Kufa Medical Journal | Vol. 19, No. 2, 2023

Original article | DOI: https://doi.org/10.36330/kmj.v19i2.12706

Submitted at: 12 July 23
Accepted at: 24 July 23

Serum levels of Interleukin-6 in patients with Idiopathic Carpal Tunnel Syndrome: A case control study in Najaf Province

Fouad Shareef [1], and Shahad Mohammad Redha [2]

Authors' Affiliations:
[1] Prof., Department of Physiology, College of Medicine, University of Kufa, Iraq.
[2] M.B.Ch.B Candidate of Master degree in Medical Physiology, Collage of medicine, University of Kufa, Iraq.
Corresponding Author: Shahadmohammad1993@gmail.com

Abstract

Background: Carpal Tunnel Syndrome (CTS) is a disease caused by a compression of the median nerve at the wrist within carpal canal that lead to multiple symptoms as paraesthesia, numbness and pain sensation in the median distribution fingers. If untreated, it leads to sensation loss, thenar muscle weakness and atrophy. It is most frequent peripheral neuropathy of upper limbs and is most predominant in female gender. The pathogenesis of CTS is yet unknown, and the majority of conditions are idiopathic.

Interleukin 6 is a cytokine that has multiple functions including pro-inflammatory and anti-inflammatory or regenerative actions. The impact of serum inflammatory cytokines on incidence and severity of CTS is still unclear.

Aim of the study: this study aims to correlate the clinical severity of CTS and the serum interleukin 6 concentrations.

Patients and methods: This is a case control study which involved 140 participants who were categorized into 70 patients with CTS and 70 healthy persons according to clinical assessment and nerve conduction study results. After that, the participants were divided to normal, mild, moderate and severe groups according to Boston carpal tunnel questionnaire (BCTQ). Then, a blood sample was taken from each participant to assess serum interleukin 6 levels. A statistical analysis by SPSS was done for the collected data.

Results: The study has shown that there was no significant correlation between serum interleukin 6 levels and the clinical severity score of CTS (P value >0.05).

Conclusion: It has been concluded that serum interleukin 6 levels did not have an impact on incidence and clinical severity of CTS and that its role in CTS is yet unclear.

Key words: Carpal tunnel syndrome, clinical severity score of CTS, Interleukin 6.

INTRODUCTION

Carpal Tunnel Syndrome (CTS) is the most frequent upper limb compression neuropathy encountered clinically. It takes place when the median nerve is entrapped as it enters the tunnel [(1)]. In general, 2–3% of people suffer from carpal tunnel syndrome [(2)]. It is

more predominant in females, more frequent in persons between 40-60 years old, and its severity increases with increment of age [3]. The majority of conditions of CTS are idiopathic, but there are numerous predisposing factors linked with increased CTS incidence, including pregnancy, obesity, systemic disease such as diabetes mellitus, hypothyroidism, and rheumatoid arthritis, space-occupying lesions such as hematoma, tumors, or ganglion cysts, repetitive use injuries, wrist fracture or surgery, hereditary disorders such as abnormal muscles, inherited small tunnel, smoking, and alcoholism [4]. The pathophysiology of CTS is thought to be a mechanical compression of the median nerve which leads to ischemic changes inside the nerve. This decrement in the intraneural blood flow, and thus oxygen flow, result in defects in axonal transport and nerve tissue fibrosis. This causes atypical impulse production, slowness of conduction gradually and lastly axonal injury [5]. Initially, sensory fibers are damaged, then motor fibers. As well as autonomic fibers, may be damaged [6]. Clinical manifestations of CTS involve disorders of sensation and motor weakness. Sensory disorders localized to the median innervated digits like first, second, third and lateral side of fourth digit and involved intermittent tingling, numbness, and pain. The symptoms exacerbate during activities that involve hand extension or flexion for a long time and are calmed by hand shaking [5]. The characteristic feature of CTS is nocturnal tingling that awakens the patient from sleep. In more advanced conditions, the intermittent tingling and numbness turn into persistent, and the nerve dysfunction may lead to thenar muscle weakness and atrophy. CTS diagnosis is dependent on the history and physical examination. It is assured by electrophysiological studies [7]. Boston carpal tunnel questionnaire (BCTQ) is valid and reliable to assess the severity of symptoms and functional impairment in patients with CTS. The symptoms severity scale (SSS) and functional status scale (FSS) are the two sections of the questionnaire. There are eleven questions in the SSS, and answers are graded between one and five points, 1=normal, 2=slight, 3=medium, 4=severe, and 5=very serious. Besides, there are eight questions in the FSS to gauge how hard it is to carry out particular tasks, and answers are graded between one and five points, grades of 1=no difficulty, 2=little difficulty, 3=moderate difficulty, 4=intense difficulty, and 5=very severe difficulty that indicate patients cannot do the activity at all [8]. Peripheral immunity maintains homeostasis and has neuroprotective functions on the damaged nervous system, and it can potentially increase neuropathic pain sensitivity at the same time [9]. IL-6 is a multifunctional cytokine that is formed by immune cells such as T-cells, B-cells, macrophages, and microglia, and non-immune cells such as endothelial cells, muscle cells, fibroblasts, adipocytes, and neurons [10].

