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Reverse T_3 or perverse T_3? Still puzzling after 40 years

FOUR DECADES AFTER reverse T_3 (3,3′5′-triiodothyronine) was discovered, its physiologic and clinical relevance remains unclear and is still being studied. But scientific uncertainty has not stopped writers in the consumer press and on the Internet from making unsubstantiated claims about this hormone. Many patients believe their hypothyroid symptoms are due to high levels of reverse T_3 and want to be tested for it, and some even bring in test results from independent laboratories.

HOW THYROID HORMONES WERE DISCOVERED

The 20th century saw important advances in knowledge of the biochemistry of thyroid hormones (**Figure 1**),[1–18] such as the isolation of thyroxine (T_4) by Kendall[1] in 1915 and its synthesis by Harington and Barger[3] in 1927. Another milestone was the isolation and synthesis of triiodothyronine (T_3) by Gross and Pitt-Rivers[5] in 1953. In 1955, Pitt-Rivers et al[6] suggested that T_3 is formed in vivo from conversion of T_4, but this theory remained unproven in humans at that time.

In 1970, Braverman et al[9] showed that T_4 is converted to T_3 in athyreotic humans, and Sterling et al[10] demonstrated the same in healthy humans. During that decade, techniques for measuring T_4 were refined,[11] and a specific radioimmunoassay for reverse T_3 allowed a glimpse of its physiologic role.[12] In 1975, Chopra et al[13] noted reciprocal changes in the levels of T_3 and reverse T_3 in systemic illnesses—ie, when people are sick, their T_3 levels go down and their reverse T_3 levels go up.

In 1977, Burman et al[17] developed a radio-

Thyroid hormones: A timeline

1907—Marine reports that iodine is necessary for thyroid function.

1915—Kendall[1] isolates thyroxine.

1926—Harington[2] determines the chemical structure of thyroxine.

1927—Harington and Barger[3] synthesize thyroxine.

1931—Loeb and Bassett extract and purify thyroid-stimulating hormone from bovine pituitaries.

1949—Hoskins describes negative feedback of thyroid hormones on the pituitary gland.

1952—Gross and Pitt-Rivers[4] demonstrate T_3 in human plasma.

1953—Gross and Pitt-Rivers[5] isolate and synthesize T_3.

1955—Pitt-Rivers et al[6] suggest T_4 is converted to T_3 in vivo.

1957—Development of the first techniques to measure T_3.[7]

1959—Galton and Pitt-Rivers[8] identify the acetic acid analogues of T_4 and T_3 (tetrac and triac) in mammalian tissues.

1970—Schally and Guilleman identify thyrotropin-releasing hormone in humans, receiving the Nobel Prize for this work in 1977.

1970—Braverman et al[9] and Sterling et al[10] discover conversion of T_4 to T_3 in humans.

1974—Chopra[11,12] develops radioimmunoassays for T_4 and reverse T_3.

1975—Chopra et al[13] describe reciprocal changes in serum concentrations of reverse T_3 and T_3 in systemic illnesses.

1976—Burman et al[14] identify reverse T_3, 3,3′-T_2, T_3, and T_4 in human amniotic fluid and in cord and maternal serum.

1976–1978—First reports of the euthyroid sick syndrome or low T_3 syndrome.[15,16]

1977—Burman et al[17,18] confirm reverse T_3 is present in the serum of normal individuals and develop a radioimmunoassay for 3,3′-T_2.

Figure 1.

