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Ultrasonography as A diagnostic Tool for Clinically Manifested Carpal Tunnel Syndrome with Normal Nerve Conduction Study

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Abstract

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Background: Carpal Tunnel Syndrome [CTS] is a prevalent condition characterized by median nerve compression at the wrist, leading to various neurological symptoms. In this study we evaluate the diagnostic accuracy of neuromuscular ultrasound in patients with clinically suspected CTS but normal nerve conduction studies [NCS].

Objective: This study aimed to evaluate the diagnostic accuracy of neuromuscular ultrasound in patients with clinically suspected CTS but normal nerve conduction studies [NCS]. Additionally, investigate the role of serum vitamin D levels in CTS and their association with symptom severity for early diagnosis and improved management.

Methods: A cross-sectional case control study was conducted involving 80 participants, divided into a patient group [n=40] with clinically suspected CTS and a control group [n=40]. Participants were recruited from the neurology, rheumatology and rehabilitation departments of Al-Zahraa University Hospital between November 2023 and July 2024. Comprehensive evaluations included nerve conduction study, ultrasonography of median nerve especially median nerve cross sectional area [MN-CSA], wrist forearm ratio, flattening ratio &bowing of flexor retinaculum, and laboratory investigations, including serum 25-hydroxy vitamin D levels.

Results: Neuromuscular ultrasound demonstrated significant differences in ultrasound parameters between patient and control group especially wrist forearm ratio which is the most specific and sensitive parameter. Also, there are significant differences in other ultrasound parameters such as MN CSA and flattening ratio. A positive correlation was found between median nerve cross-sectional area [CSA] at the wrist and disease duration [$p < 0.05$]. In addition, the study revealed a significant difference in serum 25-hydroxy vitamin D levels between the patient group and the control group with a p-value of <0.001. A negative correlation was observed between serum vitamin D levels and both wrist-forearm ratio and flattening ratio at the mid-carpal tunnel [$p < 0.05$].

Conclusion: This study highlights the value of neuromuscular ultrasound for diagnosing carpal tunnel syndrome [CTS], even when nerve conduction studies are normal. It also reveals potential links between vitamin D levels and symptom severity.

Keywords: Carpal Tunnel Syndrome; Nerve Conduction Studies; Ultrasound; Neurophysiology.

INTRODUCTION

Carpal tunnel syndrome [CTS] occurs when the median nerve is compressed within the carpal tunnel of the wrist [1]. This condition affects approximately 4.0-5.0% of the global population, with a higher prevalence in women than men. In addition, the most affected age group for CTS is between 20 and 40 years old, with significantly lower prevalence in individuals under 20 [2].

Risk factors for CTS include obesity, repetitive wrist motions [3], pregnancy, genetic predisposition, diabetes, hypothyroidism, and rheumatoid inflammation [4]. Vitamin D may play a protective role in CTS by regulating cellular processes, nerve growth, and reducing oxidative stress and inflammation and its deficiency may contribute to the development and severity of CTS [5].

The condition is characterized by hand pain, numbness, and tingling in the median nerve distribution, often affecting the thumb, index, middle, and radial side of the ring finger. [6]. Chronic CTS may also result in muscle atrophy at the base of the thumb, leading to decrease hand grip and strength [7].

Electrodiagnostic testing [EDX] is valuable in clarifying unclear diagnoses and differentiating CTS from confounding neurological conditions like radiculopathy or polyneuropathy. While EDX can quantify disease severity, its invasiveness and potential for false-negative results have led to a search for less invasive diagnostic alternatives [2]. Additionally, EDX provides physiological information about nerve conduction and axon loss but lacks anatomical details regarding the underlying cause. These limitations have prompted a growing interest in exploring other diagnostic methods for CTS patients [8]. Ultrasound of the wrists is a promising technique for detecting abnormalities in the median nerve and related structures in individuals with CTS. Increased nerve cross-sectional area, intraneural echogenic signal changes, vascularity, or abnormalities in flexor tenosynovitis or the carpal ligament are significant ultrasound findings [9].