Patients and methods

In this case-control study, the total number of participants was 140. Patients were collected from the Neurophysiology Unit at the Middle Euphrates Center for Neurological Sciences/ Al-Sader Teaching Hospital in Al-Najaf city from the beginning of November 2022 until June 2023. The inclusion criteria were participants' age (18–50 years), clinical and electrodiagnostic confirmation of CTS in the patient group, and body mass index (BMI < 30) while the exclusion criteria were history of diabetes mellitus, thyroid dysfunction, polyneuropathy, rheumatoid arthritis, acromegaly, pregnancy, systemic lupus erythematosus, cervical radiculopathy, wrist fractures, hand trauma, and any upper limb trauma or surgery for CTS.

All participants involved in the research were subjected to full history and physical examination, Boston Carpal Tunnel Syndrome Questionnaire (BCTQ), nerve conduction study

of the upper limbs, and body mass index calculation. A venous blood sample of 2.5 milliliters was collected from each participant and put in a gel tube, then serum interleukin-6 levels were measured using a human interleukin-6 ELISA kit (Sunlong, China). A patient group composed of seventy patients (11 males and 59 females) came with clinical and electrophysiological findings of CTS, and then they were classified into mild, moderate, and severe subgroups according to Boston Carpal Tunnel Syndrome Questionnaire (BCTQ). The total score of the SSS was classified into asymptomatic (11 points), mild (12–22 points), moderate (23–33 points), severe (34–44 points), and very severe (45–55 points). The total score of FSS was categorized into no difficulty (8 points), little difficulty (9–16 points), moderate difficulty (17–24 points), severe difficulty (25–32 points), and very severe (33–40 points) [11]. The control group was composed of seventy healthy participants (10 males and 60 females); they had no clinical or electrophysiological manifestations of CTS, and their age, gender, BMI, and geographical distribution were similar to the patients.

Ethical Approval

This study obtained the ethical approval from the internal ethical committee of the Medical Physiology Department/Faculty of Medicine, University of Kufa and the Health Directorate in Najaf Province. Further, a verbal voluntary consent was taken from the all patients and controls who were involved in this study.

Statistical Analysis

The data analysis was performed by the utilizing Statistical Package of Social Science (SPSS) software program version 26. Categorical variables were expressed as frequency and percentage and analyzed by using Chi-square test to measure the significance level of difference and the relationships between them. Continuous variables were stated as means and standard deviation (SD) and analyzed by using an independent t-test to compare between patient and control groups. However, utilizing ANOVA and Post Hoc test to measure the significance level of difference for continuous variables for comparing the four groups. The correlations were assessed by Bivariate Pearson Correlation (r: correlation coefficients). P value < or =0.05 was regarded significant.

Results

The participants were divided into three age groups, and the most frequent age group was 40–50 years (45.7%) for both the patient and control groups. There were 11 (15.7%) males and 59 (84.3%) females among the patient group, demonstrating that females are more commonly affected than males. Most of the patients 55 (78.6%), and controls 52 (74.3%), were overweight (BMI = 25–29.9 kg/m2). Concerning the patients' jobs, all of the patients were working in high-risk manual jobs. The female patients: 53 (89.8%) of them were housewives, and 6 (10.2%) of them were employed. The male patients: 9 (81.8%) of them were unemployed, and 2 (18.2%) were employed (Table 1). The gender had no significant effect on serum IL-6 levels in the patient group (P value= 0.4). So male and female patients are counted as one group in this study (Table 2). Independent T- test was used to compare the mean and standard deviation of serum interleukin-6 between the patient and control groups; there was no significant difference between the two groups (P value >0.05) (Table 3). According to the symptom severity score and functional status score, there was no significant difference in the mean IL-6 levels between CTS severity groups (P values = 0.76, and 0.81, respectively). When we compared the mean IL-6 of each group with the other groups, there was no significant difference between the groups (P value >0.05) (Table 4). There was no significant correlation between the CTS scales (SSS and FSS) and

serum IL-6 (Table 5) (Figure 1 & 2). There was no significant correlation between age of patients and serum interleukin-6 (P value= 0.13, r =0.18) (Figure 3).