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immunoassay for reverse T_3 that confirmed its presence in the serum of normal humans. Further, they showed that serum reverse T_3 levels were low in hypothyroid patients and in athyreotic patients receiving low daily doses of levothyroxine. Conversely, reverse T_3 levels were high in hyperthyroid patients and in athyreotic patients receiving high doses of levothyroxine (**Figure 2**).[17]

The end of the 70s was marked by a surge of interest in T_4 metabolites, including the development of a radioimmunoassay for 3,3´-diiodothyronine (3-3´T_2).[18]

The observed reciprocal changes in serum levels of T_3 and reverse T_3 suggested that T_4 degradation is regulated into activating (T_3) or inactivating (reverse T_3) pathways, and that these changes are a presumed homeostatic process of energy conservation.[19]

HOW THYROID HORMONES ARE METABOLIZED

In the thyroid gland, for thyroid hormones to be synthesized, iodide must be oxidized and incorporated into the precursors 3-monoiodotyrosine (MIT) and 3,5-diiodotyrosine (DIT). This process is mediated by the enzyme thyroid peroxidase in the presence of hydrogen peroxide.[20]

The thyroid can make T_4 and some T_3

T_4 is the main iodothyronine produced by the thyroid gland, at a rate of 80 to 100 µg per day.[21] It is synthesized from the fusion of 2 DIT molecules.

The thyroid can also make T_3 by fusing 1 DIT and 1 MIT molecule, but this process accounts for no more than 20% of the circulating T_3 in humans. The rest of T_3, and 95% to 98% of all reverse T_3, is derived from peripheral conversion of T_4 through deiodination.

T_4 is converted to T_3 or reverse T_3

The metabolic transformation of thyroid hormones in peripheral tissues determines their biologic potency and regulates their biologic effects.

The number 4 in T_4 means it has 4 iodine atoms. It can lose 1 of them, yielding either T_3 or reverse T_3, depending on which iodine atom it loses (**Figure 3**). Loss of iodine from the five-prime (5´) position on its outer ring yields T_3, the most potent thyroid hormone, produced at a rate of 30 to 40 µg per day.[21] On the other hand, when T_4 loses an iodine atom from the five (5) position on its inner ring it yields reverse T_3, produced at a rate slightly less than that of T_3, 28 to 40 µg per day.[21] Reverse T_3 is inactive.

