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Hormonal replacement therapy with L-thyroxine in chronic heart failure in patients with non-thyroidal illness syndrome (NTIS)

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Abstract

Non-thyroidal illness syndrome (NTIS) also known as euthyroid sick syndrome or low T3 syndrome is hypothyroidism caused by peripheral changes in the metabolism and thyroid hormone transport caused by severe debilitating diseases, in particular, heart failure. Recent data indicate that chronic heart failure can result in thyroid hormone metabolism disruption, which contributes to a progressive decrease in the concentration of triiodothyronine. The objective was to evaluate the effectiveness and safety of hormone replacement therapy with low doses of thyroxine in congestive heart failure in patients with low triiodothyronine syndrome. The levels of thyroid-stimulating hormone, thyroxine-binding globulin, free thyroxine, total triiodothyronine, free triiodothyronine, and reversible triiodothyronine were measured by radioimmunological assay from samples obtained from 56 patients with chronic heart failure and 19 practically healthy individuals of the control group matched by age, gender, and body mass index. Patients with low triiodothyronine syndrome were prescribed hormone replacement therapy with low doses of thyroid hormones (thyroxine 12.5-25 mcg/day) until the euthyroid state was achieved. The values of total and free triiodothyronine were significantly lower in patients with heart failure, the level of thyroxine-binding globulin was also reduced, more than twofold increase in reversible triiodothyronine level was demonstrated compared to controls. Low triiodothyronine syndrome was diagnosed in 33.9% of patients with heart failure. Hormone replacement therapy resulted in a slight improvement in contractile function in individuals with low triiodothyronine levels, 2 (10.5%) patients manifested with signs of hyperthyroidism. Advanced stages of heart failure might be linked with NTIS. Hormone replacement therapy with low doses of thyroxine can contribute to a moderate improvement in contractile function, as evidenced by the improvement in left ventricular ejection fraction.

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Introduction

Recent data indicate that chronic heart failure can result in thyroid hormone metabolism disruption, which contributes to a progressive decrease in the concentration of triiodothyronine [1]. The discussion on latent and subclinical disorders of the thyroid gland functional state arose relatively recently, predetermined by the emergence of new highly sensitive research methods, such as radioimmunological tests and immune enzyme assay (ELISA).

Non-thyroidal illness syndrome (NTIS) also known as euthyroid sick syndrome or low T3 syndrome is hypothyroidism caused by peripheral changes in the metabolism and thyroid hormone transport caused by severe debilitating diseases, in particular, heart failure, oncological pathology, massive surgical interventions, long-term protein starvation, and injuries [2,3]. The criteria for such a condition encompass a decrease in the level of triiodothyronine (T3) in the blood with normal levels of thyroid-stimulating hormone (TSH) and free thyroxine (fT4) [4]. There is some evidence that hormone replacement therapy with triiodothyronine can normalize the disturbed state of the thyroid gland in congestive heart failure and contribute to the improvement of the contractile function of the heart [5]. However, at the same time, it can cause abrupt fluctuations in the concentration of triiodothyronine in the blood serum, which leads to tachycardia onset and increases the risk of atrial fibrillation development [6].

The common approach towards hormone replacement therapy with L-thyroxine appointment remains controversial due to the difficulty of treatment monitoring, the short dosing interval, and the possibility of iatrogenic hyperthyroidism. That is, with the NTIS, the issue of prescribing hormone replacement therapy is decided individually.

Objective

The purpose of the prospective study was to evaluate the effectiveness and safety of hormone replacement therapy with low doses of thyroxine in congestive heart failure in patients with low triiodothyronine syndrome.

Materials and methods

Samples were obtained from 56 patients with NYHA stage III-IV chronic heart failure at admission, (mean age 64.3 ± 7.5 years, mean left ventricular ejection fraction, EF, 38.4 ± 7.1%) and 19 practically healthy individuals matched by age, gender, and body mass index of the control group. The levels of thyroid-stimulating hormone, thyroxine-binding globulin, free thyroxine, total triiodothyronine, free triiodothyronine, and reversible triiodothyronine were measured by radioimmunological assay. Patients with low triiodothyronine syndrome were prescribed hormone replacement therapy with low doses of thyroid hormones (thyroxine 12.5-25 mcg/day) until the euthyroid state was achieved.