Table 1. Demographic Data for Patient and Control Groups.

Variables	Patient group n (%)	Control group n (%)	P value
Age group			
18-28	15 (21.4)	16(22.9)	0.97
29-39	23 (32.9)	22(31.4)	
40-50	32 (45.7)	32(45.7)	
Occupation			
housewife	53(75.7)	51(72.9)	0.40
employed	8(11.4)	13(18.6)	
unemployed	9(12.9)	6(8.6)	
BMI status			
normal	15(21.4)	18(25.7)	0.55
overweight	55(78.6)	52(74.3)	
Dominant hand			
right hand	63(90)	65(92.9)	0.55
left hand	7(10)	5(7.1)	
Involved hand			
right hand	25 (35.7)		
left hand	11(15.7)		
both hands	34(48.6)		
Gender			
male	11(15.7)	10(14.3)	0.81
female	59(84.3)	60(85.7)	
Severity of CTS			
mild	24(34.3)		
moderate	23(32.9)		
severe	23(32.9)		

Table 2. The Relationship between Gender and IL-6 Levels in the Patient Group.

Variables	Gender	N.	Mean ±SD	P-value
IL-6 (pg/ml)	Male	11	31.55±10.92	0.4
	Female	59	28.58±7.22	

Table 3. A Comparison of Serum Interleukin 6 between CTS Patient and Control Groups.

Variables	NCS groups		P value
	Patient group N=70 mean±SD	Control group N=70 mean±SD	
IL-6 (pg/ml)	29.05±7.89	28.92±7.93	0.92

NCS: Nerve conduction study.

Table 4. Relationship of Clinical CTS Scales (SSS and FSS) with Serum IL-6.

IL_6 (pg/ml)	Scale	Normal mean±SD	Mild mean±SD	Moderate mean±SD	Severe mean±SD	P value
	SSS	28.92±7.93	27.74±2.79	28.94±8.74	30.15±9.84	0.76
	FSS	28.79±7.8	28.01±2.61	30.19±10.67	29.18±8.13	0.81

SSS: Symptom Severity Scale, FSS: Functional Status Scale.

Table 5. The Correlation between Interleukin-6 and CTS Clinical Scales.

Variables	Symptom Severity Scale SSS		Functional Status Scale FSS	
	Correlation Coefficients (r)	P-value	Correlation Coefficients (r)	P-value
IL_6(pg/ml)	0.06	0.48	0.06	0.47

