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Complete List of Authors:	Perros, Petros; Royal Victoria Infirmary, Endcorinology Van Der Feltz-Cornelis, Christina; University of York, Department of Health Sciences Papini, Enrico ; Ospedale Regina Apostolorum, Department of Endocrinology and Metabolism Nagy, Endre; University of Debrecen Medical and Health Science Center, Division of Endocrinology, Department of Internal Medicine; Weetman, Tony; Dean of the Medical School, Medical School Hegedüs, Laszlo; Odense University Hospital, Department of Endocrinology and Metabolism
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THE ENIGMA OF PERSISTENT SYMPTOMS IN HYPOTHYROID PATIENTS TREATED WITH LEVOTHYROXINE: A NARRATIVE REVIEW

Short running title: Persistent symptoms in hypothyroidism

Petros Perros[1], Christina Van Der Feltz-Cornelis[2], Enrico Papini[3], Endre V. Nagy[4], Anthony P Weetman[5], Laszlo Hegedüs[6].

[1]Department of Endocrinology, Royal Victoria Infirmary, Newcastle upon Tyne, UK, [2]Department of Health Sciences, HYMS, University of York, York, UK, [3]Department of Endocrinology and Metabolism, Regina Apostolorum Hospital, Albano, Rome, Italy, [4]Division of Endocrinology, Department of Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary, [5]Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK, [6]Department of Endocrinology, Odense University Hospital, Odense, Denmark.

Summary

A significant minority of patients with hypothyroidism report persistent symptoms despite achieving normal thyroid biochemistry after levothyroxine (L-T4) replacement. Four principal lines of thinking, which are not mutually exclusive, may explain this enigma. The “low tissue liothyronine hypothesis” emphasises the potential imperfections of L-T4 replacement therapy, that may lead to hypothyroidism in some tissues like the brain, while others (for example hypothalamus) are euthyroid. The “Somatic Symptom and Related Disorders hypothesis” draws attention to an incidental coexistence of a diagnosis of Somatic Symptom and Related Disorders in patients with treated hypothyroidism. The “autoimmune neuroinflammation hypothesis”, highlights the potential consequences of inflammatory mediators due to thyroid autoimmunity (the commonest cause of hypothyroidism) on the brain. The “comorbidities and psychosocial hypothesis” implicates a variety of physical and psychosocial factors that have been noted to be associated with a diagnosis of hypothyroidism, which may be primarily the cause of persistent complaints. Over the past twenty years a great deal of time and effort has been expended pursuing the “low tissue liothyronine hypothesis”, which has failed to yield results that translate to patient benefits. This has skewed the balance in clinical practice, in favour of pursuing answers relating to L-T4 and liothyronine combination treatment, while the alternative explanations have been downplayed and potentially useful interventions have been given insufficient attention.

Key words: hypothyroidism, thyroxine, liothyronine, quality of life

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Introduction

Overt hypothyroidism [raised serum thyroid stimulating hormone (TSH) associated with low serum free thyroxine (FT4)], and subclinical hypothyroidism (raised TSH with normal serum FT4) affect 2-10% of the population [1]. Autoimmunity is the cause of hypothyroidism in about 80% of cases [1]. While in most patients treatment with levothyroxine (L-T4) restores health, 10-15% of patients do not regain their well-being after apparently adequate treatment with L-T4. [2-4] Persistent symptoms are non-specific and include fatigue, weight gain and mood changes [1,5]. Such symptoms may lead to multiple medical consultations, patient requests for inappropriate investigations, and dissatisfaction with treatment [5-7]. Given the high prevalence of hypothyroidism, this loss of well-being in a significant fraction of patients causes considerable socio-economic burden [8] and clinical management can be difficult and frustrating both for patients and clinicians [7]. The underlying causes for persistent symptoms are unclear. Here, we outline four major hypotheses which are not mutually exclusive and review the available evidence. We also identify areas of uncertainty that are worthy of future research.

Pathophysiology of persistent symptoms in levothyroxine-treated patients

There are four explanations for persistent symptoms: (a) deficiency in tissue concentrations of liothyronine (T3), (b) Somatic Symptoms and Related Disorders (SSRD), (c) autoimmune neuroinflammation and (d) other physical and psychosocial comorbidities.

