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A novel treatment for subclinical hyperthyroidism: a pilot study on the beneficial effects of l-carnitine and selenium

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Abstract. – OBJECTIVE: The definition itself of subclinical hyperthyroidism (SHyper) and, therefore, the therapeutic approach to patients with SHyper still remains undefined and controversial. Therefore, the interest of finding a novel and alternative therapy for SHyper has caught the attention. An observational pilot study was performed to assess the effects of l-carnitine and selenium in the management of SHyper symptoms and endocrine profile in patients affected by this disease.

PATIENTS AND METHODS: Patients with TSH levels between 0.1-0.4 mIU/L and positive antibodies were recruited in this study. Subjects received orally one tablet containing 500 mg of l-carnitine and 83 mcg of selenium (L-Carn + Se), daily for 1 month. The primary outcome was the improvement of the quality of life (QoL) with the disappearance of main symptoms (subjective symptomatology) associated to SHyper, evaluated through a 9-items short form survey. Secondary outcomes included TSH, fT_3, and fT_4, TPOAb, TgAb measurement. Primary and secondary outcomes were evaluated at baseline, after the completion of treatment and after a successive month without treatment.

RESULTS: After 1-month treatment, the subjective symptomatology significantly dropped from 25.61 ± 1.19 to 12.11 ± 1.15 ($p < 0.05$). On the other hand, during the following 1-month period without treatment, it increased back to 23.33 ± 1.35 ($p < 0.05$). Thyroid hormones and auto-antibodies remained in their normal range.

CONCLUSIONS: The present pilot study has shown that L-Carn + Se significantly reduced symptoms associated with SHyper, improving QoL of patients, without significant modifications of their endocrine profile. In addition, it is noteworthy that the extension of treatment seems necessary to prevent symptoms reappearance. Prospective randomized controlled trials are needed to address clinicians to define the appropriate treatment-settings for this disorder.

Key Words:

Subclinical hyperthyroidism, L-carnitine, Selenium, Thyroid hormones, Thyroid-stimulating hormone, TSH, Plummer syndrome, Graves-Basedow's disease.

Introduction

Subclinical hyperthyroidism (SHyper) is defined as a subnormal serum thyroid-stimulating hormone (TSH) level with normal levels of serum thyroid hormones, triiodothyronine (T_3) and its prohormone, thyroxine (T_4)[1]. It may be induced by endogenous or exogenous factors, such as overproduction of thyroid hormones (Graves' disease or autonomous thyroid nodule) or excessive thyroxine therapy. SHyper may be transient or persistent, and its management is still controversial[2,3]. The incidence rate in the general population varies widely from 0.6 to 16%, due to the heterogeneity among factors influencing its occurrence, such as age and gender, diagnostic criteria, the TSH assay used and iodine intake[4]. Very rarely SHyper progresses to overt hyperthyroidism (approximately 1% per year)[5], but it has a negative impact on patients' quality of life (QoL)[6]. The persistence of symptoms and signs of SHyper such as palpitations or heart pounding, nervousness or anxiety, tremors, headache, excessive sweating, sudden weight loss, pain and "constriction" on the neck area may impair patients' QoL. SHyper in older patients is also an important risk factor for atrial fibrillation and thromboembolism[7]. This is mainly caused by excessive exposure to T_3 that increases the systolic depolarization and diastolic repolarization rate and reduces the refractory period[8]. Indeed, SHyper is correlated with a 19% increase in the cardiovascular risk and a 52% increase in the incidence of cardiovascular mortality[9]. Furthermore, an excessive secretion of thyroid hormones from the gland seems to be responsible for accelerated bone loss, due to a persistent increase in bone turnover[10–12]. Precisely, T_3 stimulates osteoclastic bone resorption indirectly exerting its effect on osteoblasts through the nuclear receptors[13,14]. Given this, some studies have demonstrated that SHyper may cause secondary osteoporosis[15,16].

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Even though SHyper seems to be a mild condition, it may turn out to be a serious long-term problem associated with many pathologies and poor QoL. Nevertheless, the therapeutic approach for SHyper patients with TSH levels between 0.1-0.4 mIU/L still remains controversial and undefined[1]. Thus, the interest of finding a novel and alternative therapy for SHyper has caught the attention.

In this view, we focused on the possible use of l-carnitine (L-Carn) and selenium (Se) because both molecules seem to have a positive impact on thyroid dysfunction. L-Carn inhibits the nuclear uptake of thyroid hormones in the peripheral tissues, thus decreasing the susceptibility of tissues to hormones and reducing the typical signs and symptoms of hyperthyroidism[17]. Se is involved in the homeostasis of thyroid hormone-dependent metabolic pathways[18] and has an important effect on the immune system as well as on the reduction of auto-antibodies, in particular, TPOAb, in patients affected by autoimmune thyroiditis[19-24].

