

Ultrasonography of Median Nerve in Carpal Tunnel Syndrome before and after Hormone Replacement in Patients with Hypothyroidism

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ABSTRACT

BACKGROUND: We evaluated the efficacy of ultrasonography in newly diagnosed hypothyroid patients suffering manifestations of median nerve entrapment before and after hormone replacement therapy.

METHODS: Forty patients with a mean age of 47.8 ± 12 years diagnosed with hypothyroidism were included in this study. Electrodiagnostic workup and ultrasonographic assessment of both right and left median nerves were done at the initial time of diagnosis and 3 months of euthyroid state after hormone replacement.

Results: Thyroid hormones at the initial time of diagnosis were (48.38 ± 30 IU/mL, 7.59 ± 2.98 pmol/L, 1.79 ± 0.81 Pmol/L) and

3 months of euthyroid state after treatment were (6.33 ± 4.75 IU/mL, 15.52 ± 4.86 pmol/L, 4.06 ± 0.62 Pmol/L) for TSH, FT4, FT3 respectively ($P = 0.001$). The comparison between right and left median nerves motor and sensory functions before and after treatment showed a significant change ($P < 0.001$). Initial values of right median nerve distal and proximal CSA were 12.5 ± 2.4 mm² and 9.6 ± 0.5 mm² respectively while on the left side values were 12.4 ± 2.4 mm² and 9.9 ± 0.5 mm² respectively. After treatment, values changed to 12.0 ± 2.4 mm² (distal) and 0.096 ± 0.004 mm² (proximal) on the right side and 12.0 ± 2.3 mm² (distal) and 9.8 ± 0.5 mm² (proximal) on the left side. 25 patients (62.5 %) showed significant electrophysiological and radiological improvement with hormonal control. While fifteen patients (37.5%) were still suffering manifestations of carpal tunnel syndrome even after hormonal control.

CONCLUSION: The median nerve cross sectional area can be used as a guide for selection of patients that may benefit from a surgical release even before commencement of medical treatment.

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Key words: Hypothyroidism; Carpal Tunnel Syndrome; Ultrasonography; Median Nerve

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INTRODUCTION

Hypothyroidism is a clinical disorder due to the deficiency of the thyroid hormone. This Hormone is a key regulator of cellular

metabolism in our body. This deficient state is estimated to affect 3.8 – 4.6 % of the general population, with a fourfold affection in women^[1]. Peripheral nerve dysfunction is a well-documented feature of clinical hypothyroidism. Thyroid hormones deficiency causes sensory neuropathy by affecting different peripheral nerves especially the median nerve^[2].

The mechanism involved in the development of neuropathy in hypothyroidism still remains unclear^[3,4]. Mononeuropathies secondary to compression caused by deposition of mucopolysaccharide or mucinous deposits in the soft tissues surrounding the peripheral nerves and a polyneuropathy due to either a demyelinating process or primary axonal degeneration are the most commonly proposed mechanisms of peripheral nerve dysfunction in hypothyroidism^[5]. Myelin structure abnormalities and dysfunction of axonal-oligodendroglial processes may also be responsible for neuropathy in patients with hypothyroidism^[6,7]. Also, hypothyroidism produces alterations of fluid balance and peripheral tissue edema, which may lead to CTS development^[4].

Carpal tunnel syndrome (CTS) is the most frequent entrapment syndrome of the upper limb; it arises owing to compression of the median nerve at the wrist, which leads to an enlargement of the median nerve cross-sectional area (CSA)^[8]. An early diagnosis based on clinical and electrodiagnostic findings is essential to preventing permanent nerve damage and functional sequelae^[8]. Consequently, treatment of hypothyroidism may help to reduce or cure CTS complaints^[6]. Ultrasonography has emerged as an important diagnostic investigation for CTS^[3,6]. A number of ultrasonographic changes have been demonstrated in CTS including swelling of the median nerve, flattening of the nerve, palmar bowing and thickening of the flexor retinaculum and changes in the median nerve appearance^[3]. The most commonly described abnormality has been enlargement of the median nerve cross sectional area (CSA) usually proximal to the carpal tunnel^[9]. The aim of this study is to evaluate the efficacy of ultrasound in newly diagnosed hypothyroid patients suffering manifestations of median nerve entrapment before and after hormone replacement therapy.