The “low tissue liothyronine hypothesis”

L-T4 has to be converted to T3 to be biologically active [1]. The goal of treatment with L-T4 is to relieve the symptoms of hypothyroidism by restoring thyroid biochemistry [9]. The “low tissue liothyronine hypothesis” proposes that persistent symptoms are due to failure to achieve normal tissue levels of T3 in some patients treated with L-T4. This arises due to differences between the hypothalamus and other tissues in type 2 deiodinase (DIO2) sensitivity to circulating serum T4 [1]. Low serum T3 concentrations may result in low intracellular T3 levels and therefore hypothyroidism

at tissue level of some organs, including the brain. This in turn can cause persistent symptoms. The reason why only a minority of patients suffer from these complaints may be explained by variations in individual susceptibilities dictated by genetic predisposition. Therefore, patients with persistent symptoms may require replacement with both L-T4 and liothyronine (L-T3) in formulations and doses that reproduce physiological tissue levels of thyroid hormones. A further consideration is that serum TSH is genetically regulated [10] and can be influenced by personal habits such as cigarette smoking [11]. Therefore, it has been argued that the target serum TSH in hypothyroid patients may need to be individualised, although studies investigating "fine-tuning" the dose of L-T4 have shown no differences in patient outcomes [12,13].

The "low tissue liothyronine hypothesis" is conceptually sound, mechanistically plausible and widely quoted [1,14,15]. The best evidence for hypothyroidism at cellular level comes from rodents. Experimental work in the mid-1990's by Escobar-Morreale and colleagues demonstrated wide differences in the ability of different tissues to maintain normal tissue T3 concentrations at different doses of administered L-T4, with cerebral cortex and brown fat being best at sustaining normal T3 tissue levels, while muscle, liver and spleen were least able to do so [16]. The same researchers demonstrated that combination of L-T4 and L-T3 treatment in thyroidectomised rats restored normal tissue levels of T3 [16]. More recently it was shown that normalisation of tissue levels of T3 and activation of T3-regulated genes in brain required a continuous supply of both L-T4 and L-T3, which could not be achieved with L-T4 or orally administered combination treatment with L-T4 and L-T3 (L-T4+L-T3) [17].

The occurrence of residual symptoms in L-T4-treated patients have been explored in some populations. Saravanan et al [3] recruited 397 L-T4-treated patients from general practice records and 551 age and sex-matched controls. Questionnaires testing psychological well-being and hypothyroid symptoms were used. Patients had significantly worse scores than controls. Wekking et al [2] assessed neurocognitive function and symptoms of 141 L-T4-treated patients and compared them with reference values. Patients with hypothyroidism performed worse than controls. Panicker et al [4] assessed anxiety and depression in 1,546 female L-T4-treated patients and compared them with a large population of mainly women controls. There was an excess of depression and anxiety symptoms in patients, which

persisted after correction for serum TSH. All three studies assumed that biochemical assessments on a single occasion reflected long-term control of hypothyroidism. Peterson and colleagues [5] performed an online survey which included 12,146 hypothyroid patients mainly from the US. The average self-rated satisfaction score was 5 out of a maximum of 10.

There are some weaknesses of the “low tissue liothyronine hypothesis”. The excess prevalence of persistent symptoms in L-T4-treated patients compared to controls have not been recapitulated in studies from Asia or in children and adolescents [18,19]. Also, studies show that following an episode of hypothyroidism, recovery of some symptoms may be delayed by 6 months or more after normalisation of TSH [20,21]. A recent study reported on 6,138 patients who had been on L-T4 for at least one year and had their serum TSH measured on two separate occasions 25-28 weeks apart [22]. Of those patients who had a normal TSH at baseline, 19% had a TSH outside the normal range at follow-up (11% hypothyroid and 8% hyperthyroid). Based on such data, there is a high probability that some participants in the three studies highlighting persistent symptoms [2-4] had experienced episodes of thyroid dysfunction in the preceding 6 months (despite normal TSH recorded at the time of the study). In other words, some patients with persistent symptoms may indeed have poorly controlled hypothyroidism despite a normal serum TSH if only measured at a single time point.

