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Subclinical Hypothyroidism as a Possible Cause of Herpes Zoster Reactivation

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ABSTRACT

Background: Hypothyroidism was considered as a predisposing factor for herpes zoster (HZ) infection. Thus, Thyroxine deficiency may be a risk factor for varicella zoster virus reactivation. The aim of this study was to test if thyroid hormone supplementation will ameliorate the clinical course of HZ infection.

Methodology: This was a prospective cohort conducted on 60 herpes zoster infected patients, who had a subclinical hypothyroidism. Serum TSH and FT4 measurements were made by using electrochemiluminescence immunoassay. All patients were divided into two groups. Group A included 30 patients who were treated with Eltroxin 25 µg daily for 3 months. Group B included 30 patients who took placebo. All were submitted to cutaneous examination (e.g., rash and new lesions). Any complications were documented. Pain was assessed before and after treatment, and any pain-controlling medications were registered. The primary endpoints were time to achieve complete pain cessation, time to cessation of the formation of the new lesions, and time to > 50% crusting/healed lesions. Secondary outcome included time to 100% crusting/healed lesions, time to complete absence of moderate to excruciating pain, time to first pain-free period, and time to absence of abnormal sensations.

Results: Both groups were comparable regarding patient age, gender, chronic medical diseases, and characteristics of herpes zoster rash. Ophthalmic zoster was reported in 6.7% and 10% of groups A and B respectively. However, group A (Eltroxin supported) had much better and rapid and rash healing of pain than group B. Finally, zoster-related complications were significantly lower in group A than group B.

Conclusions: Subclinical hypothyroidism is associated with HZ reactivation process, so hypothyroid medical treatments are effective in this case.

Keywords: Thyroid Hormone; Eltroxin; Hypothyroidism; Herpes Zoster.

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INTRODUCTION

Thyroid hormones (TH), specifically T3 and T4 play crucial regulatory roles in the normal function of almost every organ of the human body. These roles at the physiological level include proliferation, differentiation, and apoptosis, etc. Disruption of thyroid hormone synthesis or its functions lead to widespread endocrine manifestations due to inadequate iodine levels, partial or total thyroidectomy, or any genetic defects [(1)]. Consequently, the deficiency of thyroid hormones may lead to the development of serious disorders (e.g., cretinism, dementia, arrhythmias, and even death). The physiological actions of thyroid hormones are mediated through its receptor (TR), which is a transcriptional factor that controlling gene expression. Hormone inequalities have been hypothesized to affect the overall process of viral pathogenesis. Literature suggests that thyroxine plays a significant role in the herpes simplex type-1 (HSV-1) gene silencing and replication. It may also impact the viral latency and reactivation processes [(2)].

Subclinical hypothyroidism is biochemically defined as an elevated serum thyrotropin level in combination with a serum free T4 level that is within the population reference range. The overall incidence of subclinical hypothyroidism varies greatly among different populations. It usually ranges from 3 to 15%. Increasing age, with a higher incidence associated with increasing age, female sex, and a suboptimal iodine status [(3)].

The relationship between serum thyrotropin and free thyroxine (T4) is such that a small reduction in the levels of free T4 can lead to a relatively large increase in serum values of thyrotropin. This could subsequently lead to levels of thyrotropin which are above the reference values while the free thyroxin levels are still within the normal reference range. In the situations of progression to overt hypothyroidism, the thyrotropin levels typically continue to increase and the free T4 level falls below the normal reference range. In this respect, subclinical hypothyroidism can be seen as a mild form of thyroid failure, one that is caused by autoimmune thyroid disease in the majority of cases [(4)].

Alpha Human Herpes Virus (αHHV) refers to a superfamily of herpes viruses (HSV-1, HSV-2, and varicella zoster virus (VZV)). These viruses are able to infect humans, and become dormant within the neurons after the primary phase of infection. The majority of HSV-1 and HSV-2 infections are usually subclinical. However, complications such as encephalitis caused by HSV-1 reactivation responsible for nearly 10% of viral encephalitis. HSV reactivation and its mechanisms are still not fully understood. Factors such as physical and emotional stress have been considered as triggers of HSV reactivation with one of them being concurrent reduction of the thyroxine hormone levels [(5)].

