Maturitas 87 (2016) 72–78

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review article

Clinical challenges in thyroid disease: Time for a new approach?

A.G. Juby[a,*], M.G. Hanly[b,1], D. Lukaczer[c]

[a] Division of Geriatrics, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada
[b] System Laboratory Medical Director, Chief of Pathology, Baptist MD Anderson Cancer Center, Jacksonville, FL, USA
[c] Director of Medical Education at the Institute for Functional Medicine, Fife Naturopathic Clinic, 6111 20th Street East, Fife, Washington, WA 98406, USA

ARTICLE INFO

Article history:
Received 19 December 2015
Received in revised form 30 January 2016
Accepted 1 February 2016

Keywords:
Thyroid disease
Treatment
Diagnosis

ABSTRACT

Thyroid disease is common, and the prevalence is rising. Traditional diagnosis and monitoring relies on thyroid stimulating hormone (TSH) levels. This does not always result in symptomatic improvement in hypothyroid symptoms, to the disappointment of both patients and physicians. A non-traditional therapeutic approach would include evaluation of GI function as well as a dietary history and micronutrient evaluation. This approach also includes assessment of thyroid peroxidase (TPO) antibodies, T3, T4, and reverse T3 levels, and in some cases may require specific T3 supplementation in addition to standard T4 therapy. Both high and low TSH levels on treatment are associated with particular medical risks. In the case of high TSH this is primarily cardiac, whereas for low TSH it is predominantly bone health. This article discusses these important clinical issues in more detail, with some practical tips especially for an approach to the "non-responders" to the current traditional therapeutic approach.

Contents

* Corresponding author at: Division of Geriatrics, Department of Medicine, University of Alberta, 1-110 Clinical Sciences building, 11350 83 Avenue, Edmonton T6G 2P4, Canada. Fax: +1 780 492 2874.
E-mail addresses: angela.juby@albertahealthservices.ca (A.G. Juby), mhanly@sepalabs.com (M.G. Hanly), Doc@DanLukaczerND.com (D. Lukaczer).
[1] Fax: +1 912 261 0561.

http://dx.doi.org/10.1016/j.maturitas.2016.02.001
0378-5122/

1. Illustrative cases

1.1. Case 1

A slim (BMI 19), active, 86 year old woman playing tennis regularly till the age of 83 was discovered to have an elevated TSH (4.5 mIU/L) (normal range 0.2–4.0 mIU/L) on routine bloodwork. She had no symptoms of hypothyroidism, and was feeling well. Nonetheless, she was started on levothyroxine. This resulted in insomnia for which she was started on clonazepam. This led to daytime confusion, fatigue and poor balance but fortunately no falls. She could now only manage walking in her building corridors using the handrails. She noticed that she felt stronger in the afternoon and evening when the clonazepam was wearing off.

1.2. Case 2

A 52 year old lady has a long history of thyroid disease since her 20's. She has multiple symptoms of hypothyroidism including fatigue, weight gain, thinning hair, and cold intolerance. She has been on ever increasing doses of levothyroxine, with the recent addition of cytomel. Her TSH is currently 0.03 mIU/L (normal range 0.2–4.0 mIU/L). She has had no improvement in her symptoms. Her bone density confirms osteoporosis.

2. What we know

The prevalence of spontaneous overt hypothyroidism is 1–2%, ten times more common in women than men, and increases with age. 8% of women and 3% of men have subclinical hypothyroidism [1]. Studies have reported that those with higher baseline serum TSH values and/or elevated anti-thyroid antibodies have a higher propensity to progress to overt hypothyroidism [2,3].

Thyroid hormone supplement is one of the most frequently prescribed therapies in the United States and Europe, and several studies of primary care practices indicate increasing levothyroxine prescriptions over the past few decades [4,5]. If left untreated hypothyroidism can be associated with significant morbidity, particularly in the elderly, where typical symptoms may be absent or may be erroneously attributed to normal aging or coexisting disease [6]. As abnormalities of thyroid function impact all organ systems, it often manifests predominantly in the most impaired organ system, particularly in those patients with comorbid conditions [7].