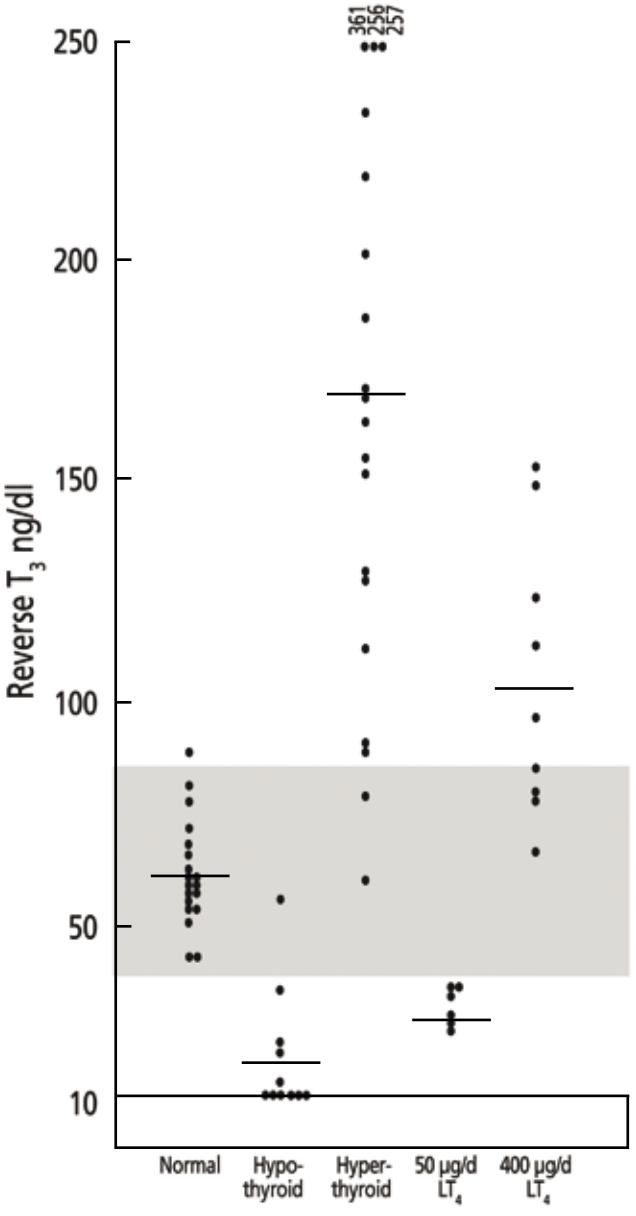

Figure 2. Individual values of serum reverse T_3 levels in normal, hypothyroid, and hyperthyroid people and in athyreotic patients who had been given 50 µg of levothyroxine (LT_4) and 400 µg of LT_4 daily.

Reproduced from Burman KD, Dimond RC, Wright FD, Earll JM, Bruton J, Wartofsky L. A radioimmunoassay for 3,3',5'-L-triiodothyronine (reverse T3): assessment of thyroid gland content and serum measurements in conditions of normal and altered thyroidal economy and following administration of thyrotropin releasing hormone (TRH) and thyrotropin (TSH). J Clin Endocrinol Metab 1977; 44(4):660–672, by permission of Oxford University Press.

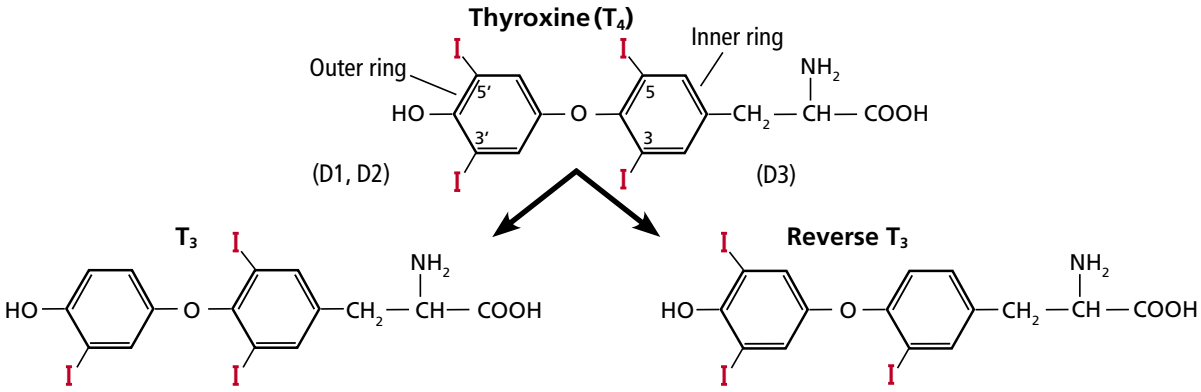

Figure 3. Thyroxine (T_4) can shed 1 iodine atom to become the active thyroid hormone 3,5,3′-triiodothyronine (T_3) in a reaction catalyzed by D1 and D2, or its inactive isomer 3,3′5′-triiodothyronine (reverse T_3) in a reaction catalyzed by D3. In further reactions (not shown) both molecules successively lose more iodine atoms, eventually becoming T_0.

Both T_3 and reverse T_3 can shed more iodine atoms, forming in turn various isomers of T_2, T_1, and ultimately T_0. Other pathways for thyroid hormone metabolism include glucuronidation, sulfation, oxidative deamination, and ether bond cleavage.[20–22]

D1 and D2 catalyze T_3, D3 catalyzes reverse T_3

When people are very sick, their T_3 levels go down and reverse T_3 levels go up

Three types of enzymes that mediate deiodination have been identified and designated D1, D2, and D3. In humans they are expressed in variable amounts throughout the body:

- D1 mainly in the liver, kidneys, thyroid, and pituitary, but notably absent in the central nervous system
- D2 in the central nervous system, pituitary, brown adipose tissue, thyroid, placenta, skeletal muscle, and heart
- D3 in the central nervous system, skin, hemangiomas, fetal liver, placenta, and fetal tissues.[23]

D1 and D2 are responsible for converting T_4 to T_3, and D3 is responsible for converting T_4 to reverse T_3.