METHODS

Patients

Patients with hypothyroidism were recruited from the internal medicine, neurology and general surgery outpatient clinics at Al-Husseini University hospital and the outpatient clinic of neurological surgery at Ainshams University hospital. Out of these patients, forty patients with carpal tunnel syndrome were selected according to an empirical electrophysiological assessment (irrespective of whether they had neurological complaints or not) during the period from March 2013 to January 2015. As they were newly diagnosed, none of these patients received any medical treatment for hypothyroidism or its complications. Patients showing other causes of neuropathy such as diabetes mellitus, alcoholism, liver and kidney disease, use of drugs known to cause neuropathy, malignancy or other serious illness and patients with a family history of neuropathy, patients with a history of wrist fracture or a previous surgery and injections in the wrist were excluded from the study.

Laboratory investigation

Blood samples were obtained after 12 hours fasting for estimation of all parameters. Laboratory investigations including complete blood count was estimated by fully automated cell counter (sysmex), urea, creatinine and random blood glucose were measured by colorimetric

technique^[10], liver enzymes were measured by NADH, Kinetic UV, IFCC rec^[11], electrolytes were measured by ion electrode, vitamin B12 and folic acid were measured by enzyme linked immunoassay^[12] using commercial kits from Monobind Inc US, tests were performed at the onset of the study in order to eliminate other possible causes of neuropathy and all tests were normal. Serum analyses were performed to confirm the hypothyroid state, after a detailed neurological examination. For this, free T3, free T4 by enzyme linked fluorescent assay^[13] using commercial kit from biomerieux and TSH level by enzyme linked fluorescent assay^[14] using commercial kit from biomerieux were evaluated. Reference values for our laboratory for TSH were between 0.25 and 5 uIU/ml, for FT4 between 10.6 and 19.4 pmol/l, and for FT3 between 4.0 and 8.3 pmol/l. Patients with FT4 levels below 10.6 pmol/ml and TSH levels above 5.0 uIU/ml were accepted as hypothyroidism and underwent the initial electrodiagnostic evaluation according to standard techniques and median nerve ultrasonography. Thereafter, all patients received appropriate doses of thyroxine treatment for hypothyroidism and were monthly followed up for FT4, FT3 and TSH levels throughout a 3 month period after they have achieved euthyroid state. At the end of this period, patients underwent control electrodiagnostic and ultrasonographic evaluation.

Table 1 Patients characteristics.

	Male	Female	Total
N.%	10/25%	30/75%	40
Age	Mean ±SD	49±12	47±12
	Range	30-65	25-65
Response to treatment	Responded	8 (80%)	17 (56.7%)
	Maintained on medical treatment	2 (20%)	8 (26.7%)
	Referred for surgery	0	5 (16.5%)

Table 2 Thyroid hormones before and after hormone replacement therapy (HRT).

	Minimum	Maximum	Mean±SD	T	P
TSH before HRT uIU/mL	16.5	125	48.38±30	9.099	0.000
TSH after HRT uIU/mL	0.5	25	6.33±4.75		
FT4 before HRT pmol/L	2.3	15	7.59±2.98	-12.694	0.000
FT4 after HRT pmol/L	9.5	26	15.52±4.86		
FT3 before HRT pmol/L	0.7	3.10	1.79±0.81	-24.612	0.000
FT3 after HRT pmol/L	2.9	5.30	4.06±0.62		

Electrodiagnostic Evaluation

The electrodiagnostic studies were performed according to standard techniques^[15,16]. Motor nerve conduction studies included the determination of conduction velocity, amplitudes and latencies after stimulation of the median nerve. Sensory nerve conduction studies included the antidromic determination of conduction velocity, latencies and amplitude of the sensory nerve action potential of the median nerve. A carpal tunnel syndrome was diagnosed when the median nerve distal motor and/or sensory latencies exceeded 4.4 and 3.5 ms, respectively^[16]. Distance between stimulation site and active electrode was 14 cm for median nerve sensory study.

