



# Does idiopathic carpal tunnel syndrome deteriorate proprioception of the hand? A case-control study

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Idiopathic carpal tunnel syndrome (CTS) is an entrapment neuropathy caused by median nerve compression at the wrist.<sup>[1]</sup> Eventually, it may slow the median nerve conduction velocity. Carpal tunnel syndrome accounts for nearly 90% of all entrapment neuropathies, and it is common between the ages of 40 and 60 years.<sup>[2]</sup> The vast majority of CTS cases have an unknown etiology. However, several risk factors have been shown to be associated with the disease including female sex, obesity, high body mass index (BMI), advanced age, and repetitive hand movements.<sup>[3]</sup>

In the early stages of CTS, there are complaints of pain, numbness, and tingling in the distribution regions of the median nerve due to the involvement of sensory nerve fibers.<sup>[4]</sup> In the following period, gradual loss of muscle strength and dexterity may occur due to the involvement of motor nerves as a result of increased compression.<sup>[4]</sup> These symptoms

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## ABSTRACT

**Objectives:** This study aims to investigate the deterioration in kinesthetic kinesthesia (KKS) and visual kinesthesia (VKS) of the hand as a component of proprioception in patients with idiopathic carpal tunnel syndrome (CTS).

**Patients and methods:** This study included a total of 90 hands of 60 patients (9 males, 51 females; mean age: 47.6±9.4 years; range, 28 to 60 years) who were diagnosed with CTS and 25 hands of 25 healthy individuals (8 males, 17 females; mean age: 42.6±14.4 years; range, 20 to 60 years) as the controls between January 2019 and January 2021. The KKS and VKS scores were compared between the groups. Clinical parameters such as pain levels, hand grip strength (HGS) values, and two-point discrimination (2PD) test scores were compared between the patients with and without KKS or VKS deficits. The association between the severity of electromyographic findings and KKS or VKS deficits was examined.

**Results:** The mean VKS score of the CTS group was 22.9±1.6 and the KKS score was 20.8±3.4, which was significantly lower than that of the control group (p=0.002 and p<0.001, respectively). The CTS patients performed less accurate repetitions in visually cued (60%) and kinesthetically cued (40%) positions than the control group (100% both). There were significantly more patients with VKS and KKS deficits in the moderate or severe CTS groups than in the mild CTS group (p<0.001 and p=0.007, respectively), and KKS or VKS deficits were significantly associated with the impaired HGS (p=0.042 and p=0.048, respectively) and functional status (p=0.020 and p=0.016, respectively) accompanied by the increased symptom severity (p=0.010 and p=0.002, respectively).

**Conclusion:** Our study results suggest that idiopathic CTS is associated with impaired proprioception and kinesthetic sense of the hand. In addition, idiopathic CTS is related to impaired hand function and severe symptoms. Screening kinesthetic sense in patients with idiopathic CTS prior to decompression surgery or postoperative hand therapy is helpful to set realistic goals and achieve superior clinical outcomes.

**Keywords:** Carpal tunnel syndrome, electromyography, kinesthetic sense, visual kinesthetic sense.

may adversely affect daily living activities and quality of life of individuals.<sup>[5]</sup>

Kinesthetic sensation is considered a component of proprioception, and is the sensation of limb position and perception of movement.<sup>[6,7]</sup> Kinesthetic sense consists of two components: kinesthetic kinesthesia (KKS) and visual kinesthesia (VKS).<sup>[8]</sup> Muscle spindles and skin-stretch receptors are the peripheral receptors of kinesthesia. In contrast, joint receptors do not seem to play a critical role, and new evidence suggests the involvement of both the cerebellum and parietal cortex.<sup>[9]</sup> Minns et al.<sup>[10]</sup> previously reported that deterioration of the kinesthetic sense of the hand might also cause loss of hand function. In addition, a previous study reported that kinesthetic sensory dysfunction affected hand skills in children with spina bifida.<sup>[11]</sup>

Previous studies have revealed an association between CTS and functional impairment;<sup>[12,13]</sup> however, the present study is the first to investigate the relationship between kinesthetic sense and functional status, clinical outcomes, and severity of electromyographic (EMG) findings in patients with idiopathic CTS. Since kinesthetic sensory tests are not a part of the CTS examination in current daily practice, there are insufficient data on the extent to which kinesthetic sense is affected in patients with CTS.