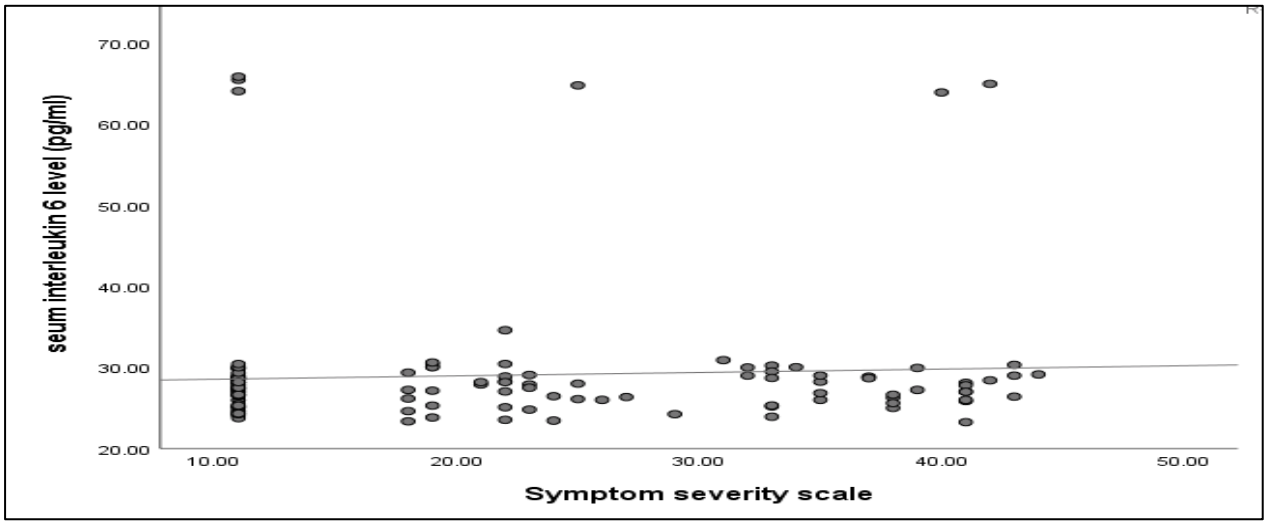

Figure 1. The Correlation between Serum Interleukin 6 and Symptom Severity Scale of CTS.

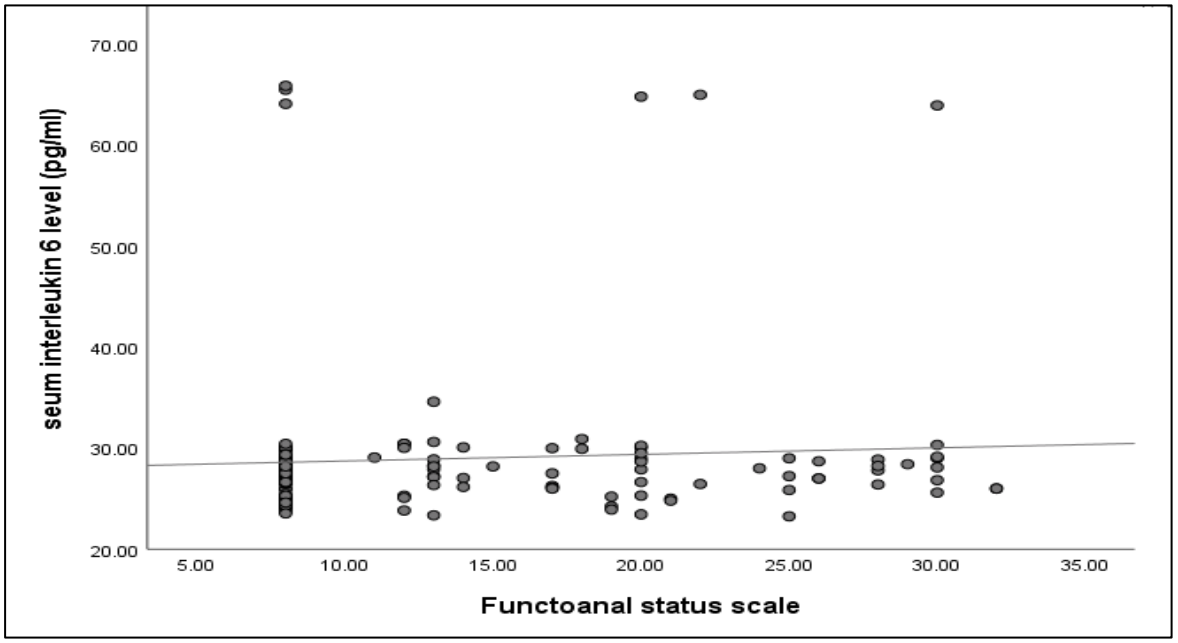

Figure 2. The Correlation between Serum Interleukin 6 and Functional Status Scale of CTS.