Ultrasonographic Examinations

All sessions were performed using a 13-to 14 –MHz machine. Patients were seated near the examiner with their arms stretched; hands in a supine position, wrists resting on a flat surface and fingers were semiflexed. To avoid causing any artificial nerve deformity no additional force was applied other than the weight of the probe. Cross-sectional area (CSA) of the median nerve was measured at the distal wrist (CSA-D), and proximal forearm (CSA-P). The CSA of

Table 3 Motor conduction parameters of tested median nerve before and after hormone replacement therapy (HRT).

	Minimum	Maximum	Mean ±SD	P
RT. Median N. Motor distal latency (m/sec) before HRT	4.42	6.70	5.01 ± 0.70	0.000
RT. Median N. Motor distal latency (m/sec) after HRT	3.10	6.20	4.0±0.58	
IT. Median N. Motor distal latency (m/sec) before HRT	4.30	6.90	4.81±0.56.	0.000
LT. Median N. Motor distal latency (m/sec) after HRT	3.30	6.30	4.17±0.47	
RT. Median N. Motor NCV(m/sec) before HRT	37.00	50.00	43.92±2.9	0.000
RT. Median N. Motor NCV(m/sec) after HRT	45.00	54.00	49.37 ± 2.26	
LT. Median N. Motor NCV(m/sec) before HRT	37.00	50.00	43.35±3.31	0.000
LT. Median N. Motor NCV(m/sec) after HRT	45.00	53.00	48.62±2	
RT. Median N. Motor amplitude(µVolt) before HRT	3.00	7.00	5.0±1.2	0.000
RT. Median N. Motor amplitude(µVolt) after HRT	4.00	7.90	6.17±1.05	
LT. Median N. Motor amplitude(µVolt) before HRT	3.00	7.10	5.04±1.19	0.000
LT. Median N. Motor amplitude(µVolt) after HRT	4.20	7.50	6.15±1.05	

Table 4 Sensory conduction parameters of tested median nerve before and after hormone replacement therapy (HRT).

	Minimum	Maximum	Mean ±SD	P
RT. Median N. Sensory distal latency (m/sec) before HRT	3.50	6.0	4.41±0.71	0.000
RT. Median N. Sensory distal latency (m/sec) after HRT	2.70	4.70	3.41±0.51	
IT. Median N. Sensory distal latency (m/sec) before HRT	3.10	6.0	4.43±0.75	0.000
LT. Median N. Sensory distal latency (m/sec) after HRT	2.60	5.0	3.5±0.59	
RT. Median N. Sensory NCV(m/sec) before HRT	29.00	47.00	37.87±5.30	0.000
RT. Median N. Sensory NCV(m/sec) after HRT	40.00	54.00	45.15±3.22	
LT. Median N. Sensory NCV(m/sec) before HRT	30.00	47.00	37.14±4.02	0.000
LT. Median N. Sensory NCV(m/sec) after HRT	37.00	52.00	44.62±3.23	
RT. Median N. Sensory amplitude(µVolt) before HRT	8.00	29.00	21.97±5.33	0.000
RT. Median N. Sensory amplitude(µVolt) after HRT	12.00	33.00	25.85±4.93	
LT. Median N. Sensory amplitude(µVolt) before HRT	8.00	29.00	22.42±5.64	0.005
LT. Median N. Sensory amplitude(µVolt) after HRT	13.00	32.00	26.02±5.20	

Table 5 Distal and proximal cross area (CSA) of median nerve before and after hormone replacement therapy (HRT).

