

# Sympathetic skin responses and electromyographic reaction times in chronic autoimmune thyroiditis: An overlooked electrodiagnostic study

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## ABSTRACT

**Objectives:** This study aims to evaluate peripheral nerve functions, sympathetic skin responses (SSRs), and electromyographic (EMG) reaction times in hypothyroid patients and to compare them to healthy individuals.

**Patients and methods:** Between January 2007 and September 2007, a total of 54 patients with Hashimoto's thyroiditis including 35 euthyroid (3 males, 32 females; mean age: 45.2±10.2 years; range, 35 to 60 years) and 19 with subclinical hypothyroidism (2 males, 17 females; mean age: 43.2±12.6 years; range, 40 to 65 years) were included in the study. The control group consisted of 35 healthy individuals (5 males, 30 females; mean age: 39.1±9.3 years; range, 29 to 52 years). Nerve conduction studies (NCSs), SSRs of the hand and foot obtained by stimulation of the contralateral median nerve, and EMG reaction times of the extensor indicis proprius muscle were performed in all subjects.

**Results:** There was no significant difference in peripheral NCSs and SSRs between patients and the control group. However, reaction times were longer in the AIT patients compared to the healthy individuals suggesting alterations in cognitive function related to the primary disease process in AIT.

**Conclusion:** Electrodiagnosis of autonomic nervous system involvement and cognitive impairment can be challenging in AIT. However, EMG reaction times and SSRs are practical and useful tools that are often overlooked. On the other hand, SSRs may be combined with more quantitative tests, such as sudomotor axon reflex testing, to allow us to better determine the extent of involvement of the autonomic nervous system in AIT.

**Keywords:** Autonomic nervous system, chronic autoimmune thyroiditis, electromyographic reaction times, peripheral neuropathy, sympathetic skin responses.

Hashimoto's thyroiditis is one of the most frequent autoimmune thyroiditis (AIT) and most common cause of primary autoimmune hypothyroidism.<sup>[1,2]</sup> Autonomic nervous system involvement and neuromuscular problems are common in patients with hypothyroidism and include polyneuropathy and proximal myopathy,

with up to 80% of patients complaining of related symptoms.<sup>[3]</sup> The most common neuropathy is carpal tunnel syndrome (CTS) with a prevalence of up to 44%.<sup>[4,5]</sup> Similarly, thermoregulatory function controlled by the sympathetic nervous system may also be affected by thyroid hormone levels; however the effects are variable.<sup>[6-10]</sup> Sympathetic skin responses

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(SSRs) facilitate the evaluation of sudomotor activity of unmyelinated sympathetic fibers belonging to the autonomic nervous system.

To the best of our knowledge, there are no studies in the literature investigating SSR in patients with subclinical hypothyroidism. Moreover, neurocognitive impairment may also be a marked feature of hypothyroidism, particularly in elderly patients.<sup>[8,9]</sup> Previous studies have shown that electromyographic (EMG) reaction times are highly sensitive parameters in providing data on cognitive and motor function.<sup>[10]</sup>

In the present study, we aimed to evaluate peripheral nerve function, SSR and EMG reaction times in hypothyroid patients and to compare the findings with healthy individuals.

## PATIENTS AND METHODS

This observational study was conducted at Baškent University Faculty of Medicine, Department of Physical Medicine and Rehabilitation between January 2007 and September 2007. Patients with a diagnosis of chronic autoimmune thyroiditis (Hashimoto's thyroiditis) were included in the study. Patients with peripheral neuropathy or suffering from an illness which could result in peripheral neuropathy or affect the autonomic nervous system including diabetes, amyloidosis, Parkinson's disease, multiple sclerosis, paraneoplastic syndrome, systemic lupus erythematosus and those who were smokers or regularly consumed alcohol were excluded from the study. Finally, a total of 54 patients with Hashimoto's thyroiditis including 35 euthyroid (3 males, 32 females; mean age: 45.2±10.2 years; range, 35 to 60 years) and 19 with subclinical hypothyroidism (2 males, 17 females; mean age: 43.2±12.6 years; range, 40 to 65 years) were included in the study. The control group consisted of 35 healthy individuals (5 males, 30 females; mean age: 39.1±9.3 years; range, 29 to 52). Data including demographic details, date of onset of hypothyroidism, previous medical and drug history, neuromuscular complaints, most recent thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4) values, anti-thyroglobulin (anti-Tg), and anti-thyroid peroxidase (anti-TPO) levels were recorded. The patient group was further divided into two groups: those who were currently euthyroid with normal TSH, T3, and T4 levels and those with subclinical hypothyroidism with elevated TSH levels and normal T3 and T4 levels according to the laboratory's normal range.

