nerve is positively correlated with the duration of hemodialysis.[31] In a study by Xin[31] the duration of hemodialysis in the H-CTS group (7.9±3.9 years) was significantly longer than that in the H-Control group (6.6±2.7 years), and there were no significant differences in CSA between an H-CTS group undergoing $\leq$5-year hemodialysis and an H-Control group. In our study, there were no significant differences in the duration of hemodialysis between the H-CTS and H-Control groups.

Table 4 Diagnostic value of the RMHD

	No. of Cases (n=68)						
Cutoff Value (%)	FP	TN	TP	FN	Specificity (%)(95% CI)	Sensitivity (%)(95% CI)	Accuracy (%)(95% CI)
2.7	6	24	36	2	80.0 (61.4-92.3)	94.7 (82.3-99.4)	88.2 (78.1-94.8)

Abbreviations: FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Cumulative evidence showed that the longitudinal movement and the transverse sliding of the median nerve during wrist and finger motion were reduced in patients with CTS.[15-20] Either the longitudinal mobility[20] or the transverse sliding[15] had been reported negatively correlated with the grade of NCS in CTS. Thickening and fibrosis of the subsynovial connective tissue within the carpal tunnel is supposed as one of the possible reasons to hinder the motion of the median nerve.[15] The US parameter proposed in our study, the RMHD, is the similar concept to determine the individualized transverse sliding of the median nerve during finger motion using a static bony landmark, the hamate hook. The RMHD is easily assessed using B-mode US at the level of the carpal tunnel outlet. Our results showed that the RMHD was significantly lower in the H-CTS group than in the H-Control and control groups. There was no significant difference in the RMHD between the H-Control group and control groups. In other words, the RMHD did not appear to be affected by the hemodialysis status. Our findings correspond to the current concept that decreased transverse sliding of the median nerve in CTS. Despite the potential usefulness of the RMHD as an adjunctive tool in diagnosing H-CTS, further studies with more patients are needed to confirm the results.

Study limitations

There are some limitations in this study. First, in evaluating the accuracy of the RMHD, our study sample was limited in number after excluding patients with diabetes or other comorbidities, such as cervical radiculopathy and polyneuropathy. Although diabetes and diabetic polyneuropathy are common comorbidities of hemodialysis, CSA of the median nerve in patients with diabetes was found larger than those of controls without diabetes in a recent network meta-analysis.[32] The authors stated they are unaware whether US could be applied in diagnosis of entrapment neuropathy for patients with diabetes. On the other hand, there is still no consensus for the CSA cut point value in the diagnosis of CTS in patients with diabetes mellitus. Therefore, we excluded patients with the comorbidities that might be a confounding factor in the diagnosis. Despite the significant intergroup difference of interest in our study, a further study with a greater number of patients and subgroup analyses according to comorbidities is necessary to further clarify the role of the RMHD in the diagnosis of H-CTS with other comorbidities. Second, the US examination timing was not unified. It was done 1 day after hemodialysis in most patients when they visited the outpatient clinic. The CSA might be different before and after hemodialysis because of water distribution around the median nerve. However, in our pilot study (20 patients in H-control group), there are no significant differences in CSA-I/O, FR-I/O, and RMHD in the hands with AVFs before and after hemodialysis (data not shown).

Conclusions

The CSA-I was significantly greater in patients without diabetes undergoing hemodialysis (H-CTS and H-Control) than in the control group, independent of the presence of CTS. Neither the CSA-I/-O or the FR-I/-O had a role in the diagnosis of H-CTS. Additionally, an RMHD cutoff value <2.7% yielded a specificity of 80.0%, a sensitivity of 94.7%, and an overall accuracy of 88.2% in the diagnosis of H-CTS. Therefore, the RMHD maybe a useful US parameter in the diagnosis of CTS in patients without diabetes undergoing hemodialysis. A further study with a greater number of patients is necessary to confirm the role of RMHD.

Suppliers

a Logiq-e R7scanner; GE Healthcare, Madison, WI.
b SAS ver. 9.4; SAS Institute, NC.

Keywords

Carpal tunnel syndrome; Diagnosis; Rehabilitation; Renal dialysis; Ultrasonography

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