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Options of Replacement Therapy in Hypothyroidism

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1. Introduction

1.1 History of replacement therapy of hypothyroidism

Before the middle of XX century treatment of hypothyroidism implied prescription to the patients animals' thyroid extracts, containing both, thyroxine and triiodothyronine [*Oppenheimer JH, 1995*]. Those drugs, in which it was almost impossible to measure the dose of thyroid hormones precisely, could not adequately provide euthyroidism. Moreover, it was rather difficult to prescribe proper doses. Furthermore there weren't any objective control parameter for dose adjustment like modern TSH-assays. Synthetic preparations of levothyroxine (L-T4) have been used since about 1958, and levotriiodothyronine (L-T3) - since 1956 (**figure 1**).

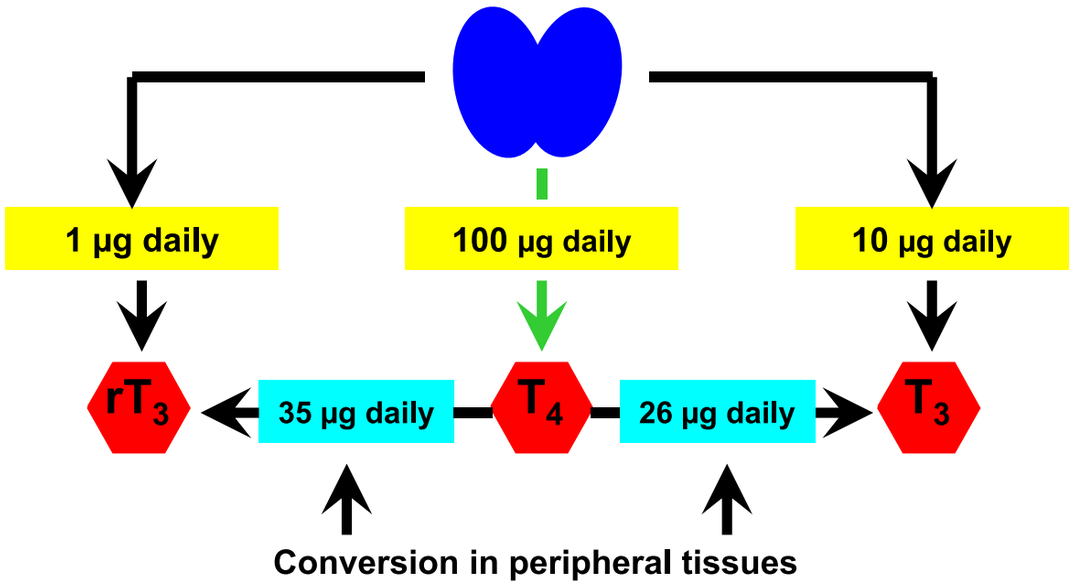

Fig. 1. Production of thyroid hormones

Based on the concept that the thyroid gland produces two hormones - thyroxine (T4) and triiodothyronine (T3), there was a long-term understanding that in the treatment of hypothyroidism it is preferable to use a combination of L-T3 and L-T4, rather than monotherapy with one of those drugs [*Oppenheimer JH, 1995*]. In the 70s, it was shown that the majority of circulating in blood T3 (80%) is produced not by the thyroid gland, but is formed by deiodination of T4 in peripheral tissues [*Braverman LE, 1970; Surks MI, 1973*]. These data allowed to consider T4 as prohormone to T3, which shows a stronger affinity to the receptors of thyroid hormones than T4. In addition, it was demonstrated, that L-T3 has unfavorable pharmacokinetics: it is rapidly and almost completely gets absorbed, the serum level of T3 reaches a peak after 2 - 4 hours, but after 6 - 8 hours it considerably declines. Thus, after taking the L-T3, the serum level of T3 reaches a non-physiological level for a short time and then rapidly gets metabolized [*Toft, 1994*]. These data led to the concept of the predominant use of replacement monotherapy with L-T4 (**figure 2**).

Year	Event
1891	Treatment with animals' thyroid extracts
1926	Description of the structure and synthesis of T4
1952	Description of the structure and synthesis of T3
1956	Start of treatment with synthetic L-T3
1958	Start of treatment with synthetic L-T4 (200-400 µg daily)
1973-74	Recommended dose of L-T4 100-150 µg daily
	The widespread use of combination with L-T4 + T3
1980-85	Appearance of highly sensitive methods for determination of TSH
	Concept of preferable use of replacement monotherapy with L-T4

Fig. 2. History of replacement therapy of hypothyroidism

Together with fundamental studies, which investigated the thyroid hormones metabolism intensive development of laboratory diagnostics led to the development of modern concepts of replacement therapy with thyroid hormones. Thus, while determining the TSH level with methods of poor sensitivity in the lower range of values (unable to distinguish the suppressed level of TSH from the low-normal value) in the 1960s a replacement dose of L-T4 was recommended, ranged between 200 and 400 micrograms daily, which was accompanied by a significant increase in T4 level in serum [*Toft, 1999*].

The situation changed in the 1980s with appearance of highly sensitive methods for the determination of TSH levels. It became obvious that the doses of L-T4, leading to suppression of TSH, even in normal levels of T4 and T3 in blood, were accompanied by

similar, but less evident changes in the liver, heart, kidneys and bones, like in thyrotoxicosis [*Gow,1987*]. Thus, by the early 1980s the concept of preferable use of replacement monotherapy with L-T4 was formulated. TSH level, determined by methods of high sensitivity, has become the main indicator for assessment the adequacy of hypothyroidism replacement therapy.

1.2 The principles of generally recommended replacement therapy

Overt hypothyroidism is an absolute indication for replacement therapy with thyroid hormones. According to current recommendations, monotherapy with L-T4 is the "gold standard" of replacement therapy, because a single daily dose of the drug can maintain euthyroid state.

To date, L-T4 is the most commonly prescribed hormonal drug. The replacement dose of L-T4 is initially calculated as 1.6 μg per kilogram of body mass. In most cases, full replacement dose for women is about 100-150 μg of L-T4 daily and about 125-200 μg for men. How long it takes to reach full replacement doses of thyroid hormones, depends on several factors, first of all on the patient's age, history and severity of hypothyroidism, and presence of comorbidity and above all, cardiac diseases. In most cases, a full replacement dose of L-T4 can be prescribed to young patients immediately. Herewith, to date there is insufficient number of studies that could investigate the advantages and disadvantages of immediate prescribing of the full replacement dose of L-T4 as compared with slow titration. The results of recently published prospective randomized double-blind study compared the safety of the prescribing immediately the full replacement dose of L-T4 (1.6 μg per kg body mass) vs. the beginning with low-dose (25 μg daily) and gradual increase every four weeks in patients with newly diagnosed overt hypothyroidism without cardiac disease history [*Roos A, 2005*]. Safety was assessed by frequency of cardiac symptoms or acute cardiovascular events, and effectiveness – by the levels of TSH, freeT4, symptoms of hypothyroidism dynamics and quality of life. Fifty patients were randomized into two groups; the groups were comparable in terms of baseline TSH levels (61 vs. 48 mU/l), fT4 (7.2 vs. 8.2 pmol/l) and age (47 vs. 47 years). During the study at baseline and after 12 and 24 weeks, there were no cardiac symptoms or acute cardiovascular events. Hypothyroidism compensation was achieved more quickly in the group of treatment with full replacement dose initition, as compared with initial low-dose treatment: in 13 and 1 patients compensation was achieved after 4 weeks, in 19 and 3 patients after 8 weeks, in 19 and 9 patients after 12 weeks, in 20 and 14 patients over 16 weeks, in 20 and 18 patients after 20 weeks and in 21 and 20 patients in 24 weeks respectively ($p = 0.005$). Nevertheless, the dynamics of hypothyroidism symptoms and quality of life parameters in both groups were rather similar. Based on these results, the authors concluded that the prescribing of a full replacement dose of L-T4 immediately in patients with overt hypothyroidism without cardiac disease anamnesis is safe and may be more convenient and cost-effective as compared with the beginning with low doses of L-T4. However, in clinical practice traditionally the most widely used is the beginning of replacement therapy with relatively low doses of L-T4, with a subsequent increase to a full replacement (“start slow and go low”). Exceptions are only pregnant women with hypothyroidism.

