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Title: Assessment of the Carpal Tunnel Syndrome in Female Patients with Hypothyroidism

Running title: Carpal Tunnel Syndrome and Hypothyroid

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Abstract

Introduction: Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy. There are several factors that influence the severity of CTS. The purpose of this study was to explore the severity of CTS in hypothyroid patients.

Methods: This cross-sectional study was conducted in the university clinic. Seventy-six participants with a clinically and electrophysiological confirmed diagnosis of CTS were included in the study. The demographic data and severity of CTS were analyzed based on the presence (n=38) or the absence (n=38) of primary hypothyroid disease. Thirty-eight hypothyroid patients who were being treated were included in this study. For assessment of the severity of CTS, the Boston questionnaire (BCTQ) and electrodiagnostic tests were used. For data analysis, an independent sample t-test and Chi-squared tests were carried out. P -value<0.05 was considered significant.

Results: The mean age of hypothyroid and non-hypothyroid CTS patients was 46.21 ± 7.22 and 44.24 ± 8.02 , respectively. BMI was higher than 30 kg/m^2 in both two groups. There was no significant difference in the respect of demographic data among the two groups. The mean score of symptom severity in hypothyroid and non-hypothyroid-CTS patients were 30.37 ± 10.84 and 35.89 ± 7.19 , and also functional status was 21.71 ± 9.04 and 25.92 ± 6.62 , respectively. There was a significant difference between the two groups, in terms of symptom severity scale ($p=0.017$, CI95%:31.14-35.48) and functional status scale ($p=0.023$, CI95%:21.95-25.67). In terms of electrophysiological findings, there was no statistically significant difference between these two groups.

Conclusion: The results of this study indicated that, contrary to expectation, the severity of CTS be higher in non-hypothyroid patients than in hypothyroid patients.

Keywords: Carpal tunnel syndrome, Severity, Hypothyroidism, Boston questionnaire, Electrodiagnostic findings

Introduction

Carpal tunnel syndrome is the most common entrapment neuropathy, which is caused by median nerve compression in the wrist (Nazish et al., 2019). The prevalence of CTS is different in several populations. A recent study in Iran reported a prevalence of 1.82% for CTS in the general population (2.23% among female subjects and 0.58% among male subjects) (Moosazadeh et al., 2018). Of the hallmark of this disorder is pain, paresthesia, and burning in the pathway of the median nerve. In the more advanced stages, weakness and atrophy of the muscles of the thenar developed that in sequence causes the inability to accomplish activities (Stevens et al., 1992). The syndrome is diagnosed according to clinical symptoms, physical examination, and electrodiagnostic tests (Karimi et al., 2021; Razavi et al., 2021). There are several risk factors involved in causing this syndrome that comprises age, obesity, Diabetic Mellitus, rheumatoid arthritis, smoking, pregnancy, hypothyroidism, congenital anomalies and wrist injury (Karimi et al., 2017; Moghtaderi et al., 2005). Evidence suggests that hypothyroidism is a significant predisposing factor for CTS. The prevalence of CTS in hypothyroid patients has been reported from 8.7% (Karimi et al., 2017). On the other hand, the prevalence of subclinical hypothyroidism was found 38.2% among the CTS patients (Roshanzamir et al., 2016). A number of researchers identified that most patients of hypothyroidism have mild carpal tunnel syndrome and none of the patients had a severe type of CTS (Asadi & Roshanzamir, 2017; Beghi et al., 1989; Karne & Bhalerao, 2016). There are a number of theories on the pathogenesis of this disease in the CTS establishment including alterations of fluid balance, dermal edema, excess deposition of glycosaminoglycans, hyaluronic acid and mucopolysaccharides in subcutaneous tissues and dysfunction of myelin and axonal (Beghi et al., 1989; Karne & Bhalerao, 2016). Hypothyroidism increases BMI and obesity and has been reported as an independent risk factor of CTS but the severity of CTS in hypothyroid patients is unclear. Up to now, few studies have assessed the role of

hypothyroidism in the severity of CTS. Given that the severity of clinical symptoms affects treatment outcome, therefore, the purpose of this investigation has been to determine the severity of CTS in hypothyroid patients.

Methods and materials

Study design

This retrospective cross-sectional research was conducted in university clinic (Bagheban) in Sari city, Mazandaran province, Iran, from December 2018 to February 2020. This study was approved by Mazandaran University of Medical Sciences and it was extracted from a medical student thesis with the project number, 10201.