	Minimum	Maximum	Mean ±SD	P
RT. Distal CSA (mm ²) before HRT	9.1	17.0	12.5±2.4	0.0001
RT. Distal CSA (mm ²) after HRT	9.0	16.5	12.0±2.4	
LT. Distal CSA (mm ²) before HRT	9.5	18.0	12.4±2.4	0.0001
LT. Distal CSA (mm ²) after HRT	9.0	16.5	12.0±2.3	
RT. Proximal CSA (mm ²) before HRT	8.5	11.0	9.6±0.5	0.202
RT. Proximal CSA (mm ²) after HRT	8.6	11.0	9.6±0.4	
LT. Proximal CSA (mm ²) before HRT	9.4	11.4	9.9±0.5	0.030
LT. Proximal CSA (mm ²) after HRT	9.4	11.4	9.8±0.5	

Table 6 Comparison between CSA of median nerve before and after HRT as regards to patient's outcome

	Responded to HRT	Maintained on HRT	Referred for surgery	χ ²	P
LT. Distal CSA (mm ²) before HRT	11.6±1.8	12.8±2.9	15.9±0.9	9.901	0.007
LT. Distal CSA (mm ²) after HRT	11.1±1.5	12.4±2.9	15.3±0.6	9.836	0.007
LT. Proximal CSA (mm ²) before HRT	9.7±0.2	10.0±0.6	10.8±0.4	11.139	0.004
LT. Proximal CSA (mm ²) after HRT	9.6±0.2	9.8±0.5	10.6±0.7	8.604	0.014
RT. Distal CSA (mm ²) before HRT	11.6±1.7	13.2±2.5	16.0±1.0	12.618	0.002
RT. Distal CSA (mm ²) after HRT	11.2±1.8	12.3±2.7	15.5±1.0	9.642	0.008
RT. Proximal CSA (mm ²) before HRT	9.5±0.4	9.6±0.5	10.1±0.4	5.021	0.081
RT. Proximal CSA (mm ²) after HRT	9.5±0.4	9.5±0.5	10.1±0.5	5.394	0.067

median nerve was measured at the proximal inlet of carpal tunnel at level of the pisiform bone as a landmark and 12 cm proximal in the forearm by tracing a continuous line around the inner hyperechoic rim of the median nerve with electronic calipers^[17]. The CSA was measured 3 times, and the average value was used for analysis.

The examining radiologist was not permitted to ask the patients about symptoms. The only information provided to the examining radiologist was a written request from the referring neurologist that the patient will be examined for the presence of median nerve thickening. Ultrasonographic assessment was performed without knowledge of the clinical and electrodiagnostic test results.

Statistical analysis

Statistical analyses were performed by using SPSS Statistics 17.0, Release 17.0(Aug 23, 2008). Data are reported as mean ± standard deviations. The Paired –Samples T Test was used to evaluate differences in the pre and post treatment values. Kruskal –Wallis H

was used to evaluate differences between more than two groups of nonparametric data.

RESULTS

There were 30 female patients (75%) with a mean age of 47 years (ranging from 25 to 65 years) and 10 male patients (25%) with a mean age of 49 years (ranging from 30 to 65 years). The pertinent values of thyroid hormones at the initial time of diagnosis and those detected months after treatment and restoration of the euthyroid state are listed at Table 2. However, a statistically significant improvement in such values can be clearly observed (*p* value < 0.001). The electrodiagnostic findings of median nerve are summarized in Tables 3 and 4. It is to be noticed that all the measured parameters demonstrated a highly significant improvement comparing pre-treatment and post-treatment data (*p* values < 0.01). For instance, the mean right median nerve sensory distal latency changed from

4.41±0.71 m/sec before commencement of hormonal replacement therapy to 3.41±0.51 m/sec after maintenance of the euthyroid state. Moreover, the mean left median nerve sensory distal latency changed from 4.43±0.75 m/sec to 3.5±0.59 m/sec.

As detailed in Table 5, the ultrasonographic assessment revealed a statistically highly significant reduction in distal median nerve cross sectional area (CSA-d) after constitution of an euthyroid state. The mean CSA-d changed from 12.5±2.4 mm² to 12.0±2.4 mm² on the right side and from 12.4±2.4 mm² to 12.0±2.3 mm² on the left side. On the other hand, the change in proximal median nerve cross sectional area (CSA-p) was much less statistically significant.