Increasing epidemiological evidence suggests subclinical hypothyroidism is associated with increased risk of coronary heart disease events, heart failure, cardiovascular mortality, and perhaps cognitive impairment, depression and fracture risk [8]. At the other end of the spectrum, two recent studies (from the UK and USA) report a cumulative rate of *over-treatment* of 9.6–16% over 5 years. [9,10] This raises the questions: is there a lack of symptomatic improvement; or are the risks of over-treatment unappreciated; or is deliberate generous treatment thought to improve symptoms? The latter possibility is also suggested by Taylor et al. who found that over-treatment was more likely if prescriptions were started for fatigue or depression [9]. It is important to remember that subclinical *hyper*thyroidism is also associated with significant health issues [11], as well as an increased risk of fracture [12].

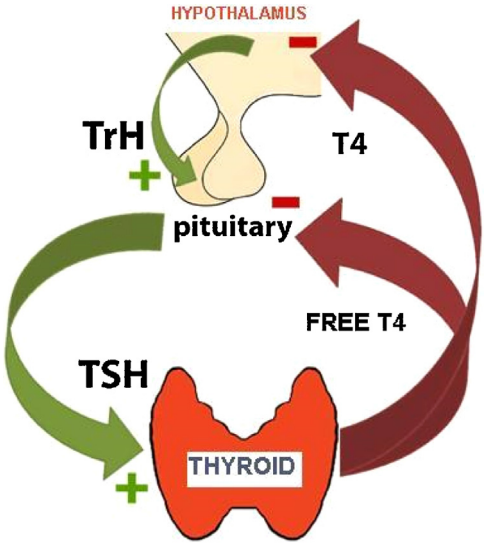

Fig. 1. Normal physiologic thyroid function (TrH: thyroid releasing hormone; TSH: thyroid stimulating hormone; T4: tetraiodothyronine).

3. Thyroid laboratory testing

Isley [7] suggested that "it is also essential to be able to distinguish between test abnormalities that indicate primary thyroid dysfunction and those that reveal an adaptive response to nonthyroidal illness".

A rational approach to the evaluation of thyroid function requires an understanding of the normal physiology of the thyroid gland. (see Fig. 1). TSH promotes thyroid gland growth and hormonal secretion. The level of TSH is regulated by circulating tetraiodothyronine/thyroxine (T4) levels. Thyroid releasing hormone (TrH) stimulates release of TSH, which then induces production of thyroxine (T4). The level of T4, influences the amount of triiodothyronine (T3) produced and both the hypothalamus and the pituitary alter production of TrH and TSH, respectively dependent on T4 levels. Elevated free (unbound to throxine binding globulin) T4 inhibits production, while low free T4 stimulates production. The thyroid secretes 90% T4, with 50% of this being deiodinated to T3. T4 is deiodinated to T3 in many cells of the body, particularly the liver and kidneys. The remainder is converted to reverse T3 (rT3). This is an inactive form of T3, and it is therefore a regulatory mechanism. More rT3 is created when the body needs to reduce the action of T3 and T4. Although both triiodothyronine (T3) and tetraiodothyronine (T4) are secreted by the thyroid gland, 80% of the circulating T3 is produced by extra thyroidal deiodination of T4. *T3 is the major active component* as it interacts with the nuclear T3 receptors in multiple tissues and subsequently affects promoter regions of genes that are positively or negatively regulated by thyroid hormones.

Nearly all T4 (99.96%) and T3 (99.6%) is bound within the circulation. The majority is bound to thyroxine binding globulin (TBG) (70%) with additional portions bound to transthyretin (10%) and albumin (15%). *Only free T3 and free T4 can enter cells to exert their actions.* The hormones are further deiodinated to diiodothyronine and monoiodothyronine in the liver and kidneys. Iodine is recycled or excreted in the urine.