Several studies have examined the relationship between serum TSH and free T3 (FT3) concentrations in L-T4-treated patients. In keeping with the “low tissue liothyronine hypothesis”, some have shown a lower FT3 concentration in L-T4-treated patients than controls[23], although in one of the studies that showed an excess of residual symptoms in patients with hypothyroidism and normal TSH, the serum FT3 concentration was normal [2]. Other published cross-sectional data also indicate that serum FT3 levels do not correlate with cognitive function, well-being [3,23] or quality of life (QoL) [24] in L-T4-treated patients. Furthermore, in a prospective study, patients with a previous diagnosis of thyroid cancer on TSH-suppressive L-T4 therapy who transitioned to normal serum TSH concentrations did not experience any negative somatic or neurocognitive symptoms, despite a reduction in serum FT3 concentrations [25].

Two small human studies have implicated genetic variants of the MCT10 thyroid hormone transporter and the DIO2 genes [26,27] in determining patient reported responses to L-T4+L-T3. However, these are preliminary data which require confirmation and the same DIO2 polymorphism had no association with serum thyroid hormones, QoL and cognitive function in either a large healthy population or in hypothyroid patients [28].

The increased prevalence of persistent symptoms in L-T4-treated patients described above [2-5] triggered an extensive research effort evaluating whether such patients might benefit from combination treatment with L-T4+L-T3. To date 15 randomised controlled trials have been published studying L-T4+L-T3 compared to L-T4 alone [29] using patient reported outcomes as endpoints (general and health-related QoL, mental health). In the three largest studies (total number of participants 939) there were no differences [30-32]. Two studies reported improved outcomes in patients treated with L-T4+L-T3. The first [33] was small (n=33), a large proportion of patients had thyroid cancer and the mean dose of L-T4 was high (175 mcg daily) reflecting an atypical patient population. The other study included more patients (n=59), but used a large and potentially unphysiological dose of T3 (20 mcg daily) [34]. Two recent systematic reviews [35,36] and a meta-analysis [37] evaluating fourteen randomised controlled trials concluded that L-T4+L-T3 and desiccated thyroid extract (DTE), which has a significantly higher T3:T4 ratio than that produced by humans, were no different to L-T4 alone in terms of QoL, neurocognitive function and somatic symptoms.

T3 has a short half-life and its use gives rise to unphysiological peaks and troughs, therefore it is plausible that “slow-release” T3 formulations may yield different results. Other shortcomings in study design of the previous trials on combination treatment have been highlighted [38] and include variable T4/T3 ratios, duration of treatment, outcome measures and other methodological problems, calling for further studies. It is of some interest that online surveys of hypothyroid patients indicate that 20-40% of patients are dissatisfied with their treatment and about 50% have poor QoL, with little difference between patients on L-T4, combination treatment, DTE or L-T3 alone [5,7]. Based on available evidence, it can be inferred that combination treatment with L-T4+L-T3 is ineffective, or that the effect size is minor and / or that the proportion of

patients that benefit is small. In contrast to L-T4, long-term safety data on L-T4+L-T3 treatments are limited, though what is available is reassuring [39].

Guidance from professional organisations on L-T4+L-T3 is variable. The American Thyroid Association contends that there is insufficient evidence for use of L-T4+L-T3 in routine practice *"outside a formal clinical trial or N-of-1 trial"* [9]. The European Thyroid Association guideline suggests that *"T4+T3 combination therapy might be considered as an experimental approach in compliant levothyroxine-treated hypothyroid patients who have persistent complaints despite serum TSH values within the reference range".* They add that treatment should be carefully titrated and monitored by accredited internists/endocrinologists [15]. The British and Italian Thyroid Associations [40,41] have adopted a similar approach to the European guidelines. Despite these recommendations, evidence suggests widespread prescribing of L-T3 and desiccated thyroid extract by non-accredited physicians, frequent purchasing of L-T3 without prescriptions, and adjustment of dose by patients based on self-evaluation of symptoms from day to day [6,7,42].