In the present study, we hypothesized that CTS was associated with impaired kinesthetic sense. The primary objective of this study was to investigate whether KKS or VKS was impaired in patients with CTS. This secondary objective was to examine the KKS or VKS deficit rates in patients with idiopathic CTS having different severity levels of pathological EMG findings.

## PATIENTS AND METHODS

This single-center, cross-sectional study was conducted at Orthopedics and Traumatology, and Neurology outpatient clinics between January 2019 and January 2021. A total of 90 hands of 60 patients (9 males, 51 females; mean age: 47.6±9.4 years; range, 28 to 60 years) who were diagnosed with CTS based on the physical examination and EMG findings. The patients were assigned into mild, moderate, and severe CTS groups according to the EMG results. These patients were assigned to groups according to the KKS or VKS deficit to compare clinical parameters, such as pain levels, hand grip strength (HGS) values, and two-point discrimination (2PD) test scores. In addition, a control group consisting of 25 age- and

sex-matched healthy volunteers (8 males, 17 females; mean age: 42.6±14.4 years; range, 20 to 60 years) was created. Exclusion criteria were diabetes mellitus, acute trauma or rheumatic disease, pregnancy, hypothyroidism or hyperthyroidism, treatment for CTS within a year, peripheral neuropathy or chronic renal failure, cervical radiculopathy, neurological or psychiatric disorders, alcoholism, history of hand or wrist surgery, and history of other conditions that may affect hand function such as Dupuytren's contracture.

## Outcomes

Demographic characteristics, BMI, duration of complaints, and hand dominance of all patients were recorded at the beginning of the study. The kinesthetic sense, HGS, pain level, and sensory examination of the involved hand were evaluated. In addition, the functional status and symptoms of the patients with idiopathic CTS were examined.

Demographic characteristics, BMI, and hand dominance of healthy volunteers were recorded. The kinesthetic sense and HGS along with sensory examination of the dominant hand in the voluntary group were assessed.

*Visual Analog Scale (VAS):* The patients in the CTS group for pain levels in the affected hand and ipsilateral wrist using the VAS score. The VAS scoring system requires patients to state their status on a line by drawing a line or making a dot or pointing (0-10 cm, with higher scores indicating more pain).<sup>[14]</sup>

*Grip strength:* A Jamar hand dynamometer (baseline hydraulic hand dynamometer; (Sammons Preston Rolyan, Bolingbrook, IL, USA) was used to assess HGS. The measurement was performed, while the patient was sitting, with the elbow placed on the table, shoulders adducted and in neutral rotation, elbow joint at 90° flexion, and forearm and wrist in the neutral position. The investigators noted the highest score in three consecutive trials.<sup>[15]</sup>

*Two-point discrimination test:* The Dellon Disk - Criminitor device (Sensory Management Services LLC, MD, USA) was used for the 2PD test. The investigators commenced the test with the patients' eyes closed, and longitudinally pricked the device with pressure on the second fingertip. They, then, determined the narrowest length at which the patient could distinguish the two touch points.<sup>[16]</sup>

