

Review Article

A 6 Dimensional approach to Diagnosing Refractory Hypothyroidism

ABSTRACT

Refractory hypothyroidism is a commonly encountered clinical challenge despite hypothyroidism being an easy condition to manage. However, truly refractory hypothyroidism accounts for only a small proportion of refractory hypothyroidism, remainder being “pseudo-refractory.” The 6-dimensional tool helps guide physicians to manage poorly controlled hypothyroid individuals better. This tool highlights some important aspects of evaluating such individuals such as dialogue, diagnosis, definition of endpoint, disturbance in assay, drug intake (L-thyroxine and concomitant drug intake), and comorbid disease. Most importantly, this simple reader friendly tool can help differentiate truly refractory from pseudo-refractory hypothyroidism. The latter being easily correctable holds the promise of improving the quality of life in such individuals.

Keywords: 6-dimensional tool, L-thyroxine, refractory hypothyroidism

INTRODUCTION

Hypothyroidism is considered an easy condition to manage. There is only one accepted replacement therapy (L-thyroxine), which is titrated according to the thyroid function.^[1] In theory, this should be a simple and straight forward task. However, in reality, the management of hypothyroidism is a complex matter. The concept of patient-centered hypothyroidism management highlights some aspects of the wide spectrum of thyroid care.^[2]

CHALLENGES

Refractory hypothyroidism is a commonly encountered clinical challenge. In spite of supposedly “optimal” L-thyroxine replacement, a significant proportion of patients do not achieve biochemical euthyroidism.^[3] Conversely, among those who do an important subset remain symptomatic. The issue of dissatisfaction with thyroid therapy has been addressed elsewhere, and explained by the tissue hypothyroidism and fatigue syndrome.^[4,5]

REFRACTORY HYPOTHYROIDISM

In this communication, we share a simple framework to help screen and address patients with refractory hypothyroidism.

We share a rubric entitled the 6-dimensional (6D) tool, which should help physicians manage most patients with poorly controlled hypothyroidism. The various causes of refractory hypothyroidism can be covered under six headings, all of which can be listed in an alliterative 6D manner [Table 1].

A common reason for inability to manage disease is the lack of a physician–patient bond characterized by shared, informed decision-making.^[6] We termed this a challenge to dialog.

At times, the treating physician may misdiagnose a clinical condition as Hashimoto’s thyroiditis, while it may be actually

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Table 1: Etiology of refractory hypothyroidism

Dialogue	Suboptimal relationship between patient and physician, leading to poor adherence/persistence
Diagnosis	Incorrect diagnosis of disease, for example, inability to recognize central hypothyroidism, sick euthyroid syndrome, obesity-related thyroid dysfunction, thyroid resistance, and pregnancy physiological increased demands
Definition of endpoint	Inappropriate choice of endpoint, for example, testing TSH at short intervals, testing only TSH in central hypothyroidism, and testing T4 in states of hypoalbuminemia
Disturbance in assay	For example, due to concomitant medication like biotin, due to wrong timing of sampling, due to the use of inaccurate assays, and the presence of TSH heterophile antibodies
Drug intake (L-thyroxine)	Lack of adherence to suggested therapeutic regimen Concomitant administration of medication which may impair absorption (antacids, iron, calcium) or increase the metabolism of L-thyroxine
Disease (comorbid)	Comorbid disease, for example, malabsorption syndromes, renal/liver impairment, hypocortisolemia

TSH: Thyroid-stimulating hormone, T4: Thyroxine

another cause of thyroid dysfunction. Recognizing the impact of illness, weight fluctuations, and pregnancy on thyroid function are equally important yet often misunderstood. An incorrect diagnosis, along with incorrect definition of endpoint, is a cause of refractoriness to treatment. This reminds us that an in-depth understanding of physiology and pathology is necessary in the endocrine management. Equally important is knowledge of biochemistry, and various factors which contribute to preanalytic, analytic, and postanalytic variability while measuring the thyroid function.^[7] The analysis-related cause of “refractoriness” are captured in the caption “disturbance in assay.”