Therefore, the aim of this paper was to assess the effects of a combined therapy with L-Carn and Se in the management of SHyper symptoms and endocrine profile in patients affected by this disease.

Patients and Methods

Nineteen patients (14 women and 5 men) with TSH levels between 0.1-0.4 mIU/L, aged 18 - 45 years were recruited from April to December 2016 in an Outpatient Unit. Patients were selected according to the following diagnosis criteria: a) Plummer syndrome or b) Graves-Basedow's disease or c) TSH levels between 0.1-0.4 mIU/L or d) positive auto-antibodies. Patients under antithyroid treatment, iatrogenic or with acute thyroiditis were excluded. This study has been conducted following the ethical principles of the Declaration of Helsinki and national laws. An oral informed consent was obtained before entering the study. All subjects, after being clinically evaluated by the same investigator, received orally for 1 month one tablet per day, containing 500 mg of L-Carn and 83 mcg of Se (L-Carn + Se). The primary outcome was the improvement of QoL with the disappearance of the main symptoms (subjective symptomatology) associated to SHyper. The secondary outcomes were TSH, fT_3, and fT_4 hormone concentrations, TPOAb and TgAb antibodies serum levels. Each outcome was evaluated at baseline (T0), after 1-month treatment with L-Carn + Se (T1) and after a successive month without treatment (T2).

Short Form Survey

The Subjective Symptomatology (SS) was evaluated by a 9-items short form survey comprising questions about the presence of local symptoms such as (1) pain localized in front of the neck, (2) feeling "constriction" in the neck area, (3) feeling oppression in the neck when lying down, (4) palpitations or heart pounding, (5) sudden weight loss, (6) nervousness or anxiety, (7) tremors, (8) headache and (9) excessive sweating. An arbitrary scale between 0=no symptoms and 4=very strong symptoms was used to determine the grade of each symptom. The occurrence of specific symptoms and signs of the thyroid was evaluated from all the patients at each timepoint (T0, T1, T2).

Laboratory and Technical Investigations

The investigation was performed over a period of 2 months. Blood samples were drawn from each patient at the 3 timepoints (T0, T1, and T2). TSH, fT_3, and fT_4 concentrations were measured using an enzyme immunometric assay (Byk-Sangtec Dietzenbach, Germany). Total plasma TPOAb and TgAb concentrations were measured using a commercial enzyme luminescence assay (Byk-Sangtec, Dietzenbach, Germany).

Statistical Analysis

Data were tested for significant differences of repeated measurements on a single group using Wilcoxon Signed-Rank test. Tests were performed comparing data at T0 *vs.* T1, T0 *vs.* T2 and T1 *vs.* T2. Data are reported as Mean ± Standard Error of the Mean (SEM). A p-value < 0.05 was considered statistically significant.

Results

In this observational pilot study, a total of 19 SHyper subjects were treated with L-Carn + Se for 1 month. A further month of follow-up without treatment was also carried out. One dropout over the trial period was recorded because of a suspected overt hyperthyroidism**.** Therefore, 18 patients (13 women and 5 men) with mean age 31.9 ± 1.65 years completed the study. After 1-month treatment, all the patients reported a clinically relevant improvement in the QoL; in fact, SS significantly dropped from 25.61 ± 1.19 to 12.11 ± 1.15 ($p < 0.05$) (Table I). Following a one-month period without treatment, a significant

Table I. Overall results of laboratory parameters: serum TSH levels, fT_3, fT_4, TgAb, TPOAb, and Subjective Symptomatology (SS).

Tests	T0	T1	T2
SS	25.61 ± 1.19	12.11 ± 1.15*	23.33 ± 1.35§
TSH µU/ml	0.25 ± 0.02	0.3 ± 0.02*	0.26 ± 0.02§
fT_3 pg/ml	3.14 ± 0.05	3.13 ± 0.08	3.23 ± 0.09
fT_4 ng/dl	1.35 ± 0.01	1.33 ± 0.02	1.37 ± 0.01
TgAb UI/ml	468.11 ± 46.98	355.77 ± 36.48*	434.17 ± 41.26§
TPOAb UI/ml	593.77 ± 34.59	460.33 ± 44.00*	572.72 ± 41.44§