The control group was formed of age- and sex-matched healthy individuals with no history of thyroid disease.

A written informed consent was obtained from the patient. The study protocol was approved by the Baškent University Faculty of Medicine Ethics Committee (No: KA06/271). The study was conducted in accordance with the principles of the Declaration of Helsinki.

### Electrophysiological evaluation

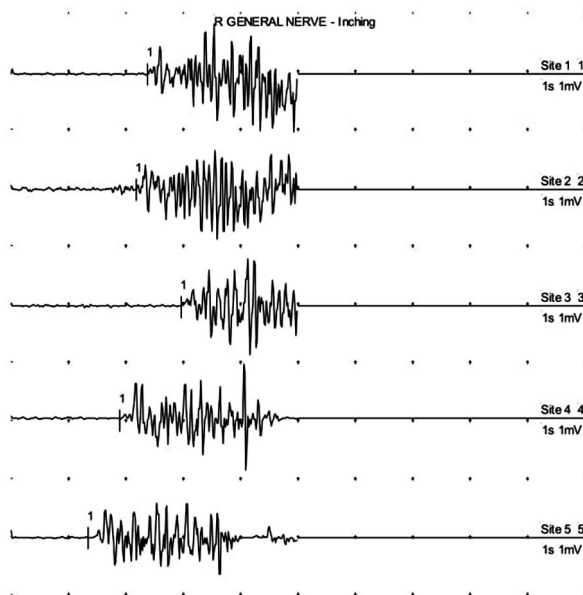
All study participants underwent electroneuromyography (ENMG) performed by a single physiatrist who was blind to the patient groups. Following the laboratory's polyneuropathy protocol, nerve conduction studies were performed. Distal motor latencies (DMLs), motor nerve conduction velocities, and compound muscle action potentials (CMAPs) were calculated using disc surface cup (Ag/AgCl) recording electrodes which were 9 mm in diameter. The time of the onset of potential was defined as DML. The height from the baseline to the first negative peak of the action potential was described as CMAP amplitude. Antidromic sensory conduction velocity, peak-to-peak sensory nerve action potential amplitudes, and distal sensory latencies were recorded using ring electrodes. When the right arm recordings were consistent with CTS, the left arm was also studied. Electrophysiological parameters were assessed according to the normal values of our laboratory. A minimum ambient temperature of 25°C and distal extremity skin temperature of >32°C was conserved during all electrophysiological studies.

### Electromyographic reaction times

Premotor reaction times of the right extensor indicis proprius were measured. The active electrode was placed on the belly of the right arm extensor indicis proprius muscle and the reference electrode on the tendon of the muscle. The initial threshold stimulus was determined by stimulating the left tibial nerve posterior to the medial malleolus. The patient was told to raise their right index finger, when they felt the stimulus. After 10 practice trials, a total of five stimuli were given at irregular intervals and the mean of the initial latencies of the responses were recorded as simple reaction time (Figure 1).<sup>[10]</sup>

### Sympathetic skin responses

Sympathetic skin responses were recorded with the active electrodes placed in the left palm and sole of the foot and the reference electrodes on the dorsum



**Figure 1.** Electromyographic reaction times recorded from the hand.

of the left hand and foot, while the patient was in the reclining position. A two-channel recording from foot and hand were obtained simultaneously by stimulating the contralateral median nerve at the level of the wrist.<sup>[11]</sup> The stimulus was increased to just above the threshold level and applied irregularly to avoid habituation. A total of five potentials were recorded and the mean values were used for analyses.

Electrophysiological studies were conducted using the Medelec® Synergy Multimedia electromyograph (Oxford Instruments, Medical System Division, England).

### Statistical analysis

Prior to study, no similar study was found on which to base a power analysis. Articles on adequate sample size in initial studies recommend a sample size of between 10 and 30 patients.<sup>[12]</sup> Therefore, a sample size between 10 and 30 patients per group was attained.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 11.5 software (SPSS Inc., Chicago, IL, USA). Continuous data were expressed in mean  $\pm$  standard deviation (SD), while categorical data were expressed in number and frequency. Normal distribution of the continuous variables was determined using the Shapiro-Wilk test. Significance of between group differences in variables was analyzed using the Mann-Whitney U test in the presence of two independent groups and using the one-way analysis of variance (ANOVA) in the presence of more than two independent groups. When the one-way ANOVA results showed a significant difference between the groups, the Tukey post-hoc test was used to identify the group responsible for the difference. The Friedman test was used to test for a within group significant change in repeated reaction times and sympathetic response values over time. When the results of the Friedman test were significant, the Friedman multiple comparison test was used to determine the reaction times responsible for the