Inadequate counseling while prescribing medication can lead to a refractory situation in treatment. L-thyroxine absorption is decreased by food intake simultaneously or within a gap of less than at least 60 min. An acidic pH during optimum fasting ensures an absorption of 70%–80% of the administered oral dose.^[8,9] The list of concomitant medications affecting absorption and metabolism of L-thyroxine is extensive and needs careful attention. A general 4-h gap between L-thyroxine and most medications may avoid such drug interactions. If these basic precautions and caveats related to the administration of L-thyroxine or concomitant medication are not followed, this may lead to suboptimal thyroid control. The importance of drug therapy in thyroid management, which includes both L-thyroxine and concomitant medication, is included in our list.^[10]

All the above-discussed situations, that is , dialogue, diagnosis, definition of endpoint, disturbance in assay, and drug intake (L-thyroxine and concomitant drug intake), may be considered as cases of “spurious” refractoriness or “pseudo-refractoriness” in most cases. These are due to errors of judgment on the part of the health-care professional.

TRULY REFRACTORY HYPOTHYROIDISM

The sixth D, comorbid disease, enlists the various causes of truly refractory hypothyroidism. This list commonly includes malabsorption syndromes, renal/liver function impairment, central hypothyroidism, and hypocortisolemic conditions.

Malabsorption syndromes such as celiac disease affect the small intestine, hampering the absorption of L-thyroxine.^[11] Gastroparesis, lactose intolerance, inflammatory bowel disease, short bowel syndrome, gastric bypass, and biliopancreatic diversion have also been demonstrated to interfere with L-thyroxine absorption.^[12] Diseases decreasing gastric acid production required for L-thyroxine absorption, such as atrophic gastritis and *Helicobacter pylori* infection are another important group of diseases to be considered besides malabsorption syndromes.^[13]

Individuals with impaired renal/liver function have decreased peripheral metabolism of T4 to T3 causing decreased T3 levels which is often difficult to optimize even with higher doses of L-thyroxine.^[14] Another consideration in such individuals is decreased thyroxine-binding proteins-like albumin in nephrotic syndrome or severe cirrhosis which can hamper the volume of distribution of L-thyroxine.^[15]

Individuals with autoimmune thyroid disease are at a higher risk of developing resistance to traditional thyroid hormone replacement therapy.^[16] Glucocorticoids usually suppress thyroid-stimulating hormone (TSH) by acting at the hypothalamic level. Hence, TSH secretion is uninhibited in Addison’s disease or any hypocortisolemic condition. The diagnosis of hypocortisolism may be difficult but is imperative before L-thyroxine therapy initiation to avert precipitating an adrenal crisis. Dysfunction in the hypothalamic–pituitary–thyroid axis or central hypothyroidism is also another cause of treatment refractory hypothyroidism.^[17]

DISCUSSION

The 6Ds are listed in a hierarchical manner, which makes it easy for the practicing clinician to follow in his or her

Table 2: Screening for biomedical causes of refractory hypothyroidism

Malabsorption syndromes	Anti-tissue transglutaminase antibodies, endoscopic biopsy
Atrophic gastritis	Gastroscopy with biopsy, gastric pH, gastric acid measurement, parietal cell antibody/intrinsic factor antibody
<i>Helicobacter pylori</i>	Invasive methods such as histology, culture and rapid urease test on endoscopic biopsy specimens Noninvasive tests such as urea breath test and stool antigen test
Renal/liver disease	Renal function tests, liver function tests including serum albumin, urine albumin: creatinine ratio
Addison's disease	8 am serum cortisol, ACTH levels

ACTH: Adrenocorticotrophic hormone

day-to-day work. It encourages the physician to review her or his style of communication, reassess the diagnosis and monitoring strategies, as well as ensure the focus on medication choice and counseling. Once the physician is reassured that all these aspects of the hierarchy of management are optimized, the next step is to screen for “biomedical” causes of refractory hypothyroidism as mentioned above. Some common diseases and their screening tests are listed in Table 2.

SUMMARY

The 6D framework explains the etiology of refractory hypothyroidism in a reader-friendly manner. This model can be used as a teaching tool and as an aid to clinical decision-making as well.

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Conflicts of interest

There are no conflicts of interest.

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