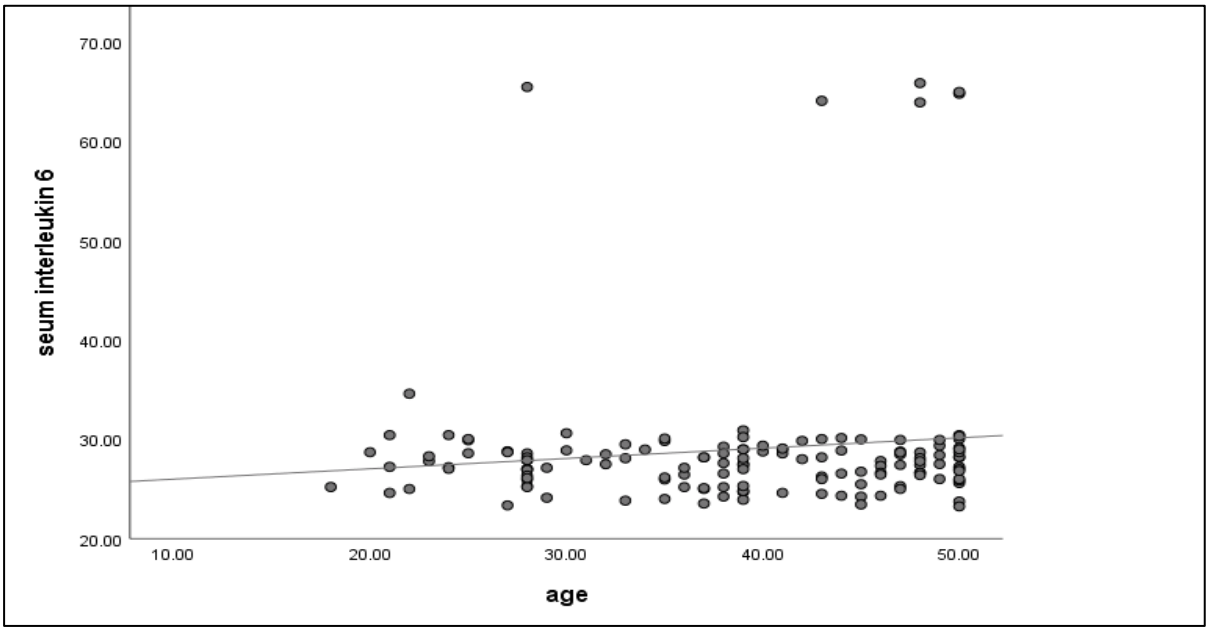

Figure 3. Correlation between Serum IL-6 Levels and Age of Patients.

Discussion

In this study, most of the patients were middle-aged (Table 1); this appears logical due to the fact that the likelihood of developing CTS is higher among working-age people than the general population, possibly due to degenerative changes resulting from repeated hand activities [(12).] Similar results were reported by numerous researches [(13,14)]. 84.3% of the patients in this study were female (Table 1); this was consistent with other researches [(15,16)], which may be a result of the fact that females have a smaller wrist canal than males [(17)]. Moreover, a woman's everyday activities inside the house might worsen her condition, and hormonal variations during pregnancy and the menstrual cycle have been found to contribute to the development of CTS [(18)]. In this research, 89.8% of the female patients were housewives. This is in agreement with another research, which showed that

housework was likely a contributing factor to CTS among women under the age of 45[19]. In this research, there was no statistical effect of gender on serum IL-6 levels (Table 2), as the increment in inflammatory mediators is associated with the progression of disease regardless of gender [20]. This research showed there was no statistically significant difference in serum interleukin-6 concentrations between the patient group and the control group (Table 3). Besides, there was no statistically significant difference in serum interleukin-6 concentrations between CTS clinical severity groups (Table 4). These findings were consistent with those of Karimi et al. (2020), who reported that blood levels of inflammatory cytokines (IL6, IL1, IL10, and TNF) did not significantly vary in persons with carpal tunnel syndrome in comparison with healthy participants and were not significantly associated with SSS and FSS of CTS [9]. According to research by Freeland et al. (2002) and Sud et al. (2005), there is no variation in the level of IL1 in the blood or tenosynovium among individuals with CTS and the control subjects. Also, the serum concentrations of PGE2 and IL-6 showed no significant difference between cases and controls. However, PGE2 and IL-6 tenosynovial concentrations were elevated in the carpal tunnel syndrome group. These studies stated that IL-6 has a local role in the pathophysiology of CTS. The researchers suggested that these changes could be due to oxidative damage resulting from repetitive ischemia and reperfusion injuries [21,22]. Taylor et al. (2017) found that individuals with CTS had higher serum concentrations of a number of cytokines, including IL-12, IL-4, and IL-9, than healthy persons while they found no significant difference in serum IL-2, IL-6, IL-7, IL-10 or IL-13 between CTS cases and controls. Taylor's study suggested that neuroinflammation had important role in the development of CTS. However, there was no correlation between plasma cytokine concentrations and the severity of the symptoms. They measured serum concentrations of twenty-seven chemokines and cytokines; so, they noted a significant difference in serum concentrations of some cytokines between CTS cases and controls [23]. While this study assayed serum concentrations of interleukin-6 only, a significant difference was not observed in IL-6 between CTS cases and controls. Ajeena et al (2021) showed that the levels of Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES chemokine) were significantly elevated in CTS patients in comparison to healthy persons. Although there was no notable variance in levels of RANTES between CTS severity groups [24]. Another research found that individuals with herniated intervertebral disks and CTS had elevated levels of IL-6 and TNF in their serum compared to healthy individuals [25]. Magrinelli et al. (2015) focused on the connection between serum proinflammatory cytokine levels and the damage of both small and big nerve cells in diabetic polyneuropathy patients. It stated that there was an association between IL6, IL10 serum concentrations and large nerve fiber axonal lesions, whereas these abnormalities are not linked to neuropathic pain or the destruction of tiny nerve fibers [26]. Although the fact that CTS is a large nerve fiber lesion, unpredictably, our study didn't notice any noteworthy dissimilarity in the blood IL-6 concentrations in cases of CTS. For Magrinelli et al. (2015), diabetic patients' serum cytokine concentrations were measured [26]. Diabetes mellitus may be related to changes in cytokine concentrations in the blood of the patients. According to research by Kawamoto et al. (2020), CTS patients with comorbid trigger finger had considerably higher levels of IL-6 released by fibroblasts originating from the tenosynovium than CTS patients without trigger finger. This could be a possible explanation for the commonly observed correlation between CTS and trigger finger [27].