In this study, we aim to evaluate the diagnostic accuracy of neuromuscular ultrasound in patients with clinically suspected CTS but normal nerve conduction studies [NCS]. Additionally, investigate the role of serum vitamin D levels in CTS and their association with symptom severity for early diagnosis and improved management.

PATIENTS AND METHODS

Study Design: This study was a cross-sectional case control study of patients with clinically suspected CTS and normal NCS and a control group of healthy individuals.

Participants: During a period from November 2023 to July 2024, all patients with a clinical doubt of CTS referred from neurology, rheumatology & rehabilitation departments of Al Zahraa University Hospital. Forty of these patients have normal NCS finding and enrolled in our study **[Group 1]**

Group 2: control group, 40 healthy participants, age and gender matched with patient group.

Inclusion Criteria: Participants aged 20 to 50, diagnosed with carpal tunnel syndrome based on the American Academy of Neurology diagnostic criteria [AANEM] and have normal nerve conduction studies.

Exclusion Criteria: Individuals with diabetes, hypo-thyroidism, or rheumatoid arthritis are excluded. Those with a history of wrist trauma, fracture, intra-articular lesions like ganglion, or a bifid median nerve are also excluded. Additionally, patients who have received local corticosteroid injections for carpal tunnel syndrome within the past six months or undergone previous carpal tunnel release surgery are not included. Finally, participants with clinical carpal tunnel syndrome confirmed by nerve conduction studies are excluded.

Methodology: All participants underwent a detailed evaluation, including history taking, physical examination, neurological assessment, provocative tests for CTS [Phalen's and compression tests], and discriminatory tests for radiculopathy [Spurling's test]. Laboratory investigations included routine blood work, HbA1c, thyroid profile, and serum 25-hydroxyvitamin D. Electrodiagnostic studies were conducted using a Neuropack NCS machine according to AANEM guidelines. Ultrasound assessment was performed using a linear array 7-11 MHz transducer [Xario200, Toshiba ultrasound machine, Japan].

EDX approach included: [EDX] approach encompassed motor conduction studies [MCS], F-responses and sensory conduction studies [SCS] of the median nerve in the affected arm in comparison to other side, MCS, SCS, and F-waves of the ulnar nerve, median-ulnar sensory studies to the ring finger, and median sensory palmer stimulation [palmer/wrist sensory nerve action potential ratio].

Ultra-sonographic Evaluation: All subjects were examined using a commercially available linear array 7-11 MHz transducer [Xario200, Toshiba ultrasound machine, Japan]. Participants were seated with the forearm resting on a table, wrist supinated, and fingers extended. Transverse images were obtained at the proximal carpal tunnel inlet, defined as the area between the pisiform and scaphoid tubercle. Median Nerve were identified as rounded hypoechoic structures with hyperechoic dots in the center of the screen deep to flexor retinaculum with the underlying tendons of flexor digitorum superficialis [FDS], flexor digitorum profundus [FDP] and flexor pollices longus [FPL] below. The transducer was maintained perpendicular to the nerve to avoid anisotropic artifacts. Minimal pressure was applied to the transducer to avoid tissue compression in the carpal tunnel.

Ultrasound Approach: Median nerve cross-sectional area [MN-CSA] was measured at the distal wrist crease then sweep the probe from the wrist toward the forearm & note the median nerve moves slightly radially and then deep to lie in the fascial plane between [FDS] and [FDP] and at a location 12 cm proximal to distal wrist crease measure MN-CSA. The wrist-to-forearm ratio was calculated using these measurements. Flattening at the wrist crease was determined by dividing maximal nerve width by maximal height. Bowing of the flexor retinaculum was measured by identifying bony landmarks,

drawing a line between them, and then measuring a perpendicular line to the flexor retinaculum.

Statistical analysis: Data analysis was conducted using SPSS version 26.0. Quantitative data were presented as mean± standard deviation and ranges for normally distributed variables, while non-normally distributed variables were presented as median with interquartile range [IQR]. Qualitative variables were presented as numbers and percentages. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess data normality. Statistical tests employed included independent-samples t-tests for comparing means, chi-square tests and Fisher's exact tests for comparing groups with qualitative data [Fisher's exact test used when expected counts were less than 5], Pearson's correlation coefficients [*r*] for assessing associations between variables, scatter plots for visualizing correlations, and receiver operating characteristic [ROC] curve analysis for determining predictive power and identifying optimal cut-off values. Sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], and accuracy were calculated. A 95.0% confidence interval and a 5.0% margin of error were set. P-values were considered significant if less than 0.05 [significant] or 0.001 [highly significant], and insignificant if greater than 0.05.