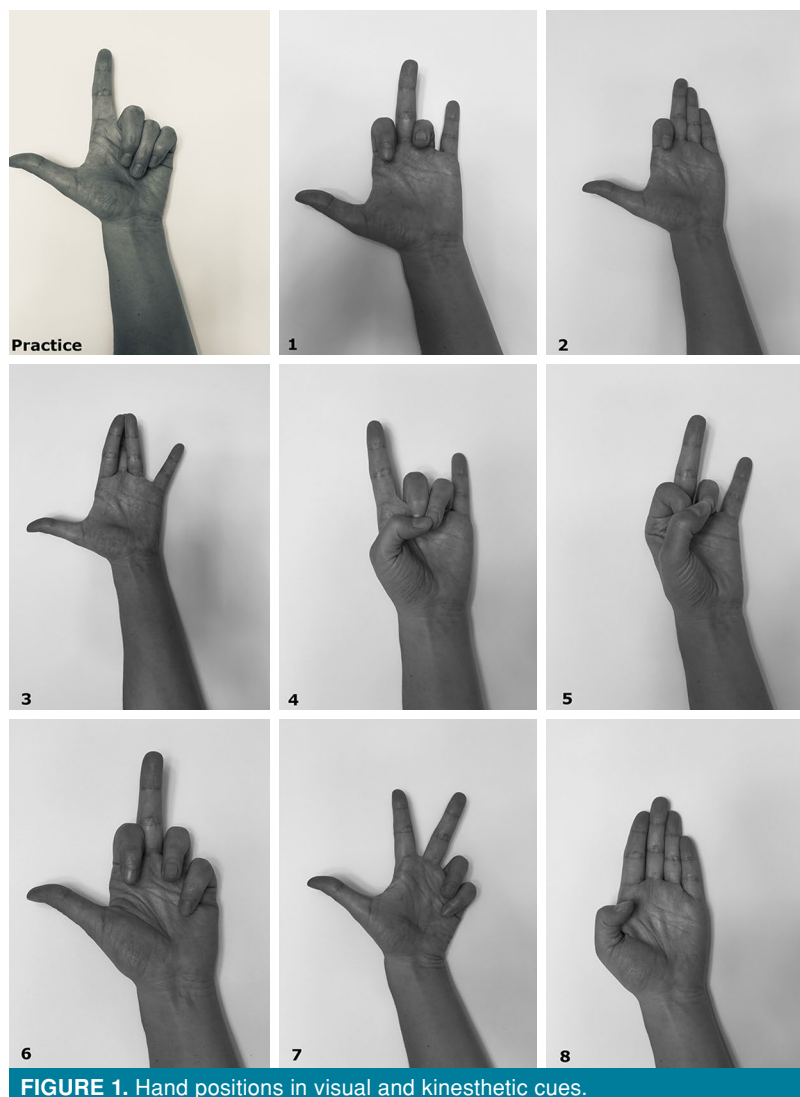
Symptom severity was assessed using the Boston Carpal Tunnel Questionnaire (BCTQ) Symptom Severity Scale (SSS), and hand function was assessed using the Functional Status Scale (FSS). The SSS is

a questionnaire specific to the disease that consists of two scales that assess symptom severity and functional capacity. The assessment was performed with 11 questions using a five-point Likert scale, and the patients scored the symptoms between "none and very severe." The scores range from 11 to 55, with higher scores indicating increased symptom severity. On the FSS, the patients answered eight questions about daily living activities requiring hand dexterity and chose their levels between "no difficulty to perform" and "unable to perform." The scores range from 8 to 49, with higher scores indicating greater impairment of hand function.<sup>[17]</sup>

Assessment of VKS and KKS tests: The participants' kinesthetic awareness level in their hands as the ability to copy different hand positions, as previously described by Grant and Watter<sup>[18]</sup> (Figure 1). The

test was performed using two different methods, by providing visual and kinesthetic cues. The VKS test requires visual perception, while the KKS test requires kinesthetic perception of the other hand as a control. Therefore, bilateral involvement of CTS could interfere with KKS test results. By virtue of this, this study evaluated both bilateral and unilateral idiopathic CTS in patients with VKS, but KKS was evaluated only in patients with unilateral CTS.

In visual cues, the participant's hand to be tested was positioned with the help of a masking plate, so that the patient could not see it. The physician, then, visually presented eight different hand positions, and the patient was asked to copy these figures with his or her hand to be assessed (Figure 1). In the kinesthetic assessment, the physician places the patient's hands behind an obstacle out of sight. The physician, then,



**FIGURE 1.** Hand positions in visual and kinesthetic cues.

passively positions one hand of the participant according to the test scheme, and asks the participant to copy it with the other hand (Figure 1). Each cue was scored between one and three points for accuracy. The physician reported the final score as the mean replication accuracy for all eight test positions or the percentage of kinesthetic sense lost.<sup>[11,19]</sup>