Conclusions

Neither the functional status of patients with carpal tunnel syndrome nor the severity of their symptoms are significantly correlated with the levels of the inflammatory cytokine interleukin 6 in their serum. Interleukin-6 doesn't appear to have an important impact on the incidence and clinical severity of CTS among Iraqi patients.

Recommendations

A measurement of other inflammatory cytokines and finding their correlation with incidence and severity of CTS is recommended.

Aknowledgements

I am grateful to the head of Medical Physiology Department in Faculty of Medicine/ University of Kufa and my special thanks to all the neurophysiologists doctors in Neurophysiology Unit/Middle Euphrates Center for Neurological Sciences/Al-Sader Teaching Hospital, who help, support and guided me during this scientific work. Furthermore, I would like to express my sincere gratitude to Prof. Dr. Huda Ghazi Hameed and Prof. Dr. Abdulkareem Al-Radhi from the Department of Community Medicine/College of Medicine/University of Kufa for their invaluable help and advice during the data analysis phase.

References

1. Otelea, M. R., Nartea, R., Popescu, F. G., Covaleov, A., Mitoiu, B. I., & Nica, A. S. The Pathological Links between Adiposity and the Carpal Tunnel Syndrome. Current Issues in Molecular Biology. 2022; 44(6), 2646-2663.
2. Habib, K. R. Estimation of carpal tunnel syndrome (CTS) prevalence in adult population in western European countries: A systematic review. Eur. J. Clin. Biomed. Sci. 2017; 3(1), 13-18.
3. Genova, A., Dix, O., Saefan, A., Thakur, M., & Hassan, A. Carpal tunnel syndrome: a review of literature. Cureus, 2020; 12(3).
4. Gautam, N., & Shrivastava, A. A Review on Risk Factors and Diagnosis of Carpal Tunnel Syndrome. ECS Transactions. 2022; 107(1), 6921.
5. Janes, J. E. (2023). Essential of plastic surgery. DMP CRC, New York, 75, 80-81.
6. Nunes, A. S. F., de Exel Nunes, L. M., Dotta, L., Chung, T. M., Battistella, L. R., & Riberto, M. A correlation between clinical severity and functional state with nerve conduction study's findings in patients with carpal tunnel syndrome: a systematic review. Acta Fisiátrica. 2017; 24(4), 200-206.
7. Preston, D. C., & Shapiro, B. E. Electromyography and neuromuscular disorders e-book: clinical-electrophysiologic-ultrasound correlations. Elsevier Health Sciences; 2021.
8. De Kleermaeker, F. G., Boogaarts, H. D., Meulstee, J., & Verhagen, W. I. Minimal clinically important difference for the Boston Carpal Tunnel Questionnaire: new insights and review of literature. Journal of Hand Surgery (European Volume). 2019; 44(3), 283-289.
9. Karimi, N., AbedianKenari, S., & Darvari, F. Serum levels of inflammatory cytokines in patients with idiopathic carpal tunnel syndrome. International Journal of Neuroscience. 2020; 131(3), 228–232.
10. Rothaug, M., Becker-Pauly, C., & Rose-John, S. The role of interleukin-6 signaling in nervous tissue. Biochimica et biophysica acta. 2016; 1863(6 Pt A), 1218–1227.
11. Almigdad, A., Odat, M., Almanasir, G., Megdadi, N., & Sharadgeh, S. Carpal