As a rule, L-T4 preparations are recommended to take in the morning upon starving, 30-40 minutes before breakfast and taking other drugs. When taken per os, about 70-80% of the

dose gets absorbed: 20% of the drug is absorbed in the duodenum and 40% - in the upper part of the ileum, the remaining 40% - in the lower ileum. The peak absorption of the drug is reached between 30 and 60 minutes after the administration, the drug is absorbed completely in 90 minutes [*Centanni M., 2006*].

The adequacy of replacement therapy of hypothyroidism is estimated over 6-8 weeks after the beginning of a full replacement dose of L-T4 or dose adjustment. The normal TSH level is the main criterion of hypothyroidism compensation. If necessary to adjust (decrease or increase) the dose, the "step" of L-T4 is 12.5-25 μg. After reaching euthyroidism, it is necessary to monitor the adequacy of therapy annually. In some cases, adjustment of the dose may be required and, therefore, further assessment of the therapy adequacy. Thus, the necessity to increase doses of L-T4 may occur in the following situations: use of the drugs that increase L-T4 clearance (phenobarbital, carbamazepine, rifampicin, phenytoin, sertraline, chloroquine); use of the drugs that hinder the absorption of L-T4 in the gut (calcium carbonat, cholestyramine, sucralfate, aluminum hydroxide, sulphate of iron, fiber supplements); in conditions of increased concentrations of thyroxine-binding globulin due to pregnancy or estrogen administration; in malabsorption or celiac disease [*Arafah B., 2000; Havrankova J., 1992; Singh N., 2000*]. Besides, thyroxine dose adjustment may be required in such diseases as lactose deficiency, hypoacidic gastritis, atrophic gastritis, chronic gastritis, associated with Helicobacter pylori, intestinal parasitic diseases [*Centanni M., 2006*].

1.3 Factors, that influence on the quality of compensation of replacement therapy

In general, replacement therapy with thyroid hormones is rather simple, but despite this fact, according to different authors, the part of patients receiving L-T4 replacement therapy and remains in decompensation varies from 32.5 to 62% [Diez J.J., 2002; Canaris G.J., 2000; Parle J., 1991].

Thus, in the study by Diez J.J., patients over 55 years with hypothyroidism, receiving replacement therapy with L-T4 were screened for TSH level. Among 385 patients, hypothyroidism was compensated only in 67.5%, and decompensated in 32.5%. The degree of compensation depended on the hypothyroidism duration, but was independent on age, sex, history and severity of hypothyroidism [Diez, 2002].

In a large-population Colorado study, which included 25 862 people, it was shown that among 1525 patients treated with L-T4, only 916 patients (60.1%) were compensated. Among 609 patients with decompensated hypothyroidism overt hypothyroidism was detected in 11 patients (0.7%) and subclinical hypothyroidism in 269 patients (17.6%) , in 13 (0.9%) – overt hyperthyroidism, and in 316 patients (20.7%) subclinical hyperthyroidism were found [*Canaris GJ, 2000*]. It is remarkable, that 92% of patients visited a physician less than one year prior to enrollment in the study.

In a small study, performed by Parle J. et al., among 97 patients with primary hypothyroidism, who received monotherapy with L-T4, 46.8% of patients were decompensated, of whom 26.8% (26 patients) had elevated TSH (and in 13 (50 %) - above 10 mU/l), while in 21% (20 patients) the TSH was decreased [*J. Parle, 1991*].

So, what are the reasons for decompensation in so many patients with hypothyroidism? It is well known, that control of any chronic disease, including hypothyroidism, is at least partly

dependents on patient compliance. **Compliance** is a patient's adherence to the recommended course of treatment. According to a number of studies the main reason for decompensation of hypothroidism is poor compliance of patients [*Hueston W., 2001; Hanna F., 1999*].

The study conducted by Leese G.P. et al. has shown that among 1180 patients, receiving replacement therapy with L-T4, *58.5%* had a decreased level of TSH, 3.5% - increased TSH, and only in 38% of patients the TSH level was within the normal range. In patients with suppressed TSH recommended dose of L-T4 was usually higher than in the group with normal TSH (114.2 ± 56.9 μg as compared with 100.4 ± 45.9 μg, $p < 0.01$). In the group with elevated TSH, the situation was different: in patients treated with lower doses of L-T4 the reason for decompensation was insufficient dose of the drug, while in patients receiving high dose of L-T4 (137.1 ± 58.8 μg) the decompensation was due to poor compliance [*Leese G., 1993*].

In clinical practice, there are some methods to improve the quality of compensation: patient's education, using of registers (patients with compensated hypothyroidism are included in the database, and their status is evaluated annually). However, the registers' formation, despite their potential economic benefits, remains difficult to be updated [*Hanna F., 1999*].

In the study by Cuthbertson D.J. et al. authors evaluated the compensation of hypothyroidism in 6205 patients, entered in the electronic register. The following parameters were entered into the database: etiology of hypothyroidism, levels of TSH and free T4 at baseline, type of the replacement therapy. The levels of TSH for patients entered in the register were measured every 18 months. In step of the of L-T4 dose adjustment, the patients were invited for a follow-up visit every 6 months. The L-T4 dose adjustment was made in accordance with the level of TSH: if TSH was above 4 mU/l, the daily dose was increased by 25 μg; if the TSH level was normal or reduced (in the range 0.03 - 0.4 mU/l), the dose remained unchanged, but if the TSH level was below 0.03 mU/l, the dose was reduced by 50 μg (with the dose of L-T4 within 225-300 μg), or 25 μg (with the dose of L-T4 175 - 200 μg). With the dose less than 150 μg a reduction was recommended only in case of increased level of free T4 above 24 pmol/l. The study demonstrated, that there were 58.5% of patients with suppressed TSH (<0.03 mU/l) before 1991. Later the rate of patient with decompensation of hypothyroidism decreased markedly to 15,7 ± 3,6% in the period from 1993 to 2001 [*Cuthbertson DJ, 2006*].