**Neurophysiological assessment:** The same neurologist assessed the participants using a Medelec Synergy 10 channel ENMG (Oxford Instruments, Oxford, UK) to diagnose CTS. The conditions such as the median nerve peak sensory conduction velocity slower than 41.25 m/sec recorded from the second finger, mixed nerve peak sensory conduction velocity slower than 34 m/sec recorded from the wrist-palm segment, stimulation of the median nerve from the wrist segment of 5 cm recorded from the abductor pollicis brevis in the motor conduction test, and/or the distal motor latency faster than 3.6 ms were considered diagnostic for CTS. The condition of normal compound sensory action potential amplitude in the median nerve sensory test, mixed conduction tests, and slow conduction velocity was assessed as mild CTS. When prolonged distal motor latency of the median nerve was added to these findings, the patient was considered to have moderate CTS. The inability to detect compound sensory action potentials in sensory conduction tests and/or detection of a decrease in the amplitude and/or presence of a decrease in the compound muscle action potential amplitude in the motor conduction

test was considered severe CTS. According to the EMG assessment, the patients were assigned into three groups: mild, moderate, and severe.<sup>[20]</sup>

### Statistical analysis

Statistical analysis was performed using IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed in mean  $\pm$  standard deviation (SD), while categorical variables were expressed in number and frequency. Normality tests of the numerical variables were performed using the Shapiro-Wilk test. An independent t-test in the analysis of numerical data showing normal distribution and Mann-Whitney U test in the analysis of numerical data not showing normal distribution were used. The chi-square test was used to compare the differences between categorical variables. A  $p$  value of  $<0.05$  was considered statistically significant.

## RESULTS

The study group included 90 hands of 60 patients with CTS (30 bilateral and 30 unilateral). The baseline characteristics of the study participants are presented in Table I.

An overall comparison between the CTS and control groups showed that the CTS group had significantly lower mean VKS ( $p=0.002$ ) and KKS ( $p<0.001$ ) scores (Table II).

The number of participants who succeeded in performing complete and accurate repetitions for

**TABLE I**  
Baseline characteristics of the participants

Variables	CTS group (n=60)		(Healthy group n=25)		$p$
	n	Mean $\pm$ SD	n	Mean $\pm$ SD	
Number of hands	90		25		-
Age (year)		47.6 $\pm$ 9.4		42.6 $\pm$ 14.4	0.06
Sex					
Female	51		17		0.134
Body mass index (kg/cm <sup>2</sup> )		29.3 $\pm$ 4.2		27.2 $\pm$ 5.5	0.06
Hand dominance (right)	55		21		0.439
Duration of complaints (month)		19.6 $\pm$ 27.8		-	-
Visual Analog Scale (cm)		3.9 $\pm$ 2.3		0.0 $\pm$ 0.0	<0.01
Hand grip strength (kg)		18.4 $\pm$ 6.4		33.3 $\pm$ 10.8	<0.01
Two-point discrimination		3.7 $\pm$ 1.8		1.6 $\pm$ 0.7	<0.01
Boston SSS		21.8 $\pm$ 8.6		11.0 $\pm$ 0.0	<0.01
Boston FSS		16.2 $\pm$ 7.9		8.0 $\pm$ 0.0	<0.01

CTS: Carpal tunnel syndrome; SD: Standard deviation; FSS: Functional status scale; SSS: Symptom severity scale;  $P<0.01$ , statistically significant.

**TABLE II**  
Comparison of visual and kinesthetic kinesthesia scores between CTS patients and healthy controls

	CTS group	Healthy group	<i>p</i>
	Mean±SD	Mean±SD	
Mean VKS Score (n=90 hands for CTS, n=25 hands for healthy group)	22.9±1.6	24±0	0.002
Mean KKS Score (n=30 hands for CTS, n=25 hands for healthy group)	20.8±3.4	24±0	<0.001

CTS: Carpal tunnel syndrome; SD: Standard deviation; VKS: Visual kinesthesia; KKS: Kinesthetic kinesthesia; P<0.05 statistically significant.

each test position (Grade 3 accuracy score) is shown in Table III. Patients with CTS performed less accurately (60%) than healthy subjects (100%) in the visually cued positions. Compared to the control group, a smaller proportion of CTS patients (40%) achieved accurate replication with kinesthetically cued positions (Table III).