Results

The values of total and free triiodothyronine were significantly lower in patients with heart failure, the level of thyroxine-binding globulin was also reduced ($p < 0.05$, respectively), more than twofold increase in reversible triiodothyronine level was demonstrated compared to controls ($p < 0.01$). The levels of thyroid-stimulating hormone and free thyroxine remained within the normal range ($p > 0.05$). Low triiodothyronine syndrome was diagnosed in 19 (33.9%) patients with heart failure. Hormone replacement therapy resulted in a slight improvement in contractile function (EF) in individuals with low triiodothyronine levels ($p < 0.05$), 2 patients (10.5%) showed signs of iatrogenic hyperthyroidism, which was immediately eliminated by reducing the dose of thyroxine.

Discussion

Hormone replacement therapy with L-thyroxine can be indicated for concomitant disorders of the lipid profile, insulin resistance, and depression, with the minimum effective dose. It is recommended to initiate replacement therapy in all patients with the syndrome of non-thyroid diseases with the appointment of L-thyroxine. Combined replacement therapy of T4 and T3 is not recommended.

Replacement therapy with L-thyroxine for young individuals with NTIS without concomitant pathology can be prescribed without restrictions at the rate of 0.9 mcg/kg/day until the normalization of the TSH level. The average daily demand for L-thyroxine in NTIS is within the range of 50 to 75 mcg. Anticipating future progression of thyroid insufficiency, some endocrinologists prescribe a full replacement dose. The starting dose is 25 mcg on average, depending on the patient's age, free thyroxine level, and serum TSH level. The level of TSH should be determined after 6-8 weeks, after which an adequate replacement dose of L-thyroxine should be established. As soon as it is possible to achieve a normal level of TSH, its level should be determined every 6 months, and then

annually. For young people, the target level of TSH should be within 0.3-3.0 mU/L. For older age groups, the TSH target level for replacement therapy may be higher. The benefit of titrating the dose of L-thyroxine to achieve lower TSH levels must be carefully weighed against the possible adverse effects of such aggressive therapy in the form of excessive TSH suppression and the development of osteoporosis.

Some authors claim that the myocardium of a patient receiving L-thyroxine better adapts to ischemia, and the administration of T3 to a patient with coronary heart disease leads to inhibition of the proliferation of myocardial fibroblasts. Replacement therapy with L-thyroxine leads to the activation of the so-called Heart Shock Protein, which is associated with better tolerance of myocardial ischemia, which confirms the role of thyroid hormones as cardiac protectors and indicates the importance of timely treatment of hypothyroidism in patients with cardiac pathology.

Replacement therapy has been suggested to reduce insulin resistance and endothelial dysfunction, but data from large randomized trials are currently lacking. Thus, the effectiveness and safety of hormone replacement therapy with low doses of thyroxine are still debatable. Replacement therapy should be prescribed with special caution in elderly people with concomitant cardiac pathology. It is considered optimal to use T4, not its combination with T3. If the conversion of T4 into the active form of T3 is unchanged, there is no need to prescribe exogenous T3, since it is practically impossible to avoid abrupt fluctuations in the concentration of the latter, which leads to undesirable adverse effects occurrence, namely iatrogenic hyperthyroidism, tachycardia, or even atrial fibrillation.

Conclusions

Advanced stages of heart failure might be linked with the onset of NTIS or low triiodothyronine syndrome in 33.9% of cases. Hormone replacement therapy with low doses of thyroxine can contribute to a moderate improvement in contractile function, as evidenced by the improvement in left ventricular ejection fraction. However, strict monitoring and timely management of symptoms of iatrogenic hyperthyroidism should be performed.

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