One of the reasons for decompensation of hypothyroidism could be the changing of **L-T4 preparation even in the same dose**. To date, several L-T4 preparations produced by different manufacturers are available in the pharmaceutical market. Preparations of L-T4 produced by different companies may be insufficiently bioequivalent. In addition, even drugs produced by one company but with different technologies may be not bioequivalent. That is why the problem of bioequivalence and interchangeability of L-T4 is recently under discussion.

In addition to the above-mentioned reasons, it has been suggested, that the **psychological state of patients** can affect the quality of compensation. In particular, patients with depression rarely take medicines regularly and correctly [*Sevinc A., 2004*]. It is well known, that depression is diagnosed more frequently in patients with hypothyroidism than in

general population; herewith, it is irrespective of the quality of the disease compensation. Sometimes hypothyroidism can be manifested with the symptoms of depression [*Lindsay RS, 1997, Weetman AP, 1997, Demet, 2003; Joffe RT, 1992; Rack SK, 2000*]. For the first time the relationship between hypothyroidism and depression was mentioned more than 100 years ago, in 1888 [*Oppenheimer J.H., 1995*]. According to some studies, the prevalence of depression in patients with hypothyroidism may be as high as 40% [*Haggerty JJ, 1995*], which is often accompanied by psychomotor retardation and a moderate decrease in cognitive function [*Pies RW, 1997*]. Thus, Munoz-Cruzado Poce et al. while examining 108 patients with depression, has found previously undiagnosed thyroid abnormalities in 24.1% of them, hypothyroidism was diagnosed in 7.4% of cases [*Munoz-Crusado Poce, 2000*]. In a similar study made by Gold MS et al., hypothyroidism was diagnosed in 20 out of 250 patients with depression [*Gold MS, 1981*]. In addition, depression may often be the first sign of subclinical hypothyroidism.

We have organized a study with the aim of investigating medical and social factors, affecting the quality of compensation in hypothyroid patients on L-T4 replacement therapy [*Fadeyev, 2006*]. The study included 200 patients with overt hypothyroidism taking L-T4 for a year or more. Patients were examined at the baseline and after 6 months. The symptoms of hypothyroidism, thyroid hormone levels and lipid profiles were analyzed. In case of decompensation, we were trying to clarify the main reasons thereof: accuracy and regularity of taking the medication and its dose; and in case of incorrect admission or taking inadequate doses of L-T4 we identified the main reasons for that (the doctor did not explain, the patient supposed the regular use of medication as unnecessary, the patient noted subjective changes in well-being, while taking the full replacement dose of L-T4). As a result only 58% (84/200) of patients were euthyroid in the beginning of the study while 26% of them had increased TSH level and 16% had low TSH.

In nearly in one third of patients (24/84; 28.6%) the main reason of decompensation was medication incompliance (the drug was taken after a meal or less than 30 minutes before breakfast; dividing the dose - one part before breakfast, another one before dinner; taking L-T4 together with calcium or iron supplements). Six months later, after the education, the hypothyroidism was decompensated only in 8 patients from this group (8/19, 42.1%). The reason for decompensation in the other 11 patients was also the incompliance in taking of medication or self-changing (increase or decrease) of the L-T4 dose. Only in 13 of 84 patients with decompensated hypothyroidism the main reason for that was the inadequate recommendations of a doctor. In this group, in 6 months after the dose adjustment, out of 9 re-examined patients the hypothyroidism was compensated in 8 cases (88.9%).

2. Challenges of the replacement therapy

2.1 Dissatisfaction with monotherapy of hypothyroidism

It is well known that in clinical practice there is a significant number of patients, who still complains about unspecific symptoms similar to hypothyroid despite the compensation of hypothyroidism and normal TSH level. The most common of them are: fatigue, muscle pain, impaired mood and poor memory [*Wekking E., 2005*]. The presence of these complaints affects the overall well-being and quality of life. The most interesting are results of the study performed in the UK by Saravanan P. et al. [*Saravanan P., 2002*]. The study included 961

patients with hypothyroidism at the age of 18 - 75 years, taking L-T4 for at least four months. The control group included healthy people of the same age. Patients completed two questionnaires: General Health Questionnaire - GHQ-12 and Thyroid symptom questionnaire - TSQ. All the participants were divided into three groups: general group of patients (n = 597), a subgroup of patients with normal TSH (n = 397) and control group (n = 551). The study showed that the mean score under 36-point GHQ scale in patients receiving L-T4 was 12.1, in patients with compensated hypothyroidism - also 12.1, whereas in control group it was 11.4 (p = 0,03 and 0.01 as compared to control, respectively), indicating greater dissatisfaction with their well-being in patients receiving L-T4. Similarly, according to the TSQ, in patients receiving L-T4 results were even worse than in other patients (12.6, 12.8 and 11.5 points respectively; p <0.001). These differences remained after the assessment with regard to other chronic illnesses, including depression. The authors concluded that patients, receiving replacement therapy with L-T4, even normal TSH have lower indicators of overall health than in the people without hypothyroidism.

It is still not quite clear, whether the results of these studies are specific to hypothyroidism, or they reflect the reducing of the overall well-being in patients with any chronic disease, sometimes regardless of its compensation, often from a patient's awareness of their illness [*Ladenson P., 2002*].

2.2 Quality of life and cognitive functioning in patients with compensated hypothyroidism

The assessment of quality of life associated with health, allows us to study the effect of the disease and its treatment on the indictors of the patient's quality of life. A questionnaire is the standard research tool in the quality of life assessment.

In general, according to various authors, the development of hypothyroidism leads to a decline of the patients' quality of life. In most cases, achieving the compensation of disease is accompanied by improvement of well-being of patients and, consequently, improves the quality of life. However, according to some authors, despite the adequate replacement therapy and stable achieving of normal TSH level, the number of parameters of quality of life of those patients (in general groupe) remains decreased compared with healhy control [*Wekking E.M., 2005; Bianchi P., 2004*].

This can be confirmed by the results of the study carried out by Wekking EM et al. [*Wekking EM, 2005*], where the authors assessed the neurocognitive function and quality of life in the patients with hypothyroidism. The study included 141 patients with compensated hypothyroidism aged from 18 to 70 years. The quality of life was assessed by the questionnaire RAND-36 (Dutch version of the questionnaire MOS SF-36). The results of the quality of life assessment were compared with the quality of life of a representative sample of the population of Denmark (n = 1063). It was shown that the levels of vitality and mental health by questionnaire RAND-36 were significantly lower in patients receiving L-T4, as compared with those in representative sample.

