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EDITORIAL COMMENTS – OPEN ACCESS

Clinical Effects of Fine-Tuning: Thyroid Hormone Replacement

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Hypothyroidism is among the most frequent endocrine disorders, and levothyroxine (L-thyroxine) is one of the most commonly prescribed drugs by internists and endocrinologists in daily practice; however, inappropriate replacement of thyroid hormone is reported to be as high as 40% (1). Considering the multisystemic effects of thyroid stimulating hormone (TSH), it is reasonable to expect consequences resulting from inappropriate treatment. Over-suppression of TSH was reported to be mainly associated with atrial fibrillation, heart failure, and increased cardiovascular and overall mortality as well as osteoporosis and increased fracture risk (2). Undertreatment with L-thyroxine may also have many deleterious effects similar to hypothyroidism itself like fatigue, weight gain, neurocognitive impairment, and cardiovascular effects like atherosclerosis, bradycardia, congestive heart failure, and hyperlipidemia (2). Many studies have investigated the relationship between osteoporosis and hypothyroidism but there is still conflicting data (3). Yılmaz et al. retrospectively studied the association between hypothyroidism and osteoporosis in postmenopausal women who were euthyroid under L-thyroxine treatment and reported no association (4).

The adequacy of L-thyroxine replacement is mainly based on the measurements of TSH, which is the most reliable marker. It is of utmost importance that the assay used can reliably differentiate between normal and subnormal TSH levels and the functional sensitivity is the index relied on for lower limit measurements of TSH. Immunoassays have improved in time based on their functional sensitivity. As minimal changes in L-thyroxine dosage may cause clinically significant swings in TSH levels, clinicians may prefer more sensitive methods for cases where subclinical thyroid dysfunction gains importance such as in pregnancy, senility, or treatment of differentiated thyroid cancers. First to fourth generation assays are available although first generation is generally out of use. Fourth generation assays are able to detect TSH at concentrations as low as 0.001–0.002 µIU/mL. Nevertheless, none of the methods fulfill all criteria of an ideal assay in terms of cost effectiveness, sensitivity, and timing. Second generation TSH assay was shown to provide results in a shorter time with a lower sample volume, while third generation TSH assay was more sensitive and accurate in patients with subclinical thyroid disorders (5).

Treatment with thyroid hormone is usually started empirically and much effort has been put into estimating the accurate initial dosage. The treatment of patients with endogenous thyroid reserve is titrated based on serial measurements of TSH; however, in case of totally thyroidectomized patients, some equations have been suggested. Body weight-based adjustment is the most frequently used one during daily practice, though it is reported in some studies that body mass index (BMI) could be a better predictor, while some other studies suggest lean body mass (LBM) (6, 7). Toomatari et al. investigated the relationship between body weight, BMI, LBM, and the dose of L-thyroxine in patient groups that had undergone total thyroidectomy for benign and malignant thyroid conditions. The authors concluded that BMI is the most favorable parameter, and they also presented new equations for predicting the accurate L-thyroxine dose based on weight, BMI, and LBM (8).

Restoring euthyroidism depends on many more factors such as patients' adherence to therapy, absorption of the drug, other medications used that may affect thyroid-binding globulin concentrations or interfere with absorption, concurrent illnesses leading to deiodinase dysfunction, and so on. Moreover, a small group of patients complain of symptoms consistent with hypothyroidism while they are biochemically euthyroid. The expressions of deiodinases, transmembrane transporters, and thyroid hormone receptors vary among tissues causing different thyroid statuses in different tissues. Biochemical euthyroidism does not necessarily mean that euthyroidism is actually achieved in the whole organism. A novel study claimed that anti-TPO antibodies may contribute to symptomatology in euthyroid patients (9). L-thyroxine replacement may cause high T4: T3 ratio with TSH in the reference range, and it is not known whether all tissues with such a diverse distribution of deiodinases and thyroid hormone receptors can remain euthyroid in this altered T4: T3 ratio (10). Also, thyroidectomized patients naturally lose T3 that is synthesized from thyroid tissue though in small concentrations, and this may be one of the factors that contribute to patients' com-

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plaints, but the trials of combination therapy with L-thyroxine and triiodothyronine in these patients have not been conclusive so far (11). In contrast, some patients do not report any symptoms even though they are not euthyroid. A recent meta-analysis concluded that treatment of subclinical hypothyroidism did not improve general quality of life or thyroid-related symptoms (12). Also another recent study reported that altering L-thyroxine doses to maintain TSH in the reference range, but in varying levels, did not have any effect on quality of life (13).

Thyroid hormone replacement is a simple treatment modality that has complex pharmacodynamics *in vivo*. In addition, even if all conditions to achieve biochemical euthyroidism are fulfilled, it does not ensure that euthyroidism is restored in all tissues.

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