Setting and participants

All female patients who were referred to our electrophysiology clinic with clinical symptoms of CTS containing numbness, tingling, paresthesia, pain, burning feeling, and weakness in unilateral or bilateral of hand or wrist, were examined (American Association of Electrodiagnostic Medicine, American Academy of Neurology, and American Academy of Physical Medicine and Rehabilitation, 2002). After a physical examination, the electrodiagnostic test was done for confirmation of CTS. Due to the effect of occupation and gender on carpal tunnel syndrome, all contributors in this research were housewives and females. CTS patients ≥ 18 years' old who had hypothyroid and were being treated with thyroxine were included in the study, along with patients with idiopathic CTS. Exclusion criteria were including pregnancy, hyperthyroidism, diabetes mellitus, other endocrinal diseases, connective tissue diseases, arthritis, wrist fracture, renal and liver diseases, acromegaly, neuropathy, radiculopathy, and aforementioned CTS surgery.

Overall, 79 patients who had a clinically and electrophysiologically confirmed diagnosis of CTS were included in the study.

Data sources and measurement

All participants filled out the Boston carpal tunnel questionnaire (BCTQ) and demographic data including, age, educational level, involved hand, duration of disease, weight, height, and body mass index. BCTQ investigates the severity of patients' symptoms and their ability to perform daily tasks. It contains 19 questions (11 items related to the severity of symptoms and 8 items allied to functional ability). Each question has five scores from no symptoms to very severe. The scores are gathered for each person and a higher score indicates more intensity of symptoms and disability (Levine et al., 1993). Carpal tunnel syndrome severity was evaluated according to BCTQ and electrophysiological parameters. The electrodiagnostic test was done by a neurologist according to guidelines of the American Association of Neuromuscular and Electrodiagnostic Medicine with Micromed MYOQUICK model electromyography apparatus (Jablecki et al., 2002). The results of the electrophysiological findings are distributed into six grades, from normal to extremely severe CTS, in accordance with Bland neurophysiological grading scale (Bland, 2000). The parameters to be measured include peak latency, amplitude and conduction velocity of the sensory median nerve and distal latency, amplitude and conduction velocity of the motor median nerve. Needle electromyography was prepared in abductor pollicis brevis muscle and other muscles in the upper limb to assess the severity of CTS and to exclude brachial plexopathy or radiculopathy. Electrodiagnostic results are considered abnormal if Peak Latency > 3.5 ms, base to peak amplitude <20.0 μ V, conduction velocity <50 m/s studies, distal motor latency >4.4 ms, base to peak amplitude <4.0 mV, and Nerve Conduction Velocity (NCV) < 49 m/s (Ali et al., 2012; Basiri & Katirji, 2015). Electrophysiological study was performed in bilateral hands and the most affected hand with worse electrophysiological findings were evaluated.

Statistical analysis

All analyses were performed using SPSS software package version statistical software version 24.0 (SPSS Inc., Chicago, IL, USA). The one-sample Kolmogorov-Smirnov test was used to test for normality; the results of this test directed that parametric tests should be performed. Quantitative data were conveyed with mean $\pm$ standard deviation, but qualitative data were evaluated in frequency and percentage. An independent sample t-test was carried out to assess quantitative data between the two groups (electrodiagnostic parameter findings and severity of CTS according to Boston score in hypothyroid and non-hypothyroid patients). A chi-squared test was applied to relate categorical variables and qualitative data. P -value <0.05 was considered significant.

Results

Seventy-six patients with clinical and electrodiagnostic evidence of CTS were included in this study between December 2018 to February 2020, of which 3[^] patients had hypothyroidism and 38 participants were idiopathic CTS (without hypothyroidism). The mean age of all patients was 45.02 ± 7.74 . Unilateral and bilateral CTS was in 26 (34.2%) and 50 (65.8%) of the patients, respectively. The patients had a body mass index (BMI) of 31.47 ± 5.26 kg/m², with a minimum 21.5 and maximum 45 kg/m². The mean duration of CTS and hypothyroidism were 29.61 ± 32.29 and 98.93 ± 64.19 months, respectively.