We also assessed the quality of life of patients with hypothyroidism and compared it with the quality of life of patients with nodular euthyroid goiter and people without thyroid disease. Thirty patients with compensated primary hypothyroidism (aged from 25 to 55

years), 28 patients with nodular (multinodular) euthyroid goiter of the same age not receiving L-T4, and 30 healthy people were assessed (**figure 3, 4**). The scores for the Short-Form 36 (SF-36) and Beck Depression Inventory Scale were analyzed. Almost all scales of the questionnaire SF-36 (except for general health and role emotional functioning) in patients with compensated hypothyroidism were significantly lower (p 0.05), than in healthy people. While comparing quality of life in patients with hypothyroidism with quality of life in patients with nodular goiter the rates of role physical functioning (p = 0.042), vitality (p = 0.015), social functioning (p = 0.0) and psychological health (p = 0.021) of patients with hypothyroidism were significantly lower compared with patients with euthyroid goiter. In assessing the severity of depression we have shown that the value on a scale of depression in patients with compensated hypothyroidism was significantly higher compared with the results of patients with nodular goiter and healthy individuals (p = 0.014). So, in patients with compensated hypothyroidism in almost all parameters the quality of life is worse than in people without thyroid disease, and on many scales (role physical functioning, vitality, social functioning and psychological health) is worse than in patients with euthyroid goiter. Severity of depression in patients with compensated hypothyroidism is higher compared to patients with nodular goiter and healthy people, which may be one of the reasons for the decrease of quality of life of these patients [*Morgunova T., Manuilova Yu.,2010*].

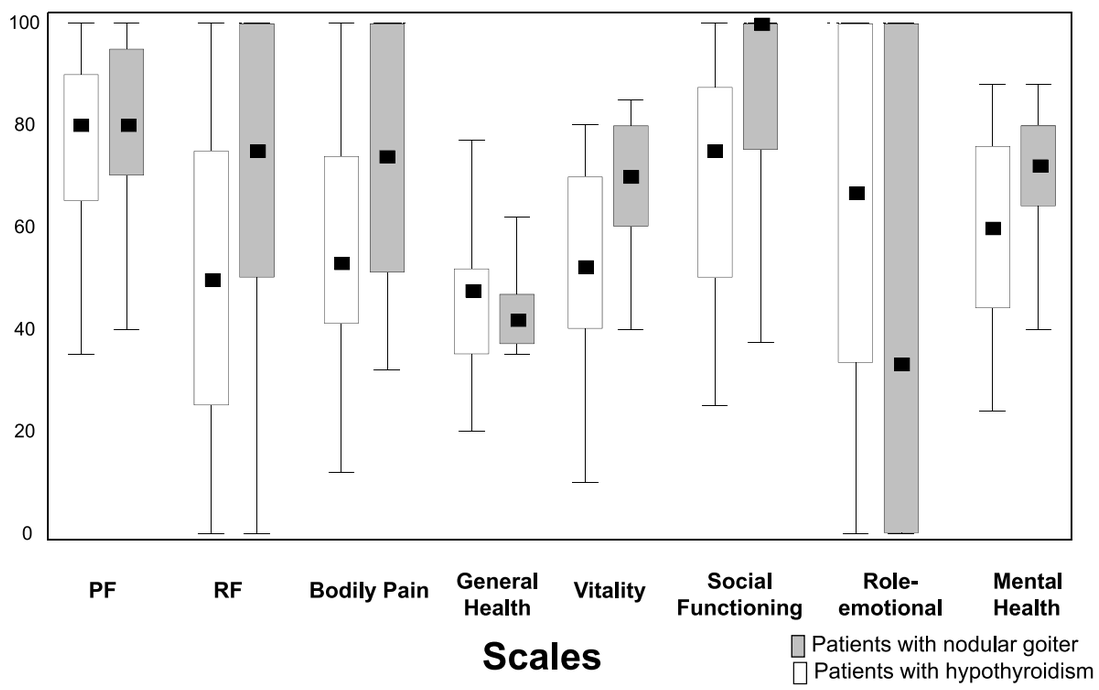

Fig. 3. Quality of life for patients with compensated hypothyroidism and with nodular goiter

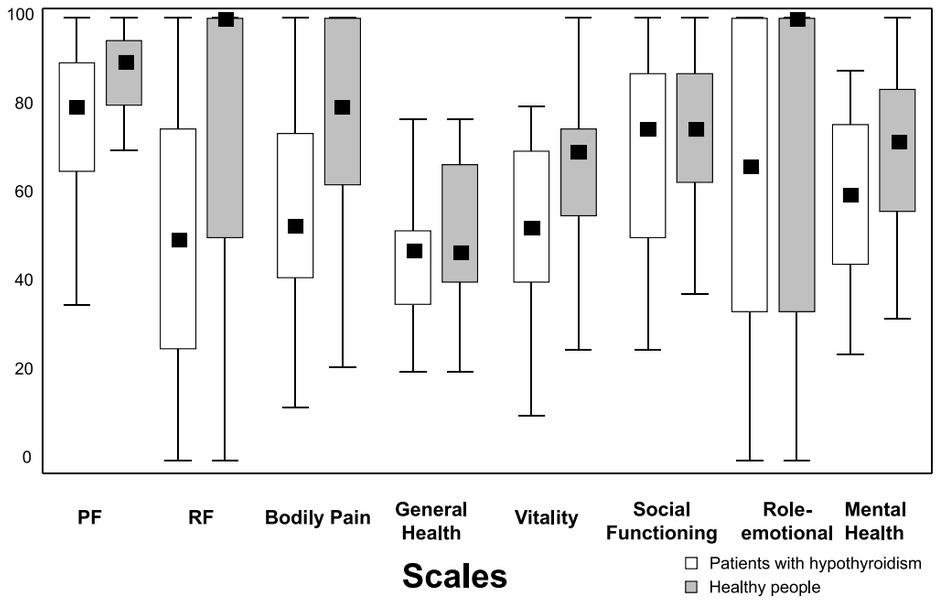

Fig. 4. Quality of life for patients with compensated hypothyroidism and healthy people

2.3 Modification of L-T4 intake (evening vs. morning)

General recommendation that L-T4 should be taken upon starving, 30-40 minutes before breakfast can lead to the poor compliance of the patients. On the other hand, failure to comply with this recommendation could result in significant worsening of the L-T4 absorption. However, as an alternative, patients can take drugs L-T4 in the evening or at night, finding the optimal time for an intake. Currently, in literature there is a discussion on a possibility of clinically significant change in TSH levels when changing the time of taking of L-T4. However, to date there are insufficient data on the feasibility and effectiveness of changing the time of taking the L-T4 drugs.

Elliott D.P. et al. have shown that the TSH level did not significantly change when shifting the time of L-T4 intake from morning (1-2 hours before breakfast) to evening hours (midnight) [*Elliott DP., 2001*].

2.4 Circadian rhythms of TSH and thyroid hormones

One of the factors which should be considered while adjusting the replacement dose of thyroid hormones is the physiological fluctuation of TSH and thyroid hormones, which is based on circadian rhythm secretion thereof. Normally, the TSH secretion occurs in a pulsating mode, whereas frequency and amplitude of pulsation increases at night, resulting in the circadian changes in TSH levels. TSH level is rising after midday, reaching a maximum of 2 - 4 hours in the morning, followed by a "plateau" for several hours and then decreasing to minimum values at midday [*Darzy KH, 2005, Persani L, 1995*]. Thus, fluctuations in TSH during the day can range from 1 to 3 mU/l. Thyroid hormone levels during the day also varies, but far less than the TSH. Thus, the study of Lucke C. et al. has

shown that the level of T4 reached a maximum from 8 to 12 a.m., and reached the minimum values from 11 p.m. to 3 a.m. T3 level was highest from 7 a.m. to 1 p.m. and the lowest - from 11 p.m. to 3 a.m. Herewith, those changes in hormone levels were insignificant and did not exceed the normal indicators [*Lucke C., 1977*].