The "Somatic Symptom and Related Disorders Hypothesis"

SSRD is a classification described in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [43], which refers to persistent bodily symptoms associated with significant functional impairment, psychological distress and high healthcare costs. It occurs in up to 40% of primary care patients [44]. SSRD is the successor of the classification "somatoform disorders" in the DSM-4, that only pertained to medically unexplained symptoms. In SSRD, the distress can concern bodily symptoms in the context of a chronic medical condition, such as hypothyroidism, or medically unexplained symptoms (MUS). A key difference in the classification of SSRD over MUS is that SSRD can occur in patients with known medical conditions and might explain the distress of patients suffering from overt and subclinical hypothyroidism. SSRD can be accompanied by anxiety or depressive disorders, and first presentations with severe distress about physical symptoms can be a masked expression of these; SSRD can also be distress about physical symptoms as standalone phenomenon without psychiatric comorbidity, which makes it important to explore such possible comorbidities in the diagnostic phase.

The possibility that hypothyroid patients with persistent symptoms may merely represent an expected overlap of two common but independent conditions was proposed several years ago [45]. The “somatic symptom and related disorders hypothesis” proposes that patients with SSRD have multiple medical consultations and inevitably thyroid function tests are ordered. Based upon an *a priori* chance and the high underlying prevalence of both disorders, approximately 10% of patients with a SSRD may also have thyroid dysfunction, usually subclinical hypothyroidism. If patient and doctor assume that the symptoms are due to hypothyroidism, L-T4 is prescribed but will not be followed by symptom resolution if the actual diagnosis is SSRD. Any benefits tend to be minor and transient, leading to escalation of the dose of L-T4, without consistent symptomatic improvement. The patient can react to this in several ways, including sustained treatment-seeking behaviour. L-T4 is declared ineffective by the patient who, having consulted blogs and patient forums, may then seek treatment with L-T4+L-T3 or DTE. The patient may encounter resistance from the doctor to prescribe these treatments leading to consultations with several specialists or alternative practitioners or purchasing L-T3 or DTE online. The difficulty that patients experience accessing their “desired” treatment may also increase the perception of a benefit of treatment when they receive it, although symptoms usually persist [5,7]. Frustration and dissatisfaction ensue and are perpetuated by the absence of effective treatment directed at the underlying cause of the symptoms.

The evidence in favour of the “SSRD hypothesis” is circumstantial. Healthcare-seeking behaviour (defined as "any action or inaction undertaken by individuals who perceive themselves to have a health problem or to be ill for the purpose of finding an appropriate remedy") [46], may contribute to the increase of thyroid function test requests [47,48] in the general population. Healthcare-seeking behaviour is suggested by a study which showed that patients with psychological morbidity are more likely to have thyroid function tests than a control population [49], although alternatively it may reflect a tendency for general practitioners wishing to rule out hypothyroidism as the cause of symptoms of suspected anxiety or depression that may also occur in the context of SSRD.

A study of women from a general population sample found no association between subclinical hypothyroidism when identified by screening with impaired well-being [50],

indicating that subclinical hypothyroidism is not itself associated with symptoms and healthcare-seeking. Similar findings were noted in another study in patients with overt hypothyroidism identified by screening [51], in contrast to patients with previously known overt hypothyroidism who reported impaired self-rated health. The authors suggested that diagnostic labelling may have a negative impact on self-perception of health. However, assuming that only patients with symptoms would seek diagnosis and treatment, the diagnostic labelling could follow the experience of symptoms and hence may not explain the perception of health *per se*. An older Korean population of people with untreated overt hypothyroidism identified by screening had a better QoL than euthyroid controls, thus introducing possibilities of demographic and cultural variables being of some importance [52].

In keeping with experience of cognitive behaviour therapy (CBT) in non-hypothyroid patients, a randomised controlled trial of CBT in 96 L-T4-treated women showed significant improvements after 12 group sessions in emotional health, energy, and general health [53]. A collaborative care model combining training with psychiatric consultation in a general practice setting was found to be effective in the treatment of patients presenting themselves with persistent medically unexplained symptoms. The majority (86%) of whom were diagnosed with an underlying and until the consultation undetected depressive or anxiety disorder [54]. Patients responded well to an intervention focusing on exploration and explanation of the physical symptoms and the proposal of a treatment plan taking biological aspects and psychiatric comorbidity into account. In that study 4.9% of the patients suffered from hypothyroidism, which suggests that such an intervention might be a useful treatment model for persistent symptoms in both overt and subclinical hypothyroidism [54]. It can secure a classification of SSRD and support the general practitioner or endocrinologist providing treatment.