Data are reported as mean ± SEM. Baseline (T0); 1 month post-treatment with l-carnitine + selenium (T1); 1-month without treatment (T2). Wilcoxon Signed-Rank - statistical differences of repeated measurements on a single group: T0 *vs*. T1 (*); T0 *vs*. T2 (*); T1 *vs*. T2 (§). *p*-value: * < 0.05, *p*-value: § < 0.05.

increase of the overall symptoms was recorded (23.33 ± 1.35, $p < 0.05$). As shown in Table I, statistical differences were observed comparing data at T1 either to baseline ($p < 0.05$) or to T2 (1-month L-Carn + Se treatment) ($p < 0.05$). Scored values from the short form survey responses of main symptoms such as palpitations, tremor, and nervousness are shown in Figure 1. Significant changes were observed since all 3 parameters decreased after 1-month treatment. The scored value for palpitations decreased significantly from 3.61 ± 0.12 to 1.05 ± 0.19 ($p < 0.05$) after 1 month supplementation of L-Carn + Se, but when the treatment was interrupted for 1 month this symptom raised back, scoring 3.44 ± 0.16 ($p < 0.05$) (Figure 1). Significance was observed for both comparison T0 *vs.* T1 ($p < 0.05$) and T1 *vs.* T2 ($p < 0.05$), but not for T0 *vs.* T2. Tremors were considerably lower following 1 month treatment, decreasing from 3.33 ± 0.14 to 0.83 ± 0.17 ($p < 0.05$) (Figure 1). However, this symptom reappeared once the treatment was discontinued (2.88 ± 0.23, $p < 0.05$) (Figure 1). Same results were obtained for the symptom "nervousness" that decreased between T0 and T1 (from 3.55 ± 0.12 to 1.22 ± 0.17, $p < 0.05$) and in-

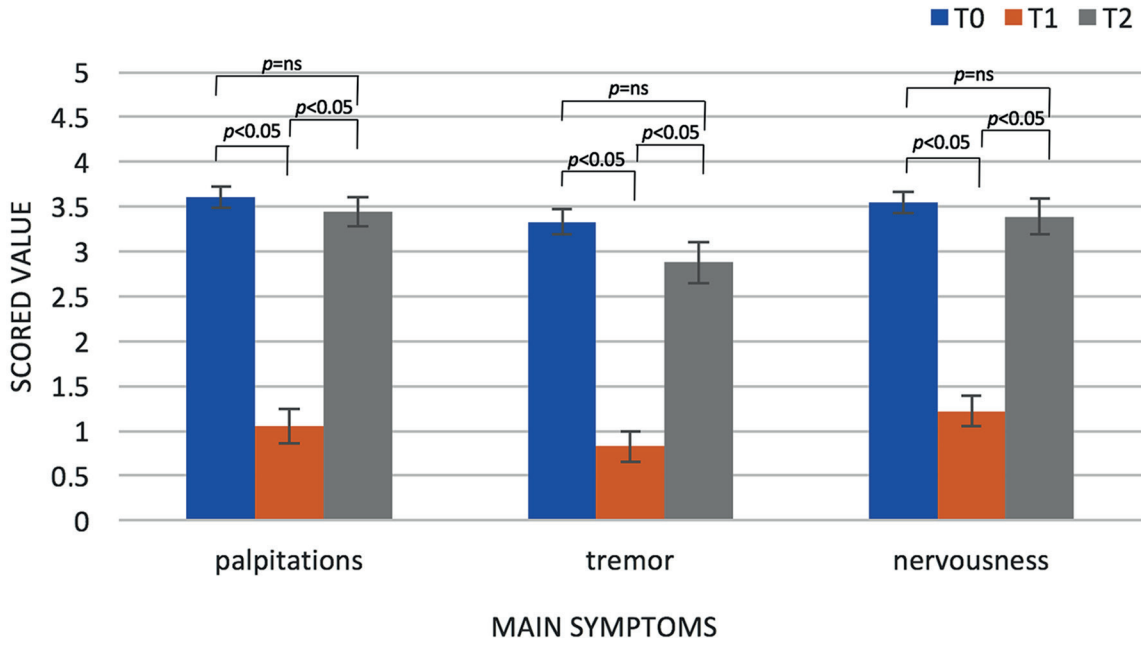

Figure 1. Scored values of main symptoms (palpitations, tremor, nervousness) obtained by the 9-items short form survey responses. Data are reported as mean ± SEM. Baseline (T0); 1 month post-treatment with l-carnitine + selenium (T1); 1-month without treatment (T2). Wilcoxon Signed-Rank - statistical differences of repeated measurements on a single group: T0 *vs*. T1; T0 *vs*. T2; T1 *vs*. T2. A *p*-value < 0.05 was considered statistically significant; not statistically significant (ns).

creased again from T1 to T2 up to 3.39 ± 0.20 ($p < 0.05$) (Figure 1). Values of TSH, fT_3, fT_4, TgAb and TPOAb at baseline, T1 and T2 are shown in Table I. During the treatment-period with L-Carn + Se no adverse effects were reported.