VZV is a pervasive human neurotropic virus, and is a member of the αHHV superfamily. Like the HSV, it can establish dormancy in the sensory ganglion neurons after the primary infection phase. Children are usually infected by the VZV. The dormant VZV can reactivate decades later to cause zoster (commonly known as shingles) as well as a number of severe optical and neurological consequences. It is hypothesized that thyroxine hormone imbalance may participate in the reactivation of VZV as well [(6)].

Following the primary assault, varicella zoster virus (VZV) may establish a dormant state of infection within the dorsal root ganglia. Reactivation may occur decades later as herpes zoster (HZ, shingles), after the patient's initial exposure (varicella, chickenpox). While usually a self-limited painful skin rash, shingles can be serious, with complications such as post-herpetic neuralgia (PHN), and the disease results in a significant economic burden. The association between thyroid hormone disturbances and the shingles pathophysiology has been previously mentioned, but this is not well-investigated [(7)].

Herpes zoster is caused by the reactivation of a primary infection by varicella zoster virus. After a primary infection, the virus lies dormant in dorsal root or cranial nerve ganglia. Reactivation causes the typical dermatomal pain and vesicular rash. Varicella zoster (commonly known as chickenpox) and herpes zoster (commonly known as shingles) are caused by the same herpes virus. Varicella follows the primary infection and causes a generalized rash, whereas HZ reactivated years later, and clinical manifestations are usually localized to a definite dermatome [(8)].

It has been previously reported that thyroid hormones partially contribute to the HSV-1 replication and reactivation [(9)]. This was the first study pointe to the link between low values of thyroxines and reactivation of VZV and proposed that thyroxines may protect from VZV reactivation.

In this study we aim to detect relation between subclinical hypothyroidism and HZ infection and possible role of thyroxine treatment on the course of HZ infection.

METHODOLOGY

This prospective cohort study was included in internal medicine and dermatology departments (New Damietta university hospital, Al-Azhar University, Egypt). It was conducted on 60 herpes zoster infected patients diagnosed with subclinical hypothyroidism whom received low dose of Eltroxin and showed significant lower rate of post herpetic neuralgia as the severity of pain and need for analgesia or anti-depressant. Patients were included if they were 18 years or older without any symptoms of hypothyroidism and did not take any hypothyroidism medication previously. Individuals who received HZ vaccine or those with any other thyroid disorder were excluded from the study. An informed consent was taken from every patient. All patients were managed following hospital protocols.

A high serum TSH level and normal free thyroxine

(FT4) level was required for the diagnosis of subclinical hypothyroidism [10]. Serum TSH and FT4 measurements were made by using electrochemiluminescence immunoassay "ECLIA" method. The analytical sensitivity for TSH is 0.005 ulU/ml and for FT4 is 0.023 ng/dL. The normal range for TSH is 0.27-4.2 ulU/ml and for FT, is 0.93–1.7 ng/dl [11].

All patients were divided into two groups. Group A: contained 30 patients who were treated with Eltroxin 25 µg daily for 3 months. Group B: contained 30 patients who took placebo. The study was approved by the ethics review committee of university and university hospital.

Cutaneous assessment was performed. It was composed of the assessment of any new lesions, including any increase in the lesion's area; the ratio of the present rash (e.g, macules/papules, vesicles, crusts), healed lesions and dissemination. Any complications were noticed and documented. Pain, burning sensations or any forms of discomfort (e.g, allodynia, paresthesia, dysesthesia, or hyperesthesia) were assessed. Pain severity was scored according to a six-point scale (0 for no pain; 1 for just noticeable pain; 2 indicates mild pain; 3 indicates moderate pain; 4 for severe pain; 5 for agonizing or excruciating pain). The pain controlling medications (e.g., analgesics and antidepressants) or other drugs were also recorded. The baseline demographic characteristics recorded included age, sex, and comorbid chronic diseases

The primary efficacy endpoints were time to complete cessation of pain, time to cessation of new lesion formation, and time to > 50% crusting/healed lesions (the time by which 50% or more of the rash had crusted over or completely healed). Secondary endpoints included time to 100% crusting/healed lesions, time to complete cessation of moderate to agonizing pain, time to first pain-free period (> 28 days without pain), and time to cessation of abnormal sensations.