Plasma concentrations of free T_4 and free T_3 are relatively constant; however, tissue concentrations of free T_3 vary in different tissues according to the amount of hormone transported and the activity of local deiodinases.[23] Most thyroid hormone actions are initiated after T_3 binds to its nuclear receptor. In this setting, deiodinases play a critical role in maintaining tissue and cellular thyroid hormone levels, so that thyroid hormone signaling can change irrespective of serum hormonal concentrations.[22–24] For example, in the central nervous system, production of T_3 by local D2 is significantly relevant for T_3 homeostasis.[22,23]

Deiodinases also modulate the tissue-specific concentrations of T_3 in response to iodine deficiency and to changes in thyroid state.[23] During iodine deficiency and hypothyroidism, tissues that express D2, especially brain tissues, increase the activity of this enzyme in order to increase local conversion of T_4 to T_3. In hyperthyroidism, D1 overexpression contributes to the relative excess of T_3 production, while D3 up-regulation in the brain protects the central nervous system from excessive amounts of thyroid hormone.[23]

REVERSE T_3 AND SYSTEMIC ILLNESS

D3 is the main physiologic inactivator of thyroid hormones. This enzyme plays a central role in protecting tissues from an excess of thyroid hormone.[23,24] This mechanism is crucial for fetal development and explains the high expression of D3 in the human placenta and fetal tissues.

In adult tissues, the importance of D3 in the regulation of thyroid hormone homeostasis becomes apparent under certain pathophysiologic conditions, such as nonthyroidal illness and malnutrition.

Whenever a reduction in metabolism is homeostatically desirable, such as in critically ill patients or during starvation, conversion to

TABLE 1

Changes in thyroid hormone levels during illness

Severity of illness	TSH	Total T_3	Free T_4	Reverse T_3	Probable cause
Mild	No change	Mildly decreased	No change	Mildly increased	Mildly decreased D2, D1
Moderate	No change or mildly decreased	Decreased	No change or mild increase or decrease	Increased	Decreased D2, D1, possibly mildly increased D3
Severe	Decreased	Markedly decreased	Mildly decreased	Mildly increased	Decreased D2, D1, possibly mildly increased D3
Recovery	Mildly increased	Mildly decreased	Mildly decreased	Mildly increased	Unknown

D1 through D3 = iodothyronine deiodinases; T_3, triiodothyronine; T_4 = thyroxine; TSH = thyroid-stimulating hormone (thyrotropin).

Adapted from Salvatore D, Davies TF, Schlumberger M, Hay ID, Larsen PR. Thyroid physiology and diagnostic evaluation of patients with thyroid disorders. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. Williams Textbook of Endocrinology. 13th ed. Philadelphia, PA; Elsevier; 2016:334–368, copyright 2016, with permission from Elsevier.

T_3 is reduced and, alternatively, conversion to reverse T_3 is increased. This pathway represents a metabolic adaptation that may protect the tissues from the catabolic effects of thyroid hormone that could otherwise worsen the patient's basic clinical condition.

Euthyroid sick syndrome or hypothyroid?

In a variety of systemic illnesses, some patients with low T_3, low or normal T_4, and normal thyroid-stimulating hormone (TSH) levels could in fact be "sick euthyroid" rather than hypothyroid. The first reports of the euthyroid sick syndrome or low T_3 syndrome date back to about 1976, and even though assays for reverse T_3 were not widely available, some authors linked the syndrome to high levels of reverse T_3.[15,16] The syndrome is also known as nonthyroidal illness syndrome.