**TABLE 1**  
Demographic and clinical data of the patients

	Euthyroid (n=35)			Subclinical hypothyroid (n=19)			Control group (n=35)			p*
	n	%	Mean $\pm$ SD	n	%	Mean $\pm$ SD	n	%	Mean $\pm$ SD	
Age (year)			45.2 $\pm$ 10.2			43.2 $\pm$ 12.6			39.1 $\pm$ 9.3	0.052
Sex										0.747
Male	3			2			5			
Height (m)			1.6 $\pm$ 0.7			1.6 $\pm$ 0.6			1.7 $\pm$ 0.9	0.180
Weight (kg)			71.0 $\pm$ 11.0			64.4 $\pm$ 11.0			72.7 $\pm$ 14.7	0.067
Time since diagnosis of AIT										
<1 year	9	25.7		13	68.5		N/A			0.927
1-5 years	16	45.7		5	26.3		N/A			0.162
6-10 years	5	14.3		0	0		N/A			0.084
>10 years	5	14.3		1	5.3		N/A			0.314
Oral thyroxine use	29	82.9		5	26.3		N/A			<0.001

SD: Standard deviation; AIT: Autoimmune thyroiditis; N/A: Not applicable; ANOVA and Chi Square test; \* p<0.05.

**TABLE 2**  
Sympathetic skin responses recorded from the hand and foot

	Latency (msec)	Amplitude (mV/ $\mu$ V)
	Mean $\pm$ SD	Mean $\pm$ SD
Hand SSR		
Euthyroid	1.3 $\pm$ 0.2	2,052.3 $\pm$ 1,260.9
Subclinical hypothyroid	1.2 $\pm$ 0.3	1,918.0 $\pm$ 1,206.0
Control	1.4 $\pm$ 0.2	1,376.1 $\pm$ 936.0
Foot SSR		
Euthyroid	2.0 $\pm$ 0.3	1,087.6 $\pm$ 816.3
Subclinical hypothyroid	2.1 $\pm$ 0.2	761.2 $\pm$ 626.3
Control	2.2 $\pm$ 0.3	789.9 $\pm$ 688.1

SD: Standard deviation; mV: Millivolt;  $\mu$ V: Microvolt; SSR: Sympathetic skin response; msec: Milliseconds.

difference. Bonferroni corrections were made for within group comparisons. The Pearson correlation test was used to determine the presence of a linear correlation between reaction times, SSR measurements and age, TSH, anti-TPO and anti-Tg. The chi-square test ( $\chi^2$ ) was used for the cross tabs of categorical data. A *p* value of <0.05 was considered statistically significant.

## RESULTS

A total of 54 patients with Hashimoto's thyroiditis (35 euthyroid and 19 patients with subclinical hypothyroid) were included in the study. A post-hoc analysis based on a total of 54 patients (n=35 vs. n=19) included in the study revealed a power of 0.69. The mean time since diagnosis of hypothyroidism was 3.1 $\pm$ 1.1 years in the euthyroid group and 1.9 $\pm$ 1.1 years in the subclinical hypothyroid group. Twenty-nine (82.9%) of the euthyroid, and five (26.3%) of the subclinical hypothyroid patients were receiving thyroxine. Demographic and clinical data of patients are shown in Table 1.

About half of the euthyroid and subclinical hypothyroid patients had comorbidities, most commonly hypertension, hyperlipidemia, osteoporosis, depression, and cardiac arrhythmias. Twelve of the euthyroid (34.3%) and six (31.6%) of the subclinical hypothyroid group had complaints of altered sensation, such as paresthesia in the hands and legs. The presence of positive sensory symptoms in the hands and feet between the patient groups was not statistically significant (*p*=0.84;  $\chi^2$ =0.041). As expected, the mean TSH level was significantly higher in the subclinical hypothyroid group (mean TSH value 12.1 $\pm$ 8.1 mU/L) compared to the euthyroid group (mean TSH value 2.0 $\pm$ 1.2 mU/L) (*p*<0.001). There was no significant difference in serum T3, T4, anti-TPO and anti-Tg levels