The clinical significance of TSH circadian variability is defined, first of all, by the diagnostics of thyroid dysfunction. If in a number of patients, whose level of TSH is identified in the early morning hours, allows to diagnose subclinical hypothyroidism, but when the test is made later, the TSH level in some patients falls within the reference range. Thus, in a prospective study, performed by Scobbo R.R. et al., in 97 out of 100 of outpatients, the level of TSH, identified early in the morning was approximately by 26.4% higher as compared with the repeated tests made later in the afternoon. Based on the second (later) TSH tests, in 6% of patients the diagnosis of subclinical hypothyroidism was renounced [*Darzy KH, 2005*].

Similar results were obtained by in our study of 27 healthy persons at the age of 18–60 years. Measurements of serum TSH, fT4, fT3 were performed at 8.00–9.00 and 14.00–16.00 during the day and at 8.00–9.00 in 4–6 weeks. The median of TSH concentrations in the morning was 2.28 mU/l, at the daytime – 1.6 mU/l (p 0.05). The amplitude of TSH circadian variability reached 58% (Me = 21.45%). According to the current TSH reference ranges (0.4–4.0 mU/l) all participants had an euthyroidism in the morning and at the daytime (**figure 5**). According to the proposed TSH reference ranges (0.4–2.5 mU/l) 12 participants (44.4%) in the morning and 4 participants (14.8%) at the daytime have been classified as having a hypothyroidism. TSH levels in 4–6 weeks differed from initial on 42.8–7.71% [*Sviridonova M., 2010*].

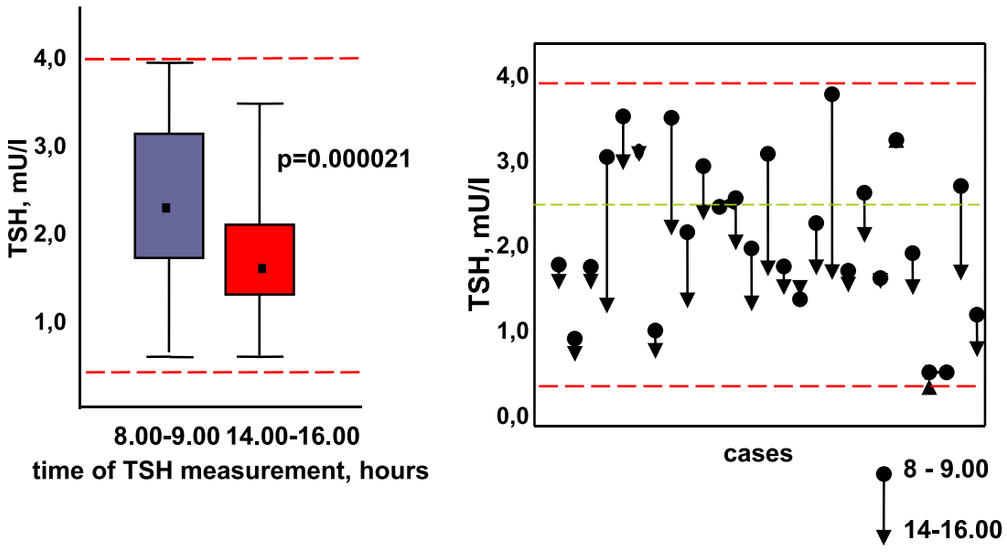

Fig. 5. Circadian variability of TSH in subjects with euthyroidism

In addition, of course, the data on circadian rhythms of TSH secretion plays an important role in assessing the adequacy of replacement therapy with thyroid hormones. Herewith, if the patients with overt hypothyroidism lose typical to healthy people increase in amplitude

and frequency of TSH secretion during the night [*Adriaanse R, 1992*], the prescribing of adequate replacement therapy with thyroid hormones leads to restore of circadian rhythm of TSH secretion [*Persani L, 1995*].

2.5 Combined therapy with T3 and T4

2.5.1 Controlled trials comparing L-T4 and L-T4 + L-T3

In the last decade the problem of combined therapy with L-T4+LT3 was in the centre of attention for many publications and some controlled randomized studies were performed. There are some publications where the authors, referring to their own clinical experience in treating of patients with hypothyroidism, are in favor of combined therapy of L-T3 + L-T4. For example, according to Mazzaferri E.L., some patients taking the preparations of thyroid gland extracts of animals (containing T3 and T4) over decades, noted the deterioration of well-being during switching to monotherapy with L-T4 [*Mazzaferri EL, 1999*].

First studies about comparison of two types of treatments, mono- and combined therapy with thyroid hormones were made in the 1970s. Thus, in 1970, Smith R.N. et al. published results of a double-blind crossover study. The study included 99 patients with primary hypothyroidism (postsurgical or after treatment with radioactive iodine), previously treated with L-T4 in the doses of 200-300 μg/day. All patients were randomized into 2 groups and within 2 months received L-T4 (200 or 300 μg) or L-T3 + L-T4 (2 or 3 tablets, respectively, 20 μg of L-T3 and 80 μg of L-T4 in each tablet). After 2 months, the treatment mode has been changed: patients from group 1 received L-T3 + L-T4, and those from group 2 received L-T4. Among 87 patients who completed the study, 42 patients (48%) did not prefer any type of therapy, 29 (33%) preferred monotherapy with L-T4 and 16 (18%) - a combination of L-T3+L-T4. During the study, a higher frequency of side effects was observed (palpitations, nervousness, feeling short of breath, etc.) on the combination of L-T3 + L-T4, as compared to monotherapy with L-T4. Authors concluded that tolerability of monotherapy with L-T4 is better as compared with the combination of L-T3 + L-T4, as well as the fact that L-T4 is effective as monotherapy and is preferable because of a longer half-life [*Smith RN, 1970*]. However, it should be noted that in this study rather large doses of thyroid hormones were prescribed, especially L-T3 (40-60 μg/day), which could lead to a high frequency of side effects.

In a relatively small study by Bunevičius R. et al., which however, attracted a high interest, the authors also compared the efficacy of monotherapy and combination therapy with L-T4 and L-T3 in patients with primary hypothyroidism. The study involved 33 patients with primary hypothyroidism, developed as a result of chronic autoimmune thyroiditis (16 patients) or after thyroidectomy due to a cancer (17 patients). All the patients at the moment of enrollment received a replacement or suppressive therapy with L-T4. Patients were randomized into 2 groups: patients from group 1 received L-T4 for 5 weeks, and then a combination of L-T4 + L-T3 for 5 weeks (when changing the type of therapy, the L-T4 dose was reduced by 50 μg and supplemented with 12,5 μg of L-T3); in group 2 patients initially received L-T3 + L-T4, followed by L-T4. The results showed that the levels of cholesterol and triglycerides in both groups were similar, whereas the level of SHBG (sex hormone-binding globulin) was significantly higher on combined therapy. The authors noted that on the

combined therapy, the pulse rate at rest was slightly higher, but blood pressure and results of neurophysiologic tests were similar on both regimens of treatment. To assess cognitive function and mood 17 tests were performed. Among 17 tests the results in 16 patients of both groups were normal. However, in six of 16 tests they were better or patients reported a better mood on the combined therapy with L-T4 and L-T3, rather than with L-T4 monotherapy. These results were confirmed by visual analogue scales. None of the performed tests demonstrated better results with L-T4 monotherapy versus combination therapy with L-T4 and L-T3. According to the results of the study, the authors concluded that: in patients with hypothyroidism, the use of combined therapy L-T3 and L-T4 leads to improved psychological and neurophysiological parameters, and the prescription of a combined therapy of L-T3 and L-T4 leads to a better quality of life than monotherapy with L-T4 [*Bunevičius R., 1999*]. Among disadvantages of this study that coud be mentioned, firstly - short treatment period (5 weeks), which is sufficient only for reaching the stable thyroid status after changing of the therapy [*Walsh JP, 2001*], but insufficient for assessment of the dynamics of the lipids, and secondly, the lack of adequate assessment of the cardiovascular system, which could help to identify possible changes in heart rate. Finally small number of patients was included in the study [*Walsh JP, 2001*].

