Triiodothyronine and thyroxine interrelationships in health and disease

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With the recent development of radioimmunoassay techniques for the measurement of serum triiodothyronine (T_3) concentration, new concepts have arisen regarding the biologic role of T_3 in health and disease and its interrelationships with thyroxine (T_4). An awareness of the influence of clinical conditions that affect binding of thyroid hormone to plasma proteins is required in the interpretation of moderately increased or decreased serum T_3 values. Hormone preparations containing T_3 may produce transient increases in T_3 concentration into the hyperthyroid range. Measurements of serum T_3 concentration appear to be particularly indicated in clinical situations in which hyperthyroidism is suspected but serum T_3 resin uptake and serum T_4 values are normal, to exclude the T_3-toxicosis syndrome. Also, when serum T_4 values are in the hypothyroid range, measurement of serum T_3 as well as serum thyrotropin (TSH) concentrations can lead to recognition of abnormalities in thyroid gland biosynthesis. Before a diagnosis of hypothyroidism is made on the basis of a low serum T_3 value, one must exclude a variety of clinical nonthyroidal conditions that can result in changes in plasma T_3 protein binding or impaired peripheral conversion of T_4 to metabolically active T_3 without producing a hypometabolic state.

Avec la mise au point récente de techniques radioimmunologiques servant à la détermination de la triiodothyronine (T_3) sérique, on a vu surgir de nouveaux concepts relatifs au rôle biologique de la T_3 dans les états sains ou pathologiques et ses interrelations avec la thyroxine (T_4). Une connaissance de l'influence des états cliniques capables de modifier la liaison protéinique de l'hormone thyroïdienne est requise pour l'interprétation des augmentations ou des diminutions modérées des concentrations sériques de T_3. Les préparations hormonales contenant de la T_3 peuvent entraîner des augmentations transitoires de la concentration de T_3 proches des valeurs retrouvées dans les cas d'hyperthyroïdie. Des déterminations de la triiodothyronine sérique semblent particulièrement indiquées lorsqu'une hyperthyroïdie est soupçonnée mais que le test de captation de la T_3 sérique et que la concentration sérique en T_4 sont normaux, afin d'exclure un syndrome de T_3-toxicose. Egalement, quand la T_4 sérique est compatible avec une hypothyroïdie, la mesure des concentrations sériques en T_3 et en hormone thyroïdostimulante (TSH) peut permettre la reconnaissance d'une anomalie de la biosynthèse thyroïdienne. Avant de conclure à un diagnostic d'hypothyroïdie en s'appuyant sur une T_3 sérique faible, on doit exclure les affections cliniques non thyroïdiennes entraînant des changements de la liaison protéinique de la T_3 ou une diminution de la conversion périphérique de la T_4 en T_3 métaboliquement active sans production d'un état hypométabolique.

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Physiologic interrelationships of triiodothyronine and thyroxine

Thyroxine (T_4), or tetraiodothyronine, was extracted from thyroid tissue by Kendall[1] in 1915 and was first demonstrated to be effective in its pure synthetic form for the treatment of myxedema in 1927 by Harington and Barger.[2] It was not until 25 years later that L-triiodothyronine (T_3) was identified,[3,4] and subsequently it was shown to be a biologically active product of the thyroid gland with at least three times the biologic potency of L-thyroxine.[5-7] The biologic role of T_3 in health and disease remained relatively unknown and neglected until the development in 1970 of a radioimmunoassay technique for the measurement of its serum concentration.[8] Experience with this sensitive radioimmunoassay,[8-12] together with