between the two patient groups (*p*=0.102, *p*=0.065, *p*=0.158 and *p*=0.433, respectively). Nerve conduction studies revealed no significant difference between all groups, except for median nerve forearm sensory conduction velocity which was lower in the patient group, compared to the control (*p*=0.019). Three of the euthyroid (8.6%), one of the subclinical hypothyroid (5.3%), and four (11.4%) of the control group patients had CTS. One of the subclinical hypothyroid patients had a moderate sensorimotor polyneuropathy. Sympathetic skin responses were obtained from all the patients. The mean latency of the five repeats of SSR of the hand and foot are given in Table 2. There was no statistically significant difference in hand and foot SSR latency and amplitudes among the groups (*p*>0.05). Similarly, there was no correlation between age and SSR in the patient groups (*p*>0.05). There was a weak, positive correlation between hand SSR latencies and age (*r*=0.44, *p*=0.012) in the control group.

In the intra-group analysis, we found no statistically significant difference in the euthyroid group (*p*=0.265), subclinical hypothyroid group (*p*=0.180), and the control group (*p*=0.369) reaction times. However, while analyzing intergroup reaction times, there was significantly longer mean reaction times in the euthyroid and subclinical hypothyroid group compared to the control group (Table 3).

**TABLE 3**  
Mean reaction times for all groups

Reaction time (msec)	Mean $\pm$ SD	<i>p</i> *
Euthyroid group	183.5 $\pm$ 49.9	
Subclinical hypothyroid group	185.3 $\pm$ 48.0	0.015
Control group	158.3 $\pm$ 38.6	

SD: Standard deviation; msec: Milliseconds; ANOVA test; \* *p*<0.05.

TABLE 4

Hand and foot SSR latencies in those being treated with thyroxine compared to those not being treated with thyroxine

	Median	IQR	<i>p</i> *
Hand latency (msec)			0.242
Thyroxine treatment	1.28	0.04	
No thyroxine treatment	1.22	0.04	
Foot latency (msec)			0.781
Thyroxine treatment	2.09	0.05	
No thyroxine treatment	2.07	0.04	

SSR: Sympathetic skin response; msec: Milliseconds; IQR: Interquartile range; Mann-Whitney U test; \* *p*<0.05.

There was no overall significant difference in hand and foot SSR latency values of those on thyroxine to those not on hormone replacement therapy both in the euthyroid and subclinical hypothyroid groups (Table 4). However, the mean reaction times were longer in patients receiving thyroxine in the euthyroid group (*p*<0.05). No significant correlation was found between TSH, anti-TPO, anti-Tg and SSR, and reaction times neither in the euthyroid nor the subclinical hypothyroid groups (*p*>0.05). However, there was a negative correlation between foot SSR latency and anti-TPO levels in the euthyroid group (*r*=0.609, *p*=0.004).

## DISCUSSION

The results of this study showed a significant prolongation in the mean reaction times in euthyroid and subclinical hypothyroid patients, but no significant differences in SSRs compared to healthy individuals. The mechanisms affecting cognitive functions in hypothyroidism have not been fully elucidated. In a study by Khedr et al.,<sup>[13]</sup> central nervous system (CNS) dysfunction was particularly apparent than the peripheral nervous system (PNS), suggesting that CNS was more vulnerable to the effect of hypothyroidism than the PNS. Event-related potentials in hypothyroid patients as a measure of CNS function were also delayed in the study by Nazliel et al.<sup>[14]</sup> Del Ser Quijano et al.<sup>[15]</sup> also found a reduction in cognitive functions such as mini-mental status examination, attention and verbal fluency in subclinical hypothyroid and mild hypothyroid patients. These findings suggest that early electrophysiological evaluation of both the CNS and PNS is important in hypothyroid patients, even in the asymptomatic ones, in detecting involvement of the CNS.

Evaluation of reaction times is a simple way of determining the level of cognitive function and sensory

perception and is influenced by motor and premotor activity. Premotor reaction time represents the time lapse between stimulus onset and muscle activity as represented by EMG. Motor time represents the time interval between onset of EMG activity and beginning of an actual movement.<sup>[16,17]</sup> In this study, the premotor times are the reaction times measured using EMG and represent the perceptual and cognitive processing time.<sup>[14,18]</sup> Reaction times begin to slow in the 50 to 60 age group; however, a more marked increase is seen in the over 70s.<sup>[19]</sup> Prolongation in reaction time in this study may be interpreted as a parameter which reflects changes in cognitive functions associated with the primary disease process. However, half of our patients had comorbidities such as depression. This is an important issue, as depression may also result in cognitive dysfunction and, thus, alteration of reaction times. The lack of evaluation of cognitive functions by validated tests prior to study commencement is a limitation of this study. In our study, the increase in reaction times in the euthyroid patients who were on thyroxine is consistent with the hypothesis that some neuromuscular changes secondary to hypothyroidism are irreversible, despite pharmacotherapy and symptomatic improvement.<sup>[20]</sup>