According to EMG findings, the patients were assigned into three groups: mild, moderate, or severe CTS and the number of patients with VKS or KKS was compared. The results showed a significantly increased number of patients with VKS deficits in the moderate or severe groups compared to the

mild group. Similarly, the moderate CTS group had significantly more patients with KKS deficits than the mild CTS group (Table IV).

The patients were also divided into a visual kinesthetic sensory loss (VKSL) (+)/(-) or KKS sense loss (KKSL) (+)/(-) group based on KKS or VKS deficits. Subsequently, the VAS, 2PD, Boston FSS, Boston SSS scores, and HGS (kg) were compared as the clinical outcome measures. The HGS was significantly lower in the VKSL (+) group than in the VKSL (-) group ( $p=0.042$ ). The Boston SSS ( $p=0.010$ ) and Boston FSS scores ( $p=0.020$ ) were significantly higher in the VKSL (+) group. A comparison of other

**TABLE III**  
Number of participants attaining Grade 3 accuracy score for each test position

	1	2	3	4	5	6	7	8
Visual Kinesthesia Score								
CTS patients (90 hands)	66	85	71	88	77	69	89	89
Healthy patients (25 hands)	25	25	25	25	25	25	25	25
Kinesthetic Kinesthesia Score								
CTS patients (30 hands)	14	23	17	24	18	17	28	28
Healthy patients (25 hands)	25	25	25	25	25	25	25	25

CTS: Carpal tunnel syndrome.

**TABLE IV**  
Visual and Kinesthetic sensory loss ratio between the CTS groups

	Mild CTS (n=44)		Moderate CTS (n=37)		Severe CTS (n=9)	
	n	%	n	%	n	%
Visual sense loss						
Yes	8 <sup>a</sup>	18.2	21 <sup>a</sup>	56.8	7 <sup>b</sup>	77.8
No	36	81.8	16	43.2	2	22.2
Kinesthetic sense loss						
Yes	8 <sup>c</sup>	18.2	9 <sup>c</sup>	24.3	1	11.1
No	36	81.8	28	75.7	8	88.9

CTS: Carpal tunnel syndrome; a: Significant difference between mild and moderate groups in terms of visual sensory loss; b: Significant difference between mild and severe groups in terms of visual sensory loss; c: Significant difference between the mild and moderate groups in terms of kinesthetic sensory loss. Statistical significance was set at  $p<0.05$ .

**TABLE V**  
Comparison of clinical parameters between visual kinesthetic sensory loss (VKSL) (+)/(-) and kinesthetic kinesthesia sensory loss (KKSL) (+)/(-) groups

	VKSL (+)	VKSL (-)	<i>p</i>	KKSL (+)	KKSL (-)	<i>p</i>
	Mean±SD	Mean±SD		Mean±SD	Mean±SD	
Visual Analog Scale (cm)	4.7±2.6	3.9±2.5	0.119	4.7±2.3	3.0±0.9	0.021
Hand grip strength (kg)	16.8±7.9	19.7±5.6	0.042	16.9±7.01	21.5±3.7	0.048
Two-point discrimination	4.3±1.5	3.6±1.7	0.061	4.4±1.8	2.7±1.9	0.013
Boston-SSS	25.4±8.7	20.5±8.2	0.010	25.7±7.8	17.0±5.3	0.002
Boston-FSS	18.9±7.7	14.9±7.8	0.020	18.4±8.3	11.8±4.3	0.016

SD: Standard deviation; SSS: Symptom severity scale; FSS: Functional status scale; P<0.01, statistically significant.

parameters between the VKSL (+) and VKSL (-) groups did not show significant differences. However, the HGS values were significantly lower in the KKSL (+) group ( $p=0.050$ ), while the other parameters such as 2PD ( $p=0.013$ ), Boston SSS ( $p=0.002$ ), Boston FSS ( $p=0.016$ ) and VAS ( $p=0.021$ ) were significantly higher than those the KKSL (-) group (Table V).