To summarise, the "Somatic Symptom and Related Disorders Hypothesis" describes how patients with subclinical and overt hypothyroidism can feel distress leading to persistent healthcare-seeking behaviour. Uncertainties about choice and effectiveness of treatment and psychiatric and somatic comorbidities may be additional contributions. This calls for a comprehensive clinical approach taking these knowledge gaps into account.

"Autoimmune neuroinflammation" hypothesis

It has been suggested that inflammation resulting from an autoimmune disease may be causally related to persistent symptoms [55]. This is supported by observational studies showing that patients with thyroid autoantibodies had more symptoms, poorer QoL and more anxiety and depression than controls [56,57], although the largest study [58] comprising more than 30,000 subjects failed to demonstrate such associations. However, this remains a plausible hypothesis and is in keeping with a recent randomised controlled trial of 147 patients with autoimmune thyroiditis [59]. Patients with persistent symptoms and high anti-thyroid peroxidase (TPO) antibodies, who had a normal serum TSH on L-T4 treatment were randomised to total thyroidectomy or no treatment. General health and fatigue scores improved impressively following total thyroidectomy, which persisted at 18 months and was accompanied by a decline in anti-TPO antibodies [59]. Post-operative morbidity included infection (4.1%), permanent hypoparathyroidism (4.1%), and recurrent laryngeal nerve injury (5.5%). This study needs to be confirmed before its findings can be applied to clinical practice, given its lack of a double-blinded control and invasive nature. Selenium supplementation in autoimmune thyroiditis has been shown to lead to reduction in anti-TPO antibodies [60] and is currently under investigation in a randomised controlled trial using a thyroid disease-specific thyroid QoL (ThyPRO) instrument [61], however selenium supplementation has not been shown to alter the course of autoimmune thyroid diseases.[62]

"Other physical and psychosocial comorbidities" hypothesis

Several other factors that affect well-being are associated with hypothyroidism. Whether these relationships are causative remains unclear.

Physical comorbidities

Undiagnosed diseases such as other autoimmune diseases, deficiencies in vitamins and iron, sleep apnoea, chronic infection, and a long list of other diagnoses can potentially present with non-specific symptoms that may be wrongly attributed to hypothyroidism [14]. Symptoms arising from known comorbidities may also add to the burden of persistent symptoms. An increased prevalence of comorbidities in patients with hypothyroidism and persistent symptoms was reported by Saravanan et al [3].

This association has been confirmed by other investigators and is bidirectional. Somatic morbidity [63] is increased in those subsequently diagnosed with hypothyroidism, but the diagnosis of hypothyroidism also increases the subsequent likelihood of further diagnoses [3,8,23]. Patients who have other comorbidities are more likely to be investigated for hypothyroidism [49], thus introducing a bias in favour of clustering of chronic symptoms and a diagnosis of hypothyroidism.

Psychiatric comorbidities

Hypothyroid patients are more likely to suffer from psychiatric illness [49,64]. A multicenter European study in patients with Major Depressive Disorder found a prevalence rate for comorbid hypothyroidism of 13.2% [65]. Patients with this comorbidity were more likely to be older, female, and suffering from more severe depression including psychotic symptoms, and from comorbid chronic somatic conditions such as cardiovascular disorders. They needed treatment with a combination of psychotropic medication including augmentation of psychopharmacological drugs, especially with antipsychotics, mood stabilisers and pregabalin to achieve treatment response [65].

Chronic medication

Patients who receive chronic medications have been shown to have compromised physical, social and psychological well-being [66]. L-T4-treated patients were shown to be more likely to be prescribed statins, beta-blockers, analgesics antidepressants and a variety of other drugs compared to controls [3,23]. Patients treated with L-T4 tablets are advised to avoid food and drink (other than plain water) and some other commonly used medications for a minimum of 30 minutes after ingestion of L-T4. These restrictions may have a negative impact on patients' wellbeing. The absorption of some formulations of L-T4 seem not to affected by food, drinks or other medications [67], however there are no robust data on the effects of different L-T4 formulations on QoL.

Physical inactivity

Small studies have shown that exercise training improved the QoL and fatigue perception in patients with L-T4-treated subclinical and overt hypothyroidism [68,69].