The autonomic nervous system, an important component of the CNS and PNS, may also be affected in AIT. In a study by Merello et al.,<sup>[21]</sup> SSRs in patients with AIT and autoimmune vitiligo were examined and the responses changed, particularly in the patients with both disorders. On the contrary, in our study, there was no significant difference in SSRs in the euthyroid, subclinical hypothyroid patients, and control group. Although this is consistent with the findings of Guatam et al.,<sup>[22]</sup> who found no significant difference in SSR between hyper-, hypo-thyroid women and the control group, the absence of pathology in SSR in our study may not rule out autonomic involvement. Sahin et al.<sup>[23]</sup> reported that subclinical hypothyroidism might affect cardiac autonomic activity in line with TSH levels. We agree with the researchers that, since SSRs are semi-quantitative tests, combining them with cardiovascular tests would be more determinative in the evaluation of autonomic nervous system functions in AIT.<sup>[7]</sup> In our study, no significant relationship was found between the age and SSR latencies in patient groups, whereas hand SSR latencies recorded in the control group were weakly correlated with age, which can be considered as a result close to the study by Drory et al.<sup>[24]</sup> The weak negative correlation between foot SSR latencies and anti-TPO levels in the

euthyroid patient group appears to be a coincidental result.

Hypothyroidism may result in a variety of reversible neuromuscular problems such as reduced muscle power, myalgia and cramps, which is reported to occur in 79 to 100% of sufferers.<sup>[1,13]</sup> Polyneuropathy and myopathy have been reported in 20 to 70% and 35 to 88% of patients respectively;<sup>[25]</sup> moreover, it is believed that sensory polyneuropathy is more common in hypothyroid patients.<sup>[26]</sup> Several studies have shown that the severity of neuromuscular symptoms are correlated with level and duration of hormonal deficiency, whereas the others show the contrary.<sup>[27,28]</sup> In the current study, only one case of sensorimotor polyneuropathy was diagnosed in a male patient in the subclinical hypothyroidism group who was on thyroxine replacement therapy. Undoubtedly, the incidence of polyneuropathy was much lower than in previous studies.<sup>[29]</sup> The main reason for this may be as this study group consisted of patients with euthyroid or subclinical hypothyroid AIT, while the literature data are usually based on cases with overt hypothyroidism. Our findings are consistent with studies which have been conducted on patients with subclinical hypothyroidism in which electrophysiological peripheral nerve functions and brain stem auditory evoked potentials have been reported to be grossly normal.<sup>[30,31]</sup>

In the current study, we found no significant difference in the incidence of CTS in the patient group. This is in contrast with previous studies conducted on patients with overt hypothyroidism.<sup>[31]</sup> Furthermore, it has been reported that build-up of mucopolysaccharides in the tendon sheaths and synovial membranes over time may place pressure on the median nerve causing CTS.<sup>[27,28]</sup> Therefore, it may be presumed that CTS may occur more commonly in severe hypothyroid patients rather than euthyroid or subclinical hypothyroid patients with longer disease duration. In this study, 71.4% of the euthyroid and 94.8% of the subclinical hypothyroid patients were diagnosed with AIT as recently as within the past four years.

There are certain limitations to the study. First, relying solely on SSR results while commenting on the function of the autonomic nervous system may have led us to draw inaccurate or incomplete conclusions. Combining SSR with more quantitative tests, such as cardiac R-R interval variability analysis and sudomotor axon reflex testing, may have been more sensitive in demonstrating autonomic nervous system involvement in AIT patients. Second, cognitive

function of the patients was not evaluated in this study. Determining the level of cognitive function of patients using validated tests may have been helpful in evaluating the correlation between prolonged reaction times and cognitive function.

Electrodiagnosis of autonomic nervous system involvement and cognitive impairment can be challenging in AIT. However, EMG reaction times and SSRs are practical and useful tools that are often overlooked. We believe that further large-scale, prospective studies including more severely hypothyroid AIT patients, focusing only on autonomic nervous system or cognitive functions, which make use of additional reliable measures are necessary to gain more insight on the influence of the course of disease on reaction times and SSRs.

#### Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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