RESULTS

The study compared the baseline characteristics, disease duration, and serum 25-hydroxyvitamin D levels between group1 [n=40] and group 2 [n=40]. Both groups were similar in terms of age, sex, and BMI, as demonstrated by non-significant differences between the groups [p>0.05]. However, a significant difference was observed in serum 25-hydroxyvitamin D levels, with the patient group exhibiting lower levels compared to the control group [p<0.001] **[Table 1].**

A significant difference was observed in the median nerve cross-sectional area [CSA] at the wrist, wrist-forearm ratio, and flattening ratio at the mid-carpal tunnel, with the patient group exhibiting higher values compared to the control group [p<0.05] **[Table 2].**

Receiver operating characteristics [ROC] curve was performed for median nerve CSA at wrist [at carpal tunnel] [MM2] and demonstrated an area under the curve of 0.845 [0.739-0.951] with P value <0.001. The best cut off value for discrimination patients and control group was >9.5 with sensitivity 90.0% and specificity 91.0% **[Figures 1, 2].**

Additionally, flattening ratio at the mid-carpal tunnel demonstrated a significant area under the curve [AUC] of 0.878 [95.0% CI: 0.787-0.968, P < 0.001]. The optimal cut-off value for discriminating between patients and controls was >3, yielding a sensitivity of 85.0% and a specificity of 92.5% **[Figure 3].** In contrast, bowing of the flexor retinaculum showed a non-significant AUC of 0.28 [95.0% CI: 0.26-0.32, P = 0.218]. The best cut-off value for this measure was >3.9, but with a low sensitivity of 30.0% and specificity of 25.0% **[Figure 4].**

Table [1]: Baseline Characteristics, Disease Duration, and Serum 25-Hydroxy Vitamin D Levels in Patient and Control Groups

Variable		Patients Group1] [n=40]	Control Group2] [n=40]	Test Value	p-value
Age [years]	**Mean ± SD** **Range**	33.25 ± 9.63 20-50	34.03 ± 9.25 20-50	-0.367	0.715
Sex	**Female, [n %]** **Male, n [%]**	34 [85.0%] 6 [15.0%]	32 [80.0%] 8 [20.0%]	0.346	0.556
BMI [kg/m²]	**Mean ± SD** **Range**	28.58 ± 4.52 18-37	27.25 ± 5.20 19-35	1.216	0.228
Disease Duration [months]	**Mean ± SD**	7.25 ± 3.22	-	-	-
	Range	1-11	-		
Serum 25 hydroxy Vit.D [ng/ml]	**Mean ± SD** **Range**	12.57 ± 3.21 7-18	24.02 ± 3.07 20-28	5.682	0.001

Using: t-Independent Sample t-test for Mean±SD; Using: x2: Chi-square test for Number [%] or Fisher's exact test, when appropriate; NS: Non-significant; S: Significant; HS: Highly significant

Table [2]: Comparison between Patients Group and Control Group according to Ultrasound parameters of median nerve.

Ultrasound of median nerve		Patients [Group1]	Control [Group2]	Test value	p-value	Sig.
Median nerve CSA at wrist [at carpal tunnel] [MM2]	**Mean±SD** **Range**	10.88±0.94 9-12.9	8.02±0.61 7-8.9	16.137	0.001	HS
Wrist forearm ratio	**Mean±SD** **Range**	1.91±0.29 1.4-2.58	1.20±0.12 1-1.4	9.124	0.001	HS
Flattening ratio at mid carpal tunnel	**Mean±SD** **Range**	3.21±0.41 2.5-3.9	1.85±0.13 1.5-2	2.219	0.027	S
Bowing of flexor retinaculum	**Mean±SD** **Range**	4.13±1.00 2.7-6.5	3.82±0.17 3-4	1.834	0.072	NS