Obesity

Obesity is a common complaint in patients with L-T4-treated hypothyroidism and is associated with poor QoL [5,24]. Obesity is also associated with a mildly serum

elevated serum TSH, which occasionally leads to improper diagnosis of subclinical hypothyroidism and L-T4 administration [70].

Demographic factors

A study of patients with hypothyroidism showed that hypothyroid symptoms at the time of diagnosis were more prevalent in women than men [71]. A hypothyroid patient survey showed a positive correlation between older age and male gender, with satisfaction with treatment and care [7], suggesting that demographic factors may influence expressions of satisfaction.

Socioeconomic factors

Unemployment is associated with somatic symptoms in patients on L-T4 treatment [72]. Hypothyroidism predicted disability and loss of life-long earning, early retirement and loss of labour market income [8]. These studies suggest an association between somatic symptoms in patients with treated hypothyroidism and adverse socioeconomic parameters.

Unrealistic patient expectations

A recent survey of hypothyroid patients showed that unrealistic patient expectations correlated with dissatisfaction [7].

Poor patient experience with health professionals

Poor experience with health professionals is frequently cited by dissatisfied hypothyroid patients [5,7] and may be due to communication barriers. Areas of concern include not being listened to by health professionals, long delays in diagnosis, lack of information about diagnosis and treatment and being denied participation and engagement in choice of investigations and treatments [5,7].

Misinformation

Poor patient knowledge and misinformation about hypothyroidism and its treatment have been shown to be barriers to positive patient outcomes [73]. Misinformation may be further amplified by social media.

Future research questions

Table 1 lists some research questions that arise as a result of considerations covered in this review.

Conclusions

Interventions using L-T4+L-T3 have been disappointing and are unlikely to unlock the persistent symptom enigma for the majority of patients, therefore other avenues need to be explored. CBT, lifestyle changes, better management of patient expectations, provision of good quality information and psychiatric consultation to support the endocrinologist or general practitioner in delivering optimal care, are interventions that merit further study.

Declarations of interest

PP, EP, EN and LH have undertaken consultancy work for IBSA Group Pharmaceuticals, Switzerland. CFC and APW have no conflicts of interest to declare. IBSA has had no involvement in the preparation of the manuscript and neither IBSA nor any other agency has supported this review financially.

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Table 1

Research questions pertaining to persistent symptoms in hypothyroid patients

- What is the relationship between persistent symptoms in hypothyroid patients and other causes such as Somatic Symptom and Related Disorders, and how can they be identified?
- Can persistent physical symptoms be traced before the onset of hypothyroidism?
- ~~What is the socioeconomic cost of persistent symptoms in hypothyroid patients?~~
- What is the impact of better long-term control of hypothyroidism using intensive biochemical monitoring and levothyroxine adjustment?
- What is the natural history of persistent symptoms in hypothyroid patients?
- Is the phenomenon of persistent symptoms in hypothyroid patients found in parts of the world other than Western Europe, North America and Australia?
- ~~How effective are formulations of L-T4 that can be taken with food and drink in hypothyroid patients with persistent symptoms?~~
- Is combination treatment with L-T4 with physiological doses of slow-release L-T3 more effective than L-T4 alone?
- How effective is treatment of obesity for persistent symptoms in hypothyroid patients?
- Is cognitive behaviour therapy effective for hypothyroid patients with persistent symptoms?
- Are exercise programmes effective for hypothyroid patients with persistent symptoms?

- Can the total thyroidectomy study in patients with autoimmune thyroiditis be confirmed?
- Can selenium supplementation and other immunomodulatory agents ~~or thyroid remnant ablation with radioiodine (augmented by administration of recombinant human TSH)~~ aimed to reducing thyroid autoantibodies improve persistent symptoms in patients with autoimmune thyroiditis?
- Does personality play a role in the development of persistent symptoms in hypothyroid patients?
- Can better information delivered to patients at the time of diagnosis of hypothyroidism prevent persistent symptoms?
- Can better management of patients' expectations at the time of diagnosis of hypothyroidism prevent persistent symptoms?
- Can psychiatric consultation in the management of hypothyroid with Somatic Symptom and Related Disorders lead to improved outcomes?