Statistical analysis of data: The collected data were fed to a personal computer compatible with IBM-computers. Continuous normally distributed data were expressed by their arithmetic mean and standard deviation and two groups were compared by student "t", independent samples-test. Otherwise, the categorical variables were expressed by the relative frequency and percentages and groups compared by Chi square test or Fisher Exact test. P value < 0.05 was considered significant.

RESULTS

Patients' characteristics were depicted in table (1). There were no significant differences between groups A and B regarding patient's age, gender and associated chronic medical diseases. Patients mean age was 55.90 and 53.95 years in the groups A and B respectively. Males represented 47% and 43% of groups A and B respectively.

The characteristics of herpes zoster rash is presented in table (2). The duration of rash was shorter in group A than group B (6.5±2.3 vs 7.1±2.3 years, respectively). However, the difference was statistically non-significant. In addition, the ophthalmic zoster was reported in 6.7% and 10% of groups A and B respectively. The difference was statistically non-significant. In addition, no significant difference was reported for associated chronic medical disease.

Results of the current work revealed that, there was significant difference between the two groups regarding Herpes Zoster-associated pain characteristics. Group A pain healing was much better than group B (Table 3). Rash healing characteristics are showed in table (4). There was significant difference between the two study groups as rash healing, which was much faster in group A than group B.

There was significant difference between two study groups regarding Zoster-related complications as complications were much lower in group A [Eltroxin] than in group B [Placebo] (Table 5).

Table (1): Baseline characteristics of the study groups.

Variable	Group A [Eltroxin] (N = 30)	Group B [Placebo] (N = 30)	P-value
Age	55.90 ± 17.84	53.95 ± 16.75	0.66
Sex			
Male	14 (46.7%)	13 (43.3%)	0.795
Female	16 (53.3%)	17 (57.3%)	
Chronic conditions/diseases			
Diabetes	11 (36.7%)	12 (40.0%)	
Kidney	5 (16.7%)	4 (13.3%)	
Heart	6 (20.0%)	7 (23.3%)	0.928
Lung	3 (10.0%)	4 (13.3%)	
Liver	5 (16.7%)	3 (10.0%)	

Table (2): HZ Rash characteristics.

Variable	Group A [Eltroxin] (N = 30)	Group B [Placebo] (N = 30)	P-value
Duration of rash (Days)	6.5 ± 2.3	7.1 ± 2.5	0.337
Ophthalmic zoster	2 (6.7%)	3 (10.0%)	0.64

Pain severity			
None to mild	10 (33.0%)	11 (36.7%)	0.944
Moderate	12 (40%)	12 (40%)	
Severe to excruciating	8 (27%)	7 (23%)	

Table (3): Herpes Zoster-associated pain through medication course.

Variable	Group A [Eltroxin] (N = 30)	Group B [Placebo] (N = 30)	P-value
Cessation of moderate to excruciating pain	7.2 ± 2.6	14.8 ± 4.3	<0.0001*
First pain-free period	28.4 ± 5.4	36.2 ± 8.9	<0.0001*
Cessation of abnormal sensations	32.7 ± 6.2	49.8 ± 13.4	<0.0001*
Cessation of pain after 100% crusting or healed lesions	19.5 ± 5.6	32.4 ± 7.9	<0.0001*

Table (4): Rash healing characteristics.

Variable	Group A [Eltroxin] (N = 30)	Group B [Placebo] (N = 30)	P-value
Cessation of new lesion formation	2.1 ± 0.6	6.6 ± 1.3	<0.0001
50% crusting or healed lesions	4.2 ± 1.2	9.6 ± 2.3	<0.0001
100% crusting or healed lesions	9.4 ± 2.4	18.4 ± 4.3	<0.0001

Table (5): Zoster-related complications through treatment course.