Later, the results of some other similar studies were published. It should be noted, that these studies differed in the number of patients, monitoring duration and the ratio of L-T4 to L-T3 in the combined regimens. The majority of studies found no benefits of combined therapy L-T4 + L-T3, as compared with monotherapy L-T4 [*Levitt A., 2002; Sawka AM, 2003; Clyde PW, 2003; Siegmund, 2004; Rodriquez, 2005*].

One of the most interesting studies, comparing mono- and combination therapy of hypothyroidism was conducted by Walsh JP et al. [*Walsh J.P., 2003*]. The double-blind controlled study with crossover design included 110 patients with compensated hypothyroidism receiving L-T4. The patients enrolled in the study were satisfied or dissatisfied with their well-being on the replacement therapy. Patients were randomized into 2 groups: one group continued to receive monotherapy with L-T4, and the patients of the second group were switched to a combined therapy with L-T4 + L-T3, while the dose of L-T4 was reduced by 50 μg and L-T3 dose of 10 μg was added. After 10 weeks of therapy and a follow-up washout period (4 weeks of monotherapy with L-T4) replacement therapy was adjusted: the patients from group 1 were switched to a combination of L-T4 + L-T3, while the patients from the second group - to L-T4 monotherapy. All patients at each stage of treatment have undergone psychological tests (General Health Questionnaire 28 - GHQ-28, a visual analog scale), quality of life assessment (Short Form 36 - SF-36) and tests for hypothyroidism symptoms (Zulewski et al. scale, Thyroid Symptom Questionnaire - TSQ), which determined the level of TSH, freeT4, freeT3, SHBG, deoxypyridinoline, osteocalcin, alkaline phosphatase and cholesterol. The study included only women, whose average age was 47.7 ± 11.7 years. According to the results, during the combined therapy with L-T4 + L-T3, the TSH level was significantly higher than that demonstrated on monotherapy with L-T4. Increased TSH was due to inadequate replacement of L-T4 50 μg by L-T3 10 μg, and there was no L-T4 dose adjustment during the study. Thus, according to the authors, the tentative positive changes in the transition to a combination of L-T4 + L-T3 were balanced by high TSH [*Walsh J.P., 2003*]. No dynamics in the body mass and blood pressure was

noted during the study. It was shown that on the combined therapy L-T4 + L-T3, the score as per Zulewski scale and total cholesterol were significantly higher than on the L-T4 monotherapy. However, given the significant increase in TSH during the combination therapy, the authors also identified a group of patients, whose TSH levels did not change. The analysis in this subgroup showed that on the L-T4 + L-T3 combined therapy, the level of freeT4 was lower than on the L-T4 monotherapy, while the total cholesterol, the sum of Zulewski scale scores and pulse rate were the same. Quality of life and psychological state of patients did not differ on those types of therapy. At the same time, indictors of anxiety were significantly higher in the combination therapy.

We also conducted a study to compare two types of replacement therapy in hypothyroidism. We conducted a randomized controlled trial with a crossover design in 36 premenopausal women with hypothyroidism. All patients were divided into two groups: Group A (n=20) was randomized to L-T4; Group B received the combined therapy first, followed by the monotherapy. The treatment periods lasted for 6 months. No significant difference between monotherapy and combined therapy was demonstrated on TSH level, ECG monitoring, densitometry, thyroid symptoms score. The lipid profiles were better during combined treatment than L-T4 alone. In the Group B during combined treatment the levels of cholesterol and LDL decreased, in the Group A during treatment with L-T4 alone the levels of cholesterol and LDL were unchanged. The levels of osteocalcin were unchanged, but the level of deoxypyridinoline decreased during combined treatment. According to other authors, there were no significant differences in total cholesterol and lipoproteins during monotherapy with L-T4 and the combination of L-T4+L-T3 [*Clyde P.W., 2003, Bunevicius R., 1999, Saravanan P., 2005*]. Apparently, the registered changes in lipoprotein profiles can be explained by the homogeneity of the groups, i.e., in this study 36 premenopausal women without any concomitant diseases were enrolled. Other studies, on the contrary, were conducted on both men and women, and the women group consisted both from women of reproductive age and women in peri- and postmenopause. According to our results, compared with L-T4 alone, replacement treatment with combination of L-T4+L-T3 shows beneficial changes in serum lipids, but higher activation of bone resorbtion [*Fadeyev, 2010*].

However, despite the lack of obvious advantages in influencing the psycho-emotional status, patients often prefer the combination compared with monotherapy L-T4 [*Saravanan P., 2005, Escobar-Morreale H.F., 2005, Appelhof B., 2005*]. According to *Escobar-Morreale H.F. et al*, of the 26 patients, 18 preferred the combination of L-T4+L-T3 [*Escobar-Morreale H.F., 2005*]. A similar result was confirmed in a large study, conducted by Appelhof B. et al [*Appelhof B., 2005*]. In this study 141 patients were randomized to receive monotherapy with L-T4, the combination of L-T4+L-T3, ratio 10:1 and L-T4+L-T3, ratio 5:1. Studied therapy was preferred to usual treatment by 29,2%, 41,3% and 52,2% in the L-T4, 10:1 ratio and 5:1 ratio groups respectively. Although patients preferred combined L-T4+L-T3 therapy to usual L-T4 therapy, but changes in mood, fatigue, well-being and neurocognitive functions could not satisfactorily explain why the primary outcome (i.e. preference of the treatment) was in favor of L-T4+L-T3 combination therapy. According to our results from 36 patients completing the study 10 preferred L-T4+L-T3 treatment (27,8 %) and 8 preferred L-T4 treatment (22,2%). It is an interesting that 50% of the patients (18 from 36) had no preference.

Among the reasons why the patients chose monotherapy with L-T4 the main ones were the following: absence of anxiety and irritability, quiet sleep. Besides, a strong reason for the patients taking 100 μg of L-T4 (i.e. 1 pill of «L-thyroxin-100») was convenient administration. Patients who preferred combination of L-T4+L-T3 noticed, improvement of mood, higher working capacity, body weight reduction (in those patients who were initially overweight; but this difference was not significant) *[Fadeyev, 2010]*.