Twenty five patients (62.5 %) had satisfactory electrophysiological, ultrasonographic and clinical (if complaining) improvement after 3 months of restoration of an euthyroid state, while fifteen patients (37.5%) failed to achieve such improvement. Out of these 15 patients, 10 (25%) patients of those with carpal tunnel syndrome were maintained on hormonal ± nonhormonal treatment for an extended period to get improved. On the contrary, five patients (12.5%) continued to suffer from intractable symptoms of carpal tunnel syndrome despite receiving available nonsurgical treatment modalities and they were referred for surgical release of the carpal tunnel according to standard techniques (Table 1). Of these five patients, three patients refused the option of surgery and preferred to continue on trials for non-surgical control while the remaining two patients were operated upon with a satisfactory post-operative outcome. As shown in Table 6, the patients who responded to hormonal replacement therapy (HRT) had smaller CSA-d ($p<.005$) on both sides than those who partially responded to therapy and who were referred for surgery.

DISCUSSION

Carpal tunnel syndrome (CTS) is a combination of signs and symptoms due to compression and trapping of the median nerve at the wrist. It is the most commonly reported peripheral nerve entrapment syndrome. A few studies performed in the United States revealed that CTS accounts for 0.2% of all ambulatory care visits^[18] and over 500,000 carpal tunnel releases in 2006^[19]. One earlier study reported that in 52% of hypothyroid patients with peripheral nervous system involvement, entrapment neuropathy was the commonest (35%) and axonal neuropathy was recorded in 9% of these patients^[20].

In this study, all our selected hypothyroid patients had significantly higher TSH levels and significantly lower FT4 and FT3 levels before the hormone replacement therapy. Also, a significant number of our patients showed nerve conduction abnormalities. At the initial time of assessment, all patients had electrodiagnostic evidence of carpal tunnel syndrome. In our patients, there were higher sensory and motor distal latencies with lower both motor, sensory nerve conduction velocities and lower motor and sensory median nerve amplitude. These findings were compatible with other investigators that revealed similar involvement of the motor portion of the median nerve and slowing of the nerve conduction velocities in different peripheral nerves but they did not mention the individual values of measured parameters like sensory distal latencies and sensory nerve conduction velocities^[15, 20, 21].

Some studies revealed that despite obtaining an euthyroid state, most patients with diagnosis of primary hypothyroidism continue to experience symptoms and electrophysiological signs of carpal tunnel syndrome^[16, 22]. In the current study, all patients were newly diagnosed cases with hypothyroidism and the carpal tunnel syndrome symptoms and/or signs and they showed a significant improvement

of symptoms and electrodiagnostic findings in 62.5% of patients ($n=25$) after their thyroid functions were normalized with hormonal replacement therapy. This was compatible with the results of Kececi and Degirmenci^[5], in their study, they found that 13 out of 15 patients with newly diagnosed hypothyroidism associated with carpal tunnel syndrome improved after 3 months of appropriate hormone replacement treatment. Also, Arafat and his colleagues^[23] concluded that 84.2% ($n=48$) of their patients had improvement in their median nerve functions after hormonal treatment, while 15.8% ($n=9$) still had carpal tunnel syndrome symptoms. This variation of response to treatment may be related to severity, duration and treatment regimens of carpal tunnel syndrome.