Comparison of CTS patients with and without hypothyroid disease

Thirty-eight of the CTS patients had hypothyroid disease and 38 did not. There was no significant difference between hypothyroid and non-hypothyroid-CTS patients in terms of age (46.21 ± 7.22 years vs. 44.24 ± 8.02 years, $p=0.225$), duration of CTS (31.89 ± 32.13 and 28.24 ± 32.60 months, $p=0.609$), and BMI (30.78 ± 5.29 and 31.89 ± 5.29 kg/m², $p=0.326$). Bilateral CTS was present in 24 (63.2%) of the 38 patients with hypothyroid disease and in 26

(68.4%) of the 38 patients without hypothyroid disease ($p=0.22$). The demographic and clinical characteristics of the study participants are presented in Table 1.

Comparison of the Boston questionnaire score in hypothyroid and non-hypothyroid-CTS patients

The mean score of SSS in hypothyroid-CTS patients and non-hypothyroid-CTS patients was 30.37 ± 10.84 and 35.89 ± 7.19 , and also FSS was 21.71 ± 9.04 and 25.92 ± 6.62 , respectively. There was significant difference between two groups, in terms of symptom severity scale (p value=0.017; CI 95%:31.14-35.48) and functional status scale (p value=0.023; CI 95%:21.95-25.67).

Comparison of the electrophysiological parameters in hypothyroid and non-hypothyroid-CTS patients

The electrodiagnostic findings, such as median nerve sensory onset latency, peak latency, amplitude, and conduction velocity and also median nerve motor distal latency, amplitude, and conduction velocity were measured at involvement hands of all participants. There was no significant difference in respect to electrophysiological parameter results in two groups. The most of participants in hypothyroid-CTS and non-hypothyroid-CTS had moderate CTS (29.70% and 34.51%, respectively). Chi-square test found no significant differences between two groups according to Bland's grading of electrodiagnostic findings (Figure 1). The mean score was obtained for each electrophysiological parameters in hypothyroid and non-hypothyroid-CTS patients (Table 2). No statistically significant difference was observed between these two groups.

The relationship of the electrodiagnostic grading and Boston score

For evaluation of the relationship between electrodiagnostic grading and clinical symptoms, mild to moderate CTS were located in one group and severe to extremely severe CTS in another

group. There was no statistically significant association between electrodiagnostic grading and SSS and also FSS in the hypothyroidism group as determined by independent t-test analysis (Table 3). In contrast, there was significant positive association between electrodiagnostic grading and clinical symptoms (p -value= 0.01; CI95%= 33.52-38.26) and also FSS (p -value=0.002; CI95%= 23.74-28.09) in non-hypothyroidism CTS patients. Table 3 shows the results obtained from this analysis.

4. Discussion

Hypothyroidism is considered a risk factor for creating of carpal tunnel syndrome ((Karimi et al., 2017; M et al., 2012; Shiri, 2014) but the severity of CTS in hypothyroid patients being treated is unclear. The aim of the present study was to compare the severity of CTS in treated hypothyroid and non- hypothyroid patients. This study was conducted on housewives, to prevent the confounding effect of sex and occupation on the CTS. The mean age of hypothyroid and non- hypothyroid-CTS patients was the same. In addition, the mean BMI was higher than 30 kg/m² in two groups, similar to previous studies (Becker et al., 2002). With respect to demographic data, hypothyroid patients were similar to non-hypothyroid patients. This study showed that the clinical symptoms of CTS in non- hypothyroid patients were more severe than treated hypothyroid patients. This finding is contrary to that of Asadi et al., who found the clinical symptoms of hypothyroid patients were more severe than non-hypothyroid patients (Asadi & Roshanzamir, 2017). In our study, all of the hypothyroid patients were under treatment with hormone replacement therapy. Therefore, treatment may be effective in reducing the severity of patients' clinical symptoms. As shown in Kasem's study, hormone replacement therapy can be effective in the amelioration of CTS (Kasem et al., 2014). In the present study, age and BMI in the hypothyroid and non-hypothyroid patients was the same. Therefore, in our opinion, thyroxine replacement therapy may play a role in reducing the severity of patients' clinical symptoms. In our study, we also found no association between the