2.5.2 Levels of thyroid hormones on the replacement monotherapy with L-T4 and combination of LT4+L-T3

Several studies have shown that in patients on replacement monotherapy with L-T4 with normal serum levels of TSH and T3, an increased level of T4 is observed [*Fish LH, 1987, Ross DS, 2001, Salmon D., 1982*]. On the contrary the normal serum levels of T4 and TSH are often accompanied by lower values of T3 than in healthy people [*Woeber KA, 2002*]. Thus, the ratio of T4 to T3 is significantly higher in patients with hypothyroidism on the replacement monotherapy with L-T4 than in healthy controls. According to Woeber K.A., a higher ratio of T4 to T3 is due to the suppression of the residual T3 secretion by the thyroid gland and low conversion of T4 to T3 in the peripheral tissues on the exogenous L-T4 therapy. It has been demonstrated in earlier studies, that replacement therapy of hypothyroidism with L-T4 is accompanied by increased ratio of T4 to T3 in the blood [*Pearce CJ, 1984, Rendell M., 1985, Stock JM, 1974*], and this ratio grows up with increasing doses of L-T4.

According to Woeber K.A., higher level of T4 and lower level of T3 during the replacement therapy with L-T4, as compared with healthy people is because TSH secretion is regulated mainly by T4. Therefore, the normal level of TSH on the monotherapy with L-T4 may be accompanied by the decreased level of T3. According to Woeber K.A., among 35 patients treated with L-T4, four patients had a reduced T3 level, and three of them had it in the lower limit of normal range [*Woeber KA, 2002*]. In addition, according to Bunevicius R. et al., in patients who received monotherapy with L-T4, total serum T3 was close to the lower limit of normal range [*Buneviči̇us R., 1999*]. Similar results were obtained by Alevizaki M. et al. in a large group of patients (114 healthy people and 130 patients with hypothyroidism on L-T4 monotherapy) the serum level of T3 and T3/T4 ratio in patients on the L-T4 therapy were significantly lower than in the healthy group [*Alevizaki M., 2002*].

A number of studies have shown that switching of patients with hypothyroidism from L-T4 to the combination of L-T4+L-T3 results in a reduction of FT4 levels [*Buneviči̇us R.,1999, Clyde P.W., 2003*], while FT3 levels increase [*Clyde P.W., 2003, Levitt A., 2002*] or remain unchanged [*Buneviči̇us R.,1999, Walsh J.P., 2003*]. This is most likely caused by the use of different L-T4 and L-T3 doses since there are no comprehensive recommendations for L-T4 and L-T3 dose calculation for combined therapy. Moreover, it is not clear how the L-T4 dose should be reduced after the addition of L-T3. According to available publications, the additional prescription of 10 μg [*Walsh J.P., 2003*] or 12.5 μg [*Buneviči̇us R.,1999*] L-T3 is associated with a reduction of L-T4 by 50 μg. However, in the study of Walsh et al, it was reported that after replacement of 50 μg of L-T4 with 10 μg of L-T3, TSH concentrations increased considerably [*Walsh J.P., 2003*]. According to Walsh et al, the increase of TSH level may be caused either by a decrease of T4 level in serum, which is considered to play the

main role in the regulation of TSH production, or by the incorrect concept about the required T3:T4-ratio, which is in fact about 4:1 or even 3:1, but not 5:1 [*Walsh J.P., 2003*].

We also conducted a study to assess the level of thyroid hormones in patients with hypothyroidism receiving L-T4 monotherapy or combination therapy with L-T4 + L-T3.Fifty-eight women with primary hypothyroidism receiving L-T4 were enrolled in the study. The patients were randomised into two groups: Group 1 (n=42) patients continued monotherapy with L-T4, and Group 2 (n=16) patients were switched to combined therapy with L-T4+L-T3 (25 μg L-T4 was replaced with 12.5 μg L-T3). The final examination was carried out 6 months thereafter. There was also a third group of 20 healthy women (control group). Under monotherapy with L-T4, serum FT4 levels were higher ($p < 0.05$) and FT3 lower ($p<0.05$) than in the control group.

Serum FT4 under combined therapy was significantly lower than in both control and monotherapy groups. FT3 levels did not differ between the two groups of combined and monotherapy subjects; the highest FT3 levels were in the control group (**figure 6**). So, monotherapy with L-T4 in hypothyroidism is associated with non-physiologically high FT4 and low FT3 levels; but therapy with L-T3 once a day does not simulate the normal production of T3 by the thyroid [*Fadeyev V., 2005*].

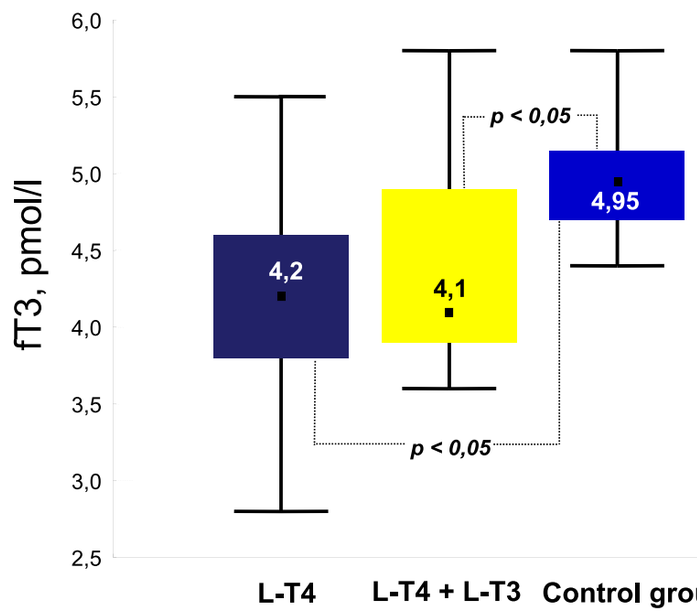

Fig. 6. Free T3 levels in patients with hypothyroidism on different replacement regimens and in controls (Me [25; 75])

2.6 Peripheral markers of thyroid hormones effects on tissues

The level of TSH is the main indicator which helps to assess the adequacy of replacement therapy of hypothyroidism. However, it reflects thyroid hormones action only on hypothalamic-pituitary axis.

Herewith, the issue of peripheral markers of replacement therapy adequacy in hypothyroidism is discussed in literature. At the same time, in clinical practice the identification of essential markers of the thyroid hormones peripheral action is difficult. In general, according to various authors, the markers of peripheral thyroid hormone effects may include: the level of total cholesterol, sex hormone-binding protein (SHBG), angiotensin-converting enzyme and markers of bone metabolism (bone formation and bone resorption) [*Ferretti E., 1999; Meier C., 2003*]. The soluble receptors of interleukin-2 may serve as a marker of the action of thyroid hormones on the lymphocytes [*Toft A.D., 2003*].

3. Target TSH level in L-T4 replacement therapy

The adequacy of the replacement therapy of hypothyroidism is estimated by the TSH level. To date, the reference range for TSH is generally accepted as 0.4 - 4.0 mU/l. However, in general population in 97% of people the TSH level is less than 5 mU/l, and upon exclusion from the sample persons with anti-thyroid-antibodies and those with goiter or close relatives with thyroid pathology, only in 8% of people the TSH level is higher than 2.5-3 mU/l [*Hollowell J., 2002*]. In 2003, the U.S. National Academy of Clinical Biochemistry has published the data that the TSH level more than 2.5 mU/l can be a predictor of hypothyroidism in the future. In addition, recommendations were given on a closer monitoring of persons with "high-normal" TSH level [*Baloch Z, 2003*].