Variable	Group A [Eltroxin] (N = 30)	Group B [Placebo] (N = 30)	P-value
Ocular involvement	2 (6.7%)	9 (30.0%)	0 .0195*
Motor neuropathy	1 (3.3%)	12 (40.0%)	<0.001*
Cutaneous	3 (10.0%)	10 (33.3%)	0.028*
Central nervous system	1 (3.3%)	7 (23.3%)	0.023*
Visceral dissemination	1 (3.3%)	6 (20.0%)	0.044*
Other	3 (10.0%)	13 (43.3%)	0.0035*

DISCUSSION

Hypothyroidism association with HZ reactivation has been investigated. The hypothesis of thyroid hormone (TH) contribution in the process of viral reactivation was first suggested in HSV-1 studies.

Bedadala *et al.* [12] reported that thyroxin receptor (TR) provokes epigenetic regulation on HSV-1 ICP0 gene expression in the neurons and could have a role in the complex processes of HSV-1 dormancy/reactivation. Also, **Hsia *et al.*** [13] proposed that tri-iodothyronine (T3) could regulate the expression of HSV-1 gene through its receptor by modification of histones in the cultured neurons.

The hypothesis was that lower thyroid hormone levels are associated with an increase in VZV reactivation and that patients with hypothyroidism on thyroid hormone supplementation maintain a better-controlled thyroxine levels, leading to a lower risk of HZ infection. It was expected that the hazard ratio (HR) comparing the herpes zoster risk between those with thyroid hormone medication and those without such medications would be close to unity.

Ajavon *et al.* [6] has been suggested that a temporary reduction of the hormone may be enough to relieve the TH-mediated suppression of HZ gene expression. Thus, initiating the process of viral reactivation. Also results demonstrated that a thyroxine hormones imbalance may affect reactivation of VZV at different incidence rates in different races and age groups.

Previous studies examined different hypothyroidism medications as additional treatment of HZ reactivation [13]. It is probable that thyroid hormone medicines, as an external source, keep the serum levels of TH at a more stable baseline. Thus, reducing the influence of hormone fluctuations. The individuals not taking TH medication are more vulnerable to HZ since their TH levels are often affected by internal/external stress stimuli [14].

In our study there was no significant difference regarding basal characteristics of both groups to overcome results bias through the study. L-thyroxine appeared to be a very efficacious in the treatment either primary or secondary hypothyroidism then we hypothesized it is a better medication for subclinical hypothyroid HZ reactivation.

There was a high prevalence of diabetes in our study groups up to 37% in group A and 40% in group B most probably due to that our population is formed of Egyptians only. **Assaad Khalil *et al.*** [15] reported high prevalence of diabetes up to 55%.

In our study there was high significant difference between study groups regarding cessation of pain and abnormal sensation. Also reaching pain free period and healing were significant faster in group A. Same results

were revealed by **Söltz-Szöts *et al.*** [16] study although used medications were different. Also, **Hsia *et al.*** [13] reported better outcomes in hypothyroidism medication group.

In our study eltroxin helped better prognosis and faster healing that decreased other systems affection and zoster-related complications through treatment course.

Joesoef *et al.* [17]**,** reported hypothyroidism as chronic medical condition associated with HZ affection and reactivation. Also, medical treatment improves medical condition and healing process.

Previous studies revealed that longer treatment course may cause more related complication [18]**,** that as accepted in our study as Zoster-related complications were significantly increased in group B which took placebo. Also, **Söltz-Szöts *et al.*** [16] reported more complications with longer treatment duration.

Conclusion:

Subclinical hypothyroidism is associated with HZ reactivation process, so hypothyroid medical treatments are effective in this case. Eltroxin is a potent hypothyroid treatment that can significantly improve and heal HZ reactivation legions. So finally, we can recommend that low dose of Eltroxin in cases of subclinical hypothyroidism associated with HZ is beneficial.

Conflict of interest

None

Financial disclosure:

None

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