Advances in techniques for measuring T_3, reverse T_3, and other iodothyronines filled a gap in the understanding of the alterations that occur in thyroid hormone economy during severe nonthyroidal diseases. In 1982, Wartofsky and Burman[25] reviewed the alterations in thyroid function in patients with systemic illness and discussed other factors that may alter thyroid economy, such as age, stress, and diverse drugs.

More recently, the low-T_3 syndrome was revisited with a generalized concept regarding the role of D3 in the syndrome.[26] D3, normally undetectable in mature tissues, is reactivated in diverse cell types in response to injury and is responsible for a fall in serum T_3 levels. Hypoxia induces D3 activity and mRNA in vitro and in vivo.[27] Recent studies have focused on the role of cytokines in the low T_3 syndrome. For instance, interleukin 6 reduces D1 and D2 activity and increases D3 activity in vitro.[28]

In the outpatient setting, diverse conditions may affect thyroid hormone homeostasis, compatible with mild or atypical forms of low-T_3 syndrome, including caloric deprivation, heart failure, and human immunodeficiency virus infection.[29]

Few clinical situations require measurement of reverse T_3 levels

POSSIBLE CLINICAL UTILITY OF MEASURING REVERSE T_3

In inpatients

Unfortunately, measuring serum reverse T_3 levels has not, in general, proven clinically useful for the diagnosis of hypothyroidism in systemically ill patients. Burmeister[30] demonstrated, in a retrospective study, that when illness complicates the interpretation of thyroid function tests, serum reverse T_3 measurements do not reliably distinguish the hypothyroid sick patient from the euthyroid sick patient. The best way to make the diagnosis, Burmeister suggested, is by clinical assessment, combined use of free T_4 and TSH measurements, and patient follow-up.

Indeed, few clinical situations require measurement of reverse T_3 levels. We believe it can potentially be used to help the differential diagnosis between hypothyroidism and euthyroid sick syndrome. Reverse T_3 should always be analyzed in combination with TSH, T_3, and free T_4 with consideration of the patient's clinical context. **Table 1** helps to interpret the results. However, even in these circumstances, serum reverse T_3 levels are not always reliable, as demonstrated by Burmeister.[30] Another situation, even rarer, is in children or adults with massive hemangiomas. These tumors express high levels of D3 that can cause hypothyroidism.[31]

In the outpatient setting, the utility of reverse T3 measurements is controversial. In intensive care units, the differential diagnosis between hypothyroidism and nonthyroidal illness syndrome can sometimes be difficult. Reverse T_3 levels can be low, normal, or high regardless of the thyroidal state of the patient.[30] Moreover, endogenous changes in the hypothalamic-pituitary-thyroid axis may be further complicated by medications commonly used in intensive care units, such as dopamine and glucocorticoids. Changes in thyroid function should be evaluated in the context of the patient's clinical condition (**Table 1**).[20] But regardless of the T_3 level, treatment with T_3 or T_4 should not be started without taking into consideration the patient's general clinical context; controlled trials have not shown such therapy to be beneficial.[20]

In outpatients

In noncritical conditions that may be associated with mild forms of low T_3 syndrome, patients generally present with low T_3 concentrations concurrently with low or normal TSH. Not infrequently, however, patients present with a serum reverse T_3 measurement and impute their symptoms of hypothyroidism to "abnormal" reverse T_3 levels, in spite of normal TSH levels.

There is no rationale for measuring reverse T_3 to initiate or to adjust levothyroxine therapy—the single test relevant for these purposes is the TSH measurement. The risks of basing treatment decisions on reverse T_3 levels include the use of excessive doses of levothyroxine that may lead to a state of subclinical or even clinical hyperthyroidism.

TAKE-HOME MESSAGE

The existence of an inactivating pathway of thyroid hormones represents a homeostatic mechanism, and in selected circumstances measuring serum reverse T_3 may be useful, such as in euthyroid sick patients. The discovery of the molecular mechanisms that lead to the reactivation of D3 in illness is an important field of research.

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