## DISCUSSION

This case-control study investigated the association between idiopathic CTS and impaired proprioception (VKS and KKS) of the hand. We determined whether the severity of EMG findings, HGS, 2PD, Boston FSS and SSS scores in CTS were associated with a deficit in VKS or KKS. The patients with CTS had significantly lower VKS and KKS scores than healthy individuals. A lower percentage of patients with idiopathic CTS could accurately repeat 16 kinesthetic and visual sensory assessment positions and cue combinations. There were significantly more patients with VKS and KKS deficits in the moderate or severe CTS groups than in the mild CTS group. In addition, deficits in KKS and VKS were significantly associated with decreased HGS values, impaired functional status, and increased symptom severity.

Patients with CTS often have difficulty in performing activities requiring hand skills such as writing, moving small objects, carrying shopping bags, or performing other activities of daily living that involve these skills. Therefore, patients' quality of life may also be adversely affected by CTS.<sup>[21-23]</sup> Previous studies have reported that patients with CTS have sensory disorders such as pain, tingling, and paresthesia, as well as impaired proprioception and kinesthetic awareness.<sup>[24]</sup> Proprioception is a component of the sensorimotor system, and proprioceptive information is required for neuromuscular control.<sup>[7,25]</sup> Previous studies

have shown that the absence or impairment of proprioception can adversely affect patients with neurological and musculoskeletal disorders in hand therapy settings.<sup>[7]</sup> Visual feedback is also required to control manual prehension.<sup>[26]</sup> This study suggests that the VKS and KKS, both of which are considered components of proprioception, are significantly impaired in CTS, particularly in later stages of the disease with more advanced pathological EMG findings. We consider it efficient to evaluate the kinesthetic sense (VKS and KKS) prior to decompression surgery or hand therapy setting to adjust to more realistic goals for both therapists and patients, as any impairment would impact proprioception and associated neuromuscular control during the rehabilitation phase.

A previous study showed that children with myelomeningocele (MMC) have worse hand function than healthy children of the same age and sex.<sup>[11]</sup> Hwang et al.<sup>[11]</sup> compared a group of healthy children aged 6 to 12 with children with MMC of similar age. They reported that decreased kinesthetic awareness led to impaired hand function. Several studies have reported that sensory disorders, kinesthetic sensory dysfunction, and tonus disorders can negatively affect hand skills in patients with spina bifida.<sup>[10]</sup> A comprehensive literature review revealed some studies evaluating hand function and proprioception in patients with CTS,<sup>[22-24]</sup> however, no studies have investigated the kinesthetic sense of the affected hand in patients with CTS. This study suggests that patients with idiopathic CTS have significantly lower VKS and KKS scores than those without idiopathic CTS. In addition, the results showed that patients with CTS performed less accurately (60%) than the control group (100%) in visually-cued positions. Likewise, a smaller proportion of CTS patients (40%) achieved complete and accurate replication in the

kinesthetic cued positions than in the control group (100%).

Previous studies have demonstrated that even if there is no significant impairment in motor function, sensitive grip performance can be adversely affected by considerable levels of sensory deficit in patients with CTS.<sup>[27]</sup> A hand dynamometer can easily measure HGS to determine the motor status of the upper extremities.<sup>[28]</sup> This study suggests that HGS is significantly reduced in CTS patients with VKS or KKS deficits compared to that in patients without deficiency, resulting in that a continuum of properly functioning sensorimotor feedback is critical for maintaining effective hand grip function and strength.<sup>[29]</sup>

Although not regarded as a universal symptom of CTS, clinicians consider it noteworthy when pain is present, and a significant relationship between pain sensation and proprioception has been previously reported.<sup>[30,31]</sup> Studies evaluating kinesthesia have shown that the primary nerve fibers of muscle spindles may be affected by pain, as these receptors also play an essential role in kinesthetic sensory perception.<sup>[32]</sup> This study suggests a significantly higher mean VAS score in CTS patients with loss of kinesthetic sense than in those without any deficit and, this finding, consistent with the current literature, suggests that pain tends to increase, when kinesthetic sense, as part of proprioception, is impaired.<sup>[29]</sup>

The 2PD test is convenient and widely used to evaluate cutaneous innervation and central somatosensory function.<sup>[16]</sup> Previous studies assessing sensory function have reported that the 2PD test can identify patients with severe and mild CTS.<sup>[5]</sup> While deterioration of 2PD is not present during early-stage CTS, it is common in the advanced phase.<sup>[5]</sup> Wolny et al.<sup>[24]</sup> reported that 2PD was associated with fine motor skills of the hand and that the 2PD test could also measure proprioceptive function. This study showed that the 2PD scores of CTS patients with kinesthetic sensory deficiency were also significantly impaired, indicating that both the 2PD and kinesthetic sensory tests can consistently confirm impaired proprioception in patients with idiopathic CTS.

