Preventing over-treatment in euthyroid patients with thyroid hormone abnormalities

Up to 12% of the U.S. population will be diagnosed with a thyroid condition. Because thyroid hormones affect every cell in the body, hypo- (low) and hyper-(high) thyroidism can be difficult to distinguish from other medical conditions. Diagnosis based on the measurement of thyroid hormones in blood is complicated by the challenges in accurately interpreting different types of hormone measurements. Overtreatment of thyroid disease is increasingly prevalent and leads to complications including heart irregularities and fractures. The choice and interpretation of thyroid tests leads to correct diagnosis and prevents unnecessary repeated testing and treatment.

The thyroid gland is a small organ at the base of the neck that produces the more abundant, though inactive, hormone containing four iodines, named thyroxine (abridged as T4). Removal of a particular iodine from T4 by body tissues produces the active hormone, T3. Both T4 and T3 circulate in the bloodstream attached (bound) to proteins: 75% to thyroxine binding globulin (TBG), 20% to transthyretin (TTR), and 5% to human serum albumin (HSA). Protein-bound thyroid hormones allow for hormone storage and only a small amount (about 1% of the total) is released and made available to enter tissues. This large amount of protein-bound hormone serves as a reserve preventing fluctuations in hormone availability independent of minute-to-minute production by the thyroid gland, as in the setting of acute illness, iodine deficiency or thyroid disease. Measurements of total T4 (TT4) and total T3 (TT3) reflect this pool of inactive protein-bound hormone. Genetic variations of thyroid hormone-binding proteins can alter their amount or their ability to carry the hormone (affinity), affecting the levels of TT3 and TT4 without altering the fraction of hormone entering tissues. In such instances an alteration in the amount of measured hormone does not indicate insufficient or excess hormone and does not require treatment. However, it must be correctly identified.

Mutations in TBG, the main carrier of thyroid hormone, cause either TBG deficiency due to defects in synthesis, disposal, or hormone binding affinity, or TBG excess due to extra copies of the gene. Changes in TBG levels are reflected in increased or decreased TT4 and TT3 concentrations, but because these individuals receive a normal supply of hormone to their body tissues, they are euthyroid. This can be confirmed by TBG gene sequencing which will precisely identify the genetic defect. Non-genetic factors can also transiently affect TBG levels. For example, reduced TBG occurs with excess testosterone or adrenal steroids, protein deficiency from liver, kidney or gastrointestinal disease, or critical illness. In contrast, elevated estrogen levels from pregnancy or oral contraceptives increases TBG. These possibilities should be considered prior to genetic testing.

Though TTR is a lesser carrier of thyroid hormone, mutations that increase its binding affinity for thyroid hormones can cause increases in TT4 that can be interpreted as representing thyroid overactivity. However, as in the case of TBG excess or increased hormone binding, these

individuals are euthyroid.

Finally, HSA, though carrying only 5% of thyroid hormone, has been found to harbor mutations that greatly increase thyroid hormone affinity. This results in an increase in blood TT4 and TT3 in different proportions depending on the type of mutation. As with all genetic conditions, the defect is inherited giving rise to a condition called familial dysalbuminemic hyperthyroxinemia (FDH), one particular mutation is frequent in individuals of Hispanic background. FDH also affects the measurement in free thyroid hormone assays giving false results.

Abnormalities in serum thyroid hormone binding proteins should be suspected when the clinical presentation does not support the thyroid function tests, particularly if family members show the same test abnormalities.

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