Using: t-Independent Sample t-test for Mean±SD; NS: Non-significant; S: Significant; HS: Highly significant

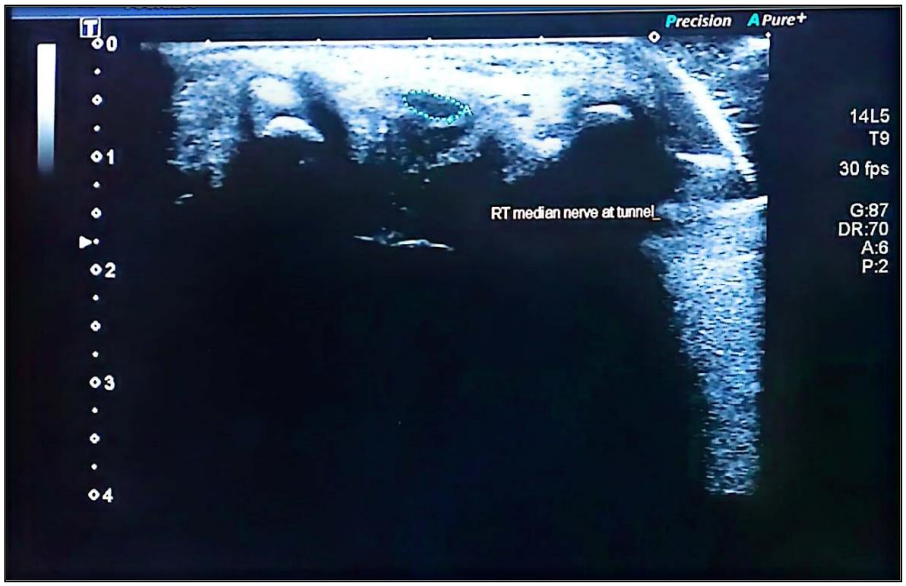

Figure [1]: Median nerve cross sectional area at wrist.