Currently, carpal tunnel syndrome is typically diagnosed by history taking, physical examination and electrodiagnostic results^[24, 25]. Although this approach is effective for localizing the site of pathology and determining the severity of the condition, electrodiagnostic study has its own limitations: it does not provide information about structures surrounding the nerve, it does not allow visualization of abnormalities intrinsic to the nerve, and it is painful^[26]. Over the past years, high-resolution ultrasonography has been proposed as a useful tool for the diagnosis of CTS^[27, 28]. The attraction of ultrasonography for diagnosis of CTS lies in its wide availability, lower cost, noninvasiveness, and shorter examination time^[24]. The measurement of cross-sectional area (CSA) of the median nerve at the wrist is the most widely used ultrasonography method in CTS diagnosis. Normal ranges for median nerve area at the distal wrist crease have varied among reports, ranging from 7.2 to 9.8 mm²^[29-32]; the values for diagnosing CTS range from 9 to 15 mm²^[33]. The sensitivity and specificity range from 70 to 88% and 57 to 97%, respectively^[17]. In our study, the means of distal CSA were 12.5 and 12.4 mm² in right and left median nerve respectively, ranging from 9 to 17 mm². Also, Tengfei et al^[34], reported that, the mean inlet CSA was 8.7 mm² in healthy controls and 14.6 mm² in CTS. Additionally, Andrea et al^[35], reported that distal CSA was 16.8 mm², Seok et al^[36] found that the distal CSA were significantly different from mild, moderate to severe (13.5 mm², 14.67 mm² and 18.74 mm²) cases of carpal tunnel syndrome respectively. In the current study, the means of proximal CSA were 9.6 and 9.9 mm² in right and left median nerve respectively, ranging from 8.6 to 11.4 mm². Seok et al^[36] reported that proximal CSAs for mild, moderate and severe were 7.14 mm², 6.57 mm² and 6.39 mm². Moreover, Andrea et al^[35] found only a small difference in proximal CSA between the patients (9.5 mm² ± 1.9) and the control subjects (8.7 mm² ± 1.6) and the proximal nerve to be slightly larger in the patients. These different results may be related to several personal risk factors such as age, sex, BMI, external wrist dimensions, severity and duration of hypothyroidism. However, these results indicate that the distal CSA may be much more useful in the diagnosis of CTS than proximal CSA and this conclusion is consistent among most studies, including ours. Furthermore, three months of euthyroid state after hormone replacement therapy, we found significant reduction in distal CSA ($p<.0001$), and much less significant reduction in proximal CSA ($P=0.03$). This means that the distal CSA is not only significant in the diagnosis of CTS but also it is important in the follow up after hormonal therapy and it may differentiate between symptoms of CTS and presence of other pathologies.

Surprisingly, we found that the 25 patients (62.5%) who showed clinical and/or electrophysiological improvement after 3 months of euthyroid state had smaller distal CSA (less than 11.6 ± 1.8 mm²). While, the 10 patients who required extended time to be cured recorded large distal CSA (ranging from 12.8 ± 2.9 mm² to 13.2 ± 2.5 mm²). In contrast, the remaining 5 patients with intractable CTS symptoms

who were referred for surgery had larger distal CSA (more than $15.9 \pm 0.9 \text{ mm}^2$) (Table 6). This suggests that the mechanism leading to carpal tunnel syndrome in patients with hypothyroidism might be reversible at early stages; on the other hand irreversible cases might have longer duration of disease or might present etiologies other than hypothyroidism. Long term accumulation of mucinous tissue is a possible cause of irreversibility^[21]. Moreover, this may reflect that a large distal CSA of more than 15.5 mm^2 may be a guide as a significant criterion for selection of patients that may be offered surgical treatment even before initiation of hormonal therapy whenever applicable.

CONCLUSION

With hormonal replacement therapy, carpal tunnel syndrome can be controlled in patients with hypothyroidism within three months of euthyroidism. In addition, in patients having a symptomatic median nerve entrapment, the median nerve cross sectional area can be used as a guide for selection of patients that may benefit from a surgical release even before commencement of medical treatment.

ETHICS STATEMENT

All patients were informed about the content of the study and gave their written approvals before enrollment. All procedures were performed in accordance with the ethical standards of Al-Azhar University's committee on human experiments.

Author Contribution

Osama A. Khamis, Hegazy M Altamimy, Salama S. Abdellatif, Hossam I. Abdul-Hamied, Ahmed Abdelfattah Mostafa and Ahmad E D Elayouty contributed equally to the manuscript.

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