Discussion

This study is the first to give a defined endocrinological assessment of the effectiveness of 1-month L-Carn + Se treatment in reducing symptoms and signs in SHyper patients. It was also observed that, after 1-month treatment with L-Carn + Se, thyroid hormones and auto-antibodies remained in their normal range. However, once the treatment was discontinued symptoms reappeared and the hormone profile worsened in 60% of cases compared to baseline. Thyroid hormones regulate metabolism and thermogenesis in the body[25,26]. Excessive thyroid hormone production promotes a hypermetabolic state characterized by increased weight loss, elevated heart rate, arrhythmias, palpitations, nervousness, irritability, insomnia, resting energy expenditure and sweating because of temperature rise in the body. The most common consequences are represented by impairment of the cardiovascular system explaining the correlation with the cardiovascular risk and mortality incidence[9]. Therefore, the necessity to make the diagnosis should be based upon the consequences of long-term untreated SHyper and on the initial related-symptoms. Treatments currently in use for overt hyperthyroidism are thyrostatics, that directly block the hormone synthesis, and beta-blockers that mainly counteract peripherally the thyroid hormones action, thus reducing the cardiovascular correlated-symptoms. These drugs are often used in case of SHyper, but minor side effects such as nausea, headaches, tiredness, etc. are quite common[27]. Other major side effects, associated with long-term use, are reduction in oxygen consumption/basal metabolic rate, bradycardia, persistent dizziness, fainting, fatigue, sleeping difficulties and erectile dysfunction.

Carnitine (3-hydroxy-4N-trimethylammoniumbutanoate) is a quaternary ammonium compound, ubiquitous in mammalian tissues[28]. It is a safe molecule, as its clinical use has reported no toxicity, teratogenicity, contraindications or interactions with drugs[17,29,30]. It plays a pivotal role in the mitochondrial transport and oxidation of fatty acids, with neuroprotective effects against neurotoxic conditions caused by mitochondrial dysfunction[31]. It has also a beneficial effect on bone mineralization[17,32,33]. Indeed, in aged people, L-Carn enhances osteoblast activity inducing cell proliferation, and decreases bone loss[34].

Se is a trace element, along with iodine, essential for the thyroid hormone synthesis and metabolism[18]. Several research studies have demonstrated the benefits and safety of Se supplementation in treating autoimmune thyroid conditions[20-24]. Patients diagnosed with Graves' disease have reduced Se levels compared to healthy patients[35]. A beneficial effect of Se has been shown on the improvement of QoL in patients with mild Graves' orbitopathy[19], where, as a matter of fact, Se may be insufficient. This might be explained by the antioxidant effect exerted by this element, that can counteract the excessive release of reactive oxygen species (ROS) in peripheral tissues, caused by the hypermetabolic state[36]. ROS may cause tissues damage leading to the common clinical signs of hyperthyroidism.

Early SHyper treatment seems to improve QoL, reduce the cardiovascular risk, and it might prevent a possible progression toward overt hyperthyroidism[37]. Therefore, it should be of interest to clinicians to find the best therapeutic approach for reducing SHyper symptoms, improving QoL and preventing after-effects. In our pilot study, it was highlighted the beneficial effect of a powerful combination, L-Carn + Se, in reducing SHyper symptoms, thus improving patients QoL, only after 1-month treatment. Additionally, the patients' endocrine parameters were maintained in their normal range. A long duration of treatment seemed to be necessary to avoid recurrence of symptoms, as well as the worsening of the hormone and auto-antibodies profile. Large prospective randomized controlled (double-blind) studies are anyway required to confirm the potential benefits of L-Carn + Se supplementation in reducing SHyper-related symptoms and improving QoL of patients affected by this disorder.

Conclusions

The effectiveness of 1-month treatment with L-Carn and Se in patients with SHyper has been evaluated. L-Carn and Se combined can be considered as a novel therapeutic approach for the management of symptoms and endocrine profile in SHyper patients. Large prospective randomized controlled (double-blind) studies are required to better define the proper treatment-setting for this disorder.

Conflict of Interest

The Author declares no conflict of interest.

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