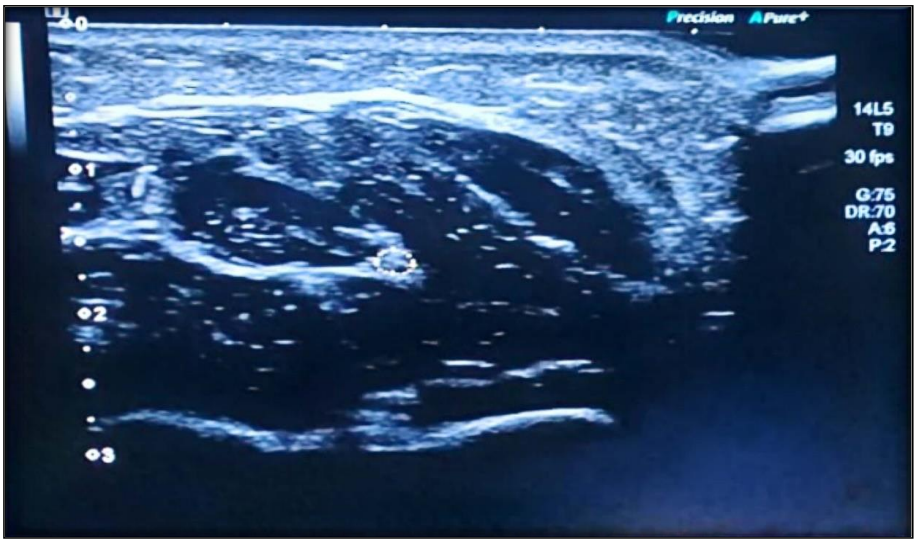

Figure [2]: Median nerve cross sectional area 12 cm proximal in forearm

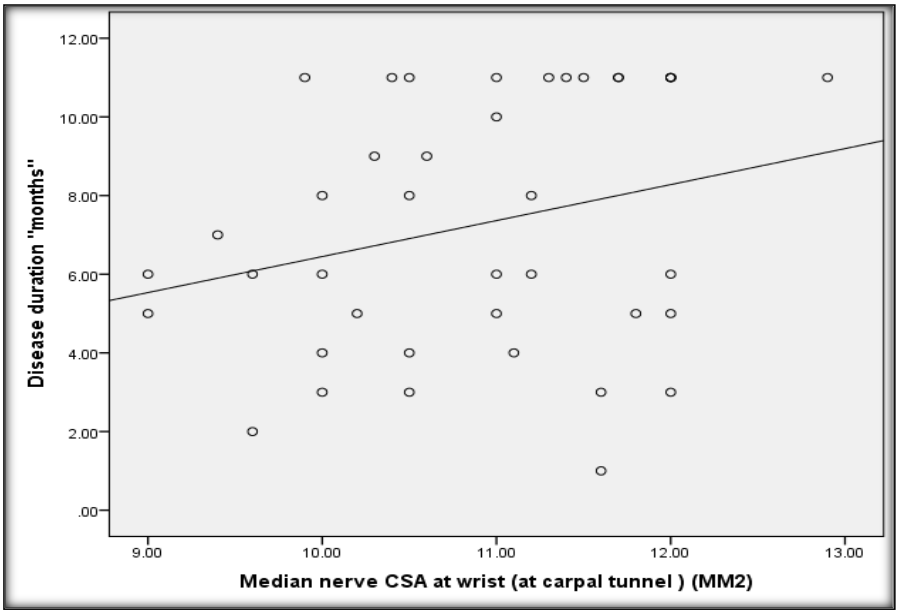

Figure [3]: Scatter plot between Median nerve CSA at wrist [at carpal tunnel] [MM2] and Disease duration "months".

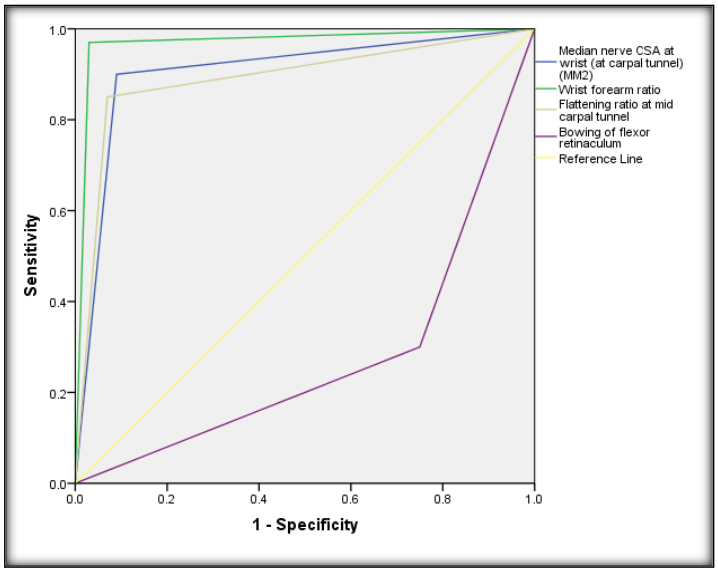

Figure [4]: Receiver-operating characteristic [ROC] curve for diagnostic accuracy of neuromuscular ultrasound between cases group and control group.

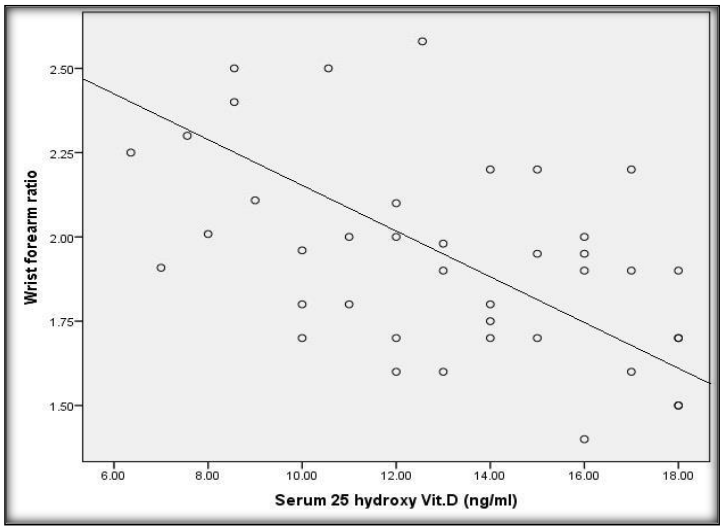

Figure [5]: Scatter plot between serum 25 hydroxy Vitamin-D [ng/ml] and wrist forearm ratio.