severity of CTS according to electrophysiological findings in hypothyroid and non-hypothyroid CTS patients. These results were the same as Asadi's study (Asadi & Roshanzamir, 2017). This study showed that although the hypothyroid disorder is considered as a possible risk factor of CTS based on other studies (Cruz et al., 1999; El-Salem & Ammari, 2006)8-9, there was no evidence that hypothyroidism affects the severity of electrophysiological parameter findings. With respect to the relationships between clinical symptoms and electrodiagnostic grading in CTS, this study indicated that the severity of clinical symptoms and functional of daily activity according to the Boston score is more related to the grading of the electrodiagnostic test in non-hypothyroid CTS patients. But it was surprising that there was no such relationship in hypothyroidism patients. This study is consistent with that of Asadi et al study who found no relationship between clinical symptoms and electrodiagnostic findings in patients with hypothyroidism (Asadi & Roshanzamir, 2017). These results may be explained by the fact that the severity of clinical symptoms may be directly related to median nerve damage. As mentioned above, a possible explanation for unrelated clinical symptoms with electrodiagnostic grading in hypothyroidism patients may be the role of thyroid replacement therapy in reducing symptoms, regardless of its effect on electrodiagnostic parameters. Aldaghri et al., reported more than two-thirds of those with hypothyroidism were asymptomatic and the presence of thyroid abnormality doesn't affect the duration of carpal tunnel syndrome (Aldaghri et al., 2020).

Conclusion

The results of this study indicated that the severity of CTS be higher in non-hypothyroid patients than hypothyroid patients. It can, therefore, be assumed that thyroid replacement therapy plays a role in decreasing clinical symptoms. This is an important issue for future research.

Conflict of interest

The authors have no financial conflicts of interest.

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Figure 1. Electrodiagnostic grading according to Bland study in hypothyroid and non-hypothyroid CTS patients

Table 1. Demographic characteristics of participants

Variables	Hypothyroid -CTS	Non-hypothyroid -CTS	* <i>p</i> -value
<i>Age; Mean (SD)</i>	46.21(7.2)	44.24(8.1)	0.225
<i>Age group; n (%)</i>			
18-29	0(0)	2(3.4)	
30-39	6 (15.7)	13(22.4)	
40-49	15 (39.4)	24(41.3)	
50-59	14(44.73)	14(29.3)	
≥60	1 (0)	2(3.4)	0.160
<i>Body parameters; Mean (SD)</i>			
Wight	78.97(14.1)	82.72(14.4)	0.225
Height	160(0.4)	161 (0.5)	0.127
BMI	30.78(5.2)	31.89(5.2)	0.326
<i>CTS sites; n (%)</i>			
Bilateral	24(63.2)	26 (68.4)	
Unilateral	14 (36.8)	12 (31.6)	0.220
<i>Duration of CTS to month;</i>			
<i>Mean (SD)</i>	31.89(32.13)	28.24(32.60)	0.609

**p*-value <0.05 is significant. SD= standard deviation; CTS=carpal tunnel syndrome

Table 2. Electrophysiological parameters of the median nerve in hypothyroid and Non-hypothyroid-CTS patients

Median nerve Parameters	Hypothyroid-CTS	Non-Hypothyroid-CTS	* p-value
	Mean(SD)	Mean(SD)	
Sensory peak Latency(ms)	3.75(2.33)	3.07(2.19)	0.322
Sensory amplitude (μ v)	25.36(15.17)	28.61(11.31)	0.373
Sensory conduction velocity(m/s)	34.23(11.25)	38.04(6.13)	0.141
Motor distal latency(ms)	6.16(2.06)	5.90(1.66)	0.553
Motor amplitude (mv)	10.73(4.08)	11.43(5.94)	0.550
Motor conduction velocity (m/s)	55.67(4.97)	55.98(6.26)	0.602

* p -value <0.05 is significant. SD=standard deviation; CTS= carpal tunnel syndrome; ms=millisecond; μ v=microvolt; m/s= meter/ second; mv= millivolt.

Table 3. Association between electrodiagnostic grading and clinical symptoms according to BCTQ

BCTQ	Hypothyroid-CTS			Non-Hypothyroid-CTS		
	Mild to moderate	Severe	* p -value	Mild to moderate	Severe	* p -value
SSS (SD)	28.27 (10.43)	33.47 (11.04)	0.15	33.05 (5.05)	38.73 (7.42)	0.01
FSS (SD)	19.32 (8.11)	24.42 (9.40)	0.08	22.21 (4.93)	29.63 (6.05)	0.002

* p -value <0.05 is significant. SSS: symptom severity scale; FSS: functional status scale. BCTQ= Boston carpal tunnel questionnaire; CTS= carpal tunnel syndrome; SD=standard deviation