However, to date there is insufficient evident data about advantages and disadvantages of maintaining “low-” or “high-normal” TSH levels on L-T4 replacement therapy. In 2006 were published results of a double-blind study examining the psycho-emotional state, cognitive function and some biochemical parameters in patients with hypothyroidism taking different doses of L-T4 [*Walsh J.P., 2006*]. The study included 56 women with hypothyroidism taking L-T4 and having normal TSH level at the time of enrollment. Patients took L-T4 in small, medium and high doses (dose was changed to 25 μg) for 8 weeks at each stage. According to the results, statistically significant changes were observed in the level of biochemical markers of thyroid hormones effects: the level of sex hormone binding globulin (SHBG), total cholesterol, alkaline phosphatase and deoxypyridinoline. The levels of SHBG, alkaline phosphatase and deoxypyridinoline with high L-T4 dose were significantly higher, and total cholesterol level was lower than the parameters with low-dose of L-T4. However, there was no statistically significant dynamics in quality of life parameters, symptoms of hypothyroidism and cognitive function when the dose of L-T4 was changed. The authors concluded that there are no clear advantages to maintain “low-normal” TSH levels in patients receiving L-T4 in terms of impact on psycho-emotional status and quality of life [*Walsh J.P., 2006*].

Thus, by now according to clinical studies there is not enough evidance to recommend maintenance of TSH levels in the lower range of normal values for patients with hypothyroidism on L-T4 replacement therapy.

Interesting results were obtained in the study of McDermott M.T. et al. According to a survey conducted among members of the American Thyroid Association (ATA) and general practitioners, it was found that more than 40% of the ATA-members considered the target TSH levels on L-T4 replacement therapy should be within the range of 0.5-2.0 mU/l and for

elderly patients - 1.0-4.0 mU/l. GPs more often designated the target TSH levels within 0.5 - 5.0 mU/l [*McDermott M.T., 2001*].

4. Replacement therapy of hypothyroidism in specific conditions

4.1 Elderly patients with concomitant disorders

The question of the beginning of replacement therapy in elderly patients especially in the presence of concomitant cardiac pathology should be discussed separately. It is generally recommended and agreed to start replacement therapy in these situations with small doses of L-T4 (12.5 - 25 μg) with a gradual increase to full replacement during 4 – 6 months or sometimes even longer. Although treatment of hypothyroidism with L-T4 could improve myocardial function and reduce peripheral vascular resistance, it could increase the need for oxygen in the myocardium. In patients with an already compromised myocardial blood supply due to coronary atherosclerosis, L-T4 treatment may provoke anginal symptoms. Patients with preexisting angina should be evaluated for obstructive coronary lesions before the beginning of L-T4 therapy.

4.2 Secondary hypothyroidism

Replacement therapy with thyroid hormones in the secondary hypothyroidism (SH) has some special features. First of all, as secondary hypothyroidism in adults is often associated with deficit of other pituitary hormones, the symptoms of thyroid hormone deficiency are "disguised" by deficiency of other hormones. In addition the level of TSH in SH is often normal at the time of diagnosis [*Ferretti E.,1999, Alexopoulou, 2004*], and decreases after the beginning of replacement therapy (in 2/3 of patients) [*Carrozza V, 1999*]. Corticosteroids taking for secondary hypocorticism also lead to reducing the TSH level. Thus, the TSH level cannot be a criterion for the compensation of SH. That is why generally recommended marker for its compensation is free T4 level which suggested to be in the upper third of the reference range in combination with normal level of free T3. Although the T3 level in spite of L-T4 substitution is often reduced. Thus, according to Alexopoulou et al, the level of free T3 is reduced in more than half of patients, despite normal levels of freeT4 [*Alexopoulou, 2004*].

Monotherapy with L-T4 is a preferred method of treatment in secondary hypothyroidism. Estimated dose, as in the situation with primary hypothyroidism, is about 1.6 μg per kilogram of body weight on average. However, the dose of L-T4 may differ significantly between patients often due to the effect of some medications. Most frequently, the L-T4 dose adjustment is required when patients are taking injections of growth hormone leading to increase of T4 to T3 deiodination in peripheral tissues finally leading to increase of L-T4 dose. The same situation could be due to estrogens replacement therapy in women. The adequacy of replacement therapy with L-T4 should be assessed in 4 - 6 weeks after the appointment of full replacement dose. After the adjustment of adequate L-T4 dose, the level of thyroid hormones is also advisable to control at least once per year.

4.3 Pregnancy

The recommended treatment of hypothyroidism during pregnancy is with oral L-T4. According to Guidelines of the American thyroid association the goal of L-T4 treatment is to

normalize maternal serum TSH values within the trimester-specific pregnancy reference range (first trimester, 0,1-2,5 mIU/L; second trimester, 0,2-3,0 mIU/L; third trimester, 0,3-3,0 mIU/L).

Clinical studies have confirmed that the increased requirement for L-T4 occurs beginning from 4-6 weeks of gestation. About 50-85% of women with compensated hypothyroidism (receiving L-T4) need to increase the dose of L-T4 during pregnancy [*Abalovich M., 2002, Mandel S.J., 1990, Alexander E.K., 2004*]. The greater dose increase will required to the patients with hypothyroidism after radioablation, surgery in comparison with women with autoimmune thyroiditis [*Kaplan M.M., 1996, Loh J.A., 2009*].

4.4 Subclinical hypothyroidism

Whether or not subclinical hypothyroidism in adults should be treated was and still is hotly debated; there are strong defenders as well as strong opponents to levothyroxine treatment. Pregnancy or the desire to become pregnant in case of infertility are the indications for replacement therapy.

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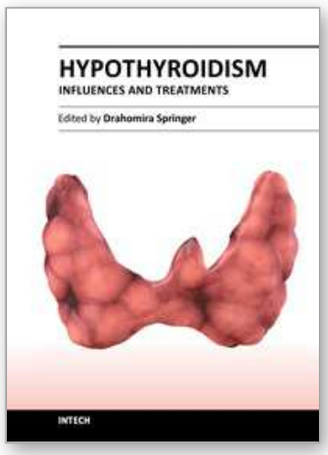

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Hypothyroidism is the most common thyroid disorder and it is significantly more frequent than presented - millions of people suffer from this disease without knowing it. People with this condition will have symptoms associated with slow metabolism. Estimates of subclinical hypothyroidism range between 3 to 8 %, increasing with age, whereas it more likely affects women than men. About 10% of women may have some degree of thyroid hormone deficiency. Hypothyroidism may affect lipid metabolism, neurological diseases or other clinical conditions. The book includes studies on advancements in diagnosis, regulation and replacement therapy, thyroid ultrasonography and radioiodine therapy for hypothyroidism. "Hypothyroidism - Influences and Treatments" contains many important specifications, results of scientific studies and innovations for endocrine practice.

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