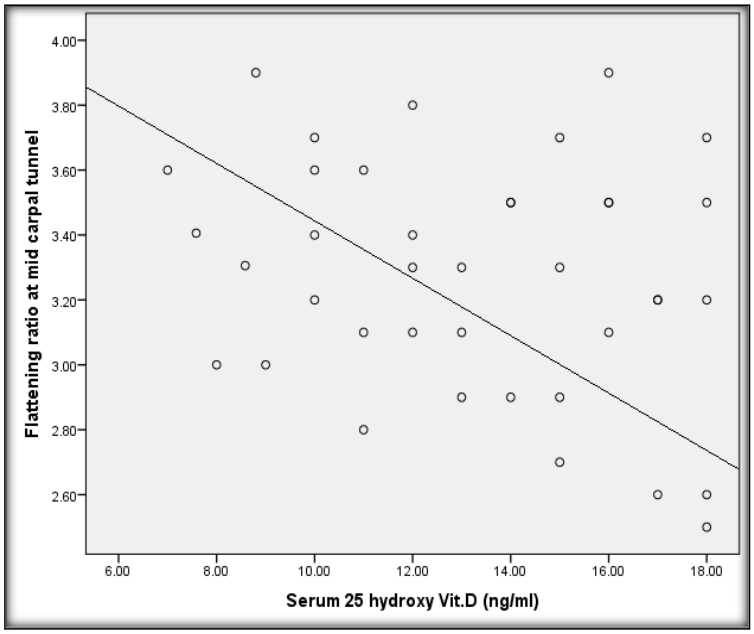

Figure [6]: Scatter plot between serum 25 hydroxy Vitamin-D [ng/ml] and fattening ratio at mid carpal tunnel.

DISCUSSION

This study aimed to evaluate the effectiveness of ultrasonography in diagnosing CTS in patients with normal NCS and explore the relationship between serum vitamin D levels and CTS severity. Results of the current study showed that, all nerve conduction parameters of the median nerve were within normal, despite presenting with symptoms indicative of CTS, which may suggest that NCS is less sensitive in detecting early or mild forms of the condition. The study assessed the diagnostic accuracy of four sonographic parameters: median nerve CSA at the distal wrist crease, FR within the carpal tunnel, PB of the flexor retinaculum, and wrist-forearm ratio. NCS served as the reference standard. The mean CSA of the median nerve at the wrist in the patient group [10.88 ± 0.94 mm^2] was significantly higher than in the control group [8.02 ± 0.61 mm^2].

Our study identified a cut-off value of 9.5 mm^2 for median nerve cross-sectional area [CSA] at the wrist as the optimal diagnostic threshold for CTS. This value demonstrated high sensitivity [90.0%] and specificity [91.0%], indicating strong predictive accuracy for the condition. These findings align with previous research, like the studies by **Al-hashel et al. [10], Borire et al. [11], Joseph et al. [12], El-Najjar et al. [13]** which consistently reported increased CSA in CTS patients. The elevated CSA is attributed to nerve compression-induced inflammation and swelling within the carpal tunnel. This objective measurement offers potential advantages for early diagnosis, severity assessment, and treatment planning, reducing reliance on subjective patient symptoms.

The results of the study demonstrate a statistically significant difference in the flattening ratio at the mid-carpal tunnel between patients with CTS and a control group. The mean flattening ratio in the patient group [3.21±0.41] was notably higher than that in the control group [1.85±0.13], with a p-value of <0.05. This finding suggests that the flattening ratio is a promising indicator for the diagnosis of CTS in this cohort. Furthermore, a cut-off value of >3 for the flattening ratio exhibited a sensitivity of 85.0% and a specificity of 92.5%, highlighting its potential as a reasonably sensitive and highly specific marker for CTS diagnosis.