tunnel syndrome: correlation of the severity of the clinical picture and electrophysiological studies. Journal of the Korean Society for Surgery of the Hand; 2022.
12. Puchalski P, Szlosser Z, Żyluk A. Familial occurrence of carpal tunnel syndrome. Neurologia i Neurochirurgia Polska. 2019; 53 (1):43-46.
13. Spahn, G., Wollny, J., Hartmann, B., Schiele, R., & Hofmann, G. O. Metaanalysis for the evaluation of risk factors for carpal tunnel syndrome (CTS) Part I. General factors. Zeitschrift fur Orthopadie und Unfallchirurgie. 2012; 150(5), 503-515.
14. Yurdakul, F. G., Bodur, H., Ateş, C., Sivas, F., Eser, F., & Taşdelen, Ö. Y. On the severity of carpal tunnel syndrome: diabetes or metabolic syndrome. Journal of Clinical Neurology, (2015). 11(3), 234-240.
15. Alex, B., Kattoor, M. J., & Edayalamuriyil, S. S. Assessment of the diagnostic accuracy of nerve conduction study and the correlation between severity of symptoms and nerve conduction studies in carpal tunnel syndrome. International Journal of Research in Orthopaedics, (2019). 5(4), 559.
16. Sasaki, T., Koyama, T., Kuroiwa, T., Nimura, A., Okawa, A., Wakabayashi, Y., & Fujita, K. Evaluation of the Existing Electrophysiological Severity Classifications in Carpal Tunnel Syndrome. Journal of clinical medicine. 2022; 11(6), 1685.
17. Lakshminarayanan K, Shah R, Li M. Sex-related differences in carpal arch morphology. PLoS ONE; (2019); 14(5).
18. Mohammadi A, Naseri M, Namazi H, Ashraf J, Ashraf A. Correlation between Female Sex Hormones and Electrodiagnostic Parameters and Clinical Function in Post-menopausal Women with Idiopathic Carpal Tunnel Syndrome. J Menopausal Med.; (2016); 22(2):80- 86.
19. Rhode, B., & Rhode, W. Occupational risk factors for carpal tunnel syndrome. MOJ Orthop Rheumatol, (2016); 4(2), 00131.
20. Pourmemari H, Heliövaara M, Juntura E, Shiri R. Carpal tunnel release: lifetime prevalence, annual incidence, and risk factors. (2018); *Muscle Nerve;* 58:497–502.
21. FREELAND, ALAN E. "Biochemical Evaluation of Serum and Flexor Tenosynovium in Carpal Tunnel Syndrome." Microsurgery. 2002; 22(8): 378–85.
22. Sud, V., & Freeland, A. E. Biochemistry of carpal tunnel syndrome. Microsurgery: Official Journal of the International Microsurgical Society and the European Federation of Societies for Microsurgery, 2005; 25(1), 44-46.
23. Taylor G, Baharuddin B, Bennett B, Krishnan A, Huynh W. Immune dysregulation in patients with carpal tunnel syndrome. Scientific Reports; 2017; 7:8218.
24. Ajeena, I. M., Al-Mudhafar, R. H., Al-Awadi, I. J., Al-Khalidi, H. A., & Alsalihi, N. J. Diagnosis of Carpal Tunnel Syndrome: The Role of RANTES eISSN 1303-5150. NeuroQuantology, (2021); 19(4), 65–70.
25. Coe, C. L., Muller, D. A., & Schell, K. Altered cytokine levels in the blood and cerebrospinal fluid of chronic pain patients. Journal of neuroimmunology. 2008; 195(1-2), 157-163.
26. Magrinelli, F., Briani, C., Romano, M., Ruggero, S., Toffanin, E., Triolo, G., ... & Tamburin, S. The association between serum cytokines and damage to large and small nerve fibers in

diabetic peripheral neuropathy. Journal of diabetes research; 2015.

27. Kawamoto, H., Iwatsuki, K. & Hirata, H. Interleukin-6 secretion by fibroblasts in carpal tunnel syndrome patients is associated with trigger finger and inhibited by tranilast. Muscle and Nerve. 2020; 61(3), 408–415.

28.