In addition to conventional assessment methods for entrapment neuropathies, patient-reported outcome measures (PROMs) are also used as assessment tools.<sup>[31]</sup> The Boston questionnaire is a PROM explicitly developed to investigate the functional status and disability in patients with CTS.<sup>[17]</sup> This study reported that the Boston-FSS and Boston SSS scores, both subscales of the Boston

questionnaire, were significantly higher in CTS patients having visual and kinesthetic sensory deficits. In this study, the loss of visual or kinesthetic sense negatively affected upper extremity function and caused patients to participate less in activities while increasing the severity of symptoms.

Numerous studies have investigated the association between clinical and EMG findings in CTS.<sup>[31]</sup> In routine practice, patients with mild or moderate CTS are usually treated with medical therapy, whereas decompression surgery is preferred in patients with severe CTS.<sup>[5]</sup> However, no previous study has investigated the relationship between kinesthetic or visual sensory deficits in the hand and severity of EMG findings, yet. This study also classified the patients with CTS according to the severity of their EMG findings. The percentage of patients with KKS or VKS deficits tended to increase in patient groups with more advanced EMG findings of CTS. These results suggest that advanced CTS is associated with increased kinesthetic or visual sensory deficits and impaired hand proprioception.

Nonetheless, this study has some limitations. This is a single-center, cross-sectional study and the study group may not represent the entire population of patients with idiopathic CTS. Moreover, we did not conduct a power analysis before commencing the study and were unable to investigate the causality effect of parameters associated with severity or prognosis. In addition, this study did not include a quantitative assessment of pain, 2PD, or kinesthetic measurement. However, it is the first to examine the relationship between proprioception (kinesthetic and visual sense) of the hand and other clinical parameters such as functional status, clinical outcomes, and severity of EMG findings in patients with CTS.

Proprioceptive training achieved the most remarkable improvement in sensorimotor control as part of therapeutic and preventive rehabilitation interventions. Practical and easy-to-apply clinical assessment tools are essential for patients with CTS to accurately determine hand function and help them perceive difficulties in daily life, eventually planning a convenient and effective treatment program. However, kinesthetic or proprioceptive assessments have been neglected in CTS; therefore, this study attempted to investigate both the kinesthetic and visual components of proprioceptive sense in patients with CTS. The study results suggest that patients with idiopathic CTS have significantly deteriorated kinesthetic and visual sensory components of proprioception compared to healthy individuals. In addition, KKS and VKS deficits are significantly

associated with decreased HGS and functional status along with increased symptom severity.

In conclusion, our study results show that deteriorated kinesthetic sense in patients with CTS is associated with impaired hand function and symptom severity. We believe that assessing kinesthetic sense (both kinesthetic and visual sensory subscales) in CTS patients before a hand therapy setting would contribute to setting more realistic goals for both surgeons, therapists, and patients. In addition, these results would be useful to increase awareness regarding the need for the implementation of more personalized rehabilitation programs for idiopathic CTS patients with deteriorated KKS or VKS.

**Ethics Committee Approval:** The study protocol was approved by the Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (date: 07.09.2018, no: 2018\197). The study was conducted in accordance with the principles of the Declaration of Helsinki.

**Patient Consent for Publication:** A written informed consent was obtained from each patient.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Author Contributions:** Provided input into the concept and design of the study, and provided the materials: M.Y., C.K.T.; Collected and assembled the data: M.Y., C.K.T.; Analyzed the data: M.Y., C.K.Y.; Carried out literature review: M.Y.; Wrote the article: M.Y.; All authors have critically revised the article, read and approved the final version at the time of submission.

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