Akcar *et al*. found a significant difference in the flattening ratio between CTS patients [mean: 2.7 ± 0.7] and controls [mean: 2.4 ± 0.5, $p < 0.05$] [14]. However, **Vo *et al***. [15] reported a non-significant difference [$p = 0.215$]. The increased flattening ratio in CTS patients may be due to median nerve compression and subsequent swelling.

In this study, the flexor retinaculum bowing was assessed in both individuals with CTS and a control group. While a modest increase in bowing was noted in the CTS group [4.13±1.00 mm compared to 3.82±0.17 mm in controls], this difference was not statistically significant [p=0.072]. Consequently, flexor retinaculum bowing does not appear to be a reliable diagnostic indicator for CTS in this study population. This study found a highly significant difference in the mean wrist-forearm ratio between the patient group [1.91 ± 0.29] and the control group. The optimal cut-off value for diagnosing CTS was >1.4, with a sensitivity of 97.5% and a specificity of 96.5%. These findings align with **Zhang et al. [16],** which reported a significant difference in the wrist-to-forearm ratio between CTS and control groups, with an optimal cut-off value of 1.41 [sensitivity: 81.8%, specificity: 68.2%].

In cases where nerve conduction studies do not reveal abnormalities, patients may still experience clinical symptoms, as demonstrated in this study. This discrepancy underlines the importance of incorporating ultrasound imaging as an adjunctive diagnostic tool, particularly when NCS results are normal. Ultrasound findings, such as increased median nerve cross-sectional area [CSA], can provide crucial evidence of nerve compression that might not yet affect conduction. The contrast between normal NCS results and positive ultrasound findings in this study suggests that ultrasound may be more sensitive in detecting anatomical changes in the median nerve at earlier stages of CTS, thus complementing nerve conduction studies in the diagnostic process.

The results of the study demonstrate a significant difference in serum 25-hydroxy vitamin D [Vit. D] levels between patients with CTS and a control group. The mean serum 25-hydroxy Vit. D level in the patient group [12.57±3.21 ng/ml] was substantially lower than that in the control group [24.02±3.07 ng/ml], with a p-value of <0.001, suggesting a strong association between CTS and lower Vit. D levels. **Okasha *et al***. found significantly lower 25[OH]D levels in CTS patients [7.0%, 19.4%] compared to controls [21.0%, 52.5%, p = 0.003] [17]. Similar findings were reported **Zakaria *et al*** [18].

The exact mechanisms underlying the association between vitamin D deficiency and carpal tunnel syndrome [CTS] remain unclear. However, several potential mechanisms have been proposed. One hypothesis suggests that vitamin D deficiency may contribute to increased inflammation, which can exacerbate nerve compression within the carpal tunnel [19].

Also, Vitamin D potentially increasing the risk of nerve compression [20]. Additionally, vitamin D's antioxidant properties help protects against oxidative stress, which can damage nerve cells and contribute to CTS development [21].

A statistically significant positive correlation was found between median nerve CSA at the wrist and disease duration [$p < 0.05$]. Conversely, a statistically significant negative correlation was observed between serum 25-hydroxyvitamin D levels and both wrist-forearm ratio and flattening ratio at the mid-carpal tunnel [$p < 0.05$]. In addition, a statistically significant negative correlation was observed between serum 25-hydroxy Vit. D levels and both the wrist-forearm ratio and the flattening ratio at the mid-carpal tunnel, indicating that lower Vit. D levels were associated with more pronounced anatomical changes in the median nerve. These findings support the hypothesis that vitamin D may play a role in the development or progression of CTS [22]. Moreover, a study by **Tanik and colleagues** revealed a correlation between the severity of carpal tunnel syndrome [CTS] and vitamin D levels in individuals with vitamin D deficiency [23].

Conclusion: This study demonstrates the utility of neuromuscular ultrasound as a valuable diagnostic tool for identifying structural changes in the median nerve associated with carpal tunnel syndrome [CTS] and normal NCS. Significant differences in ultrasound parameters between patient and control groups highlight the potential of ultrasound for early diagnosis and management of CTS. Additionally, the study suggests a possible correlation between serum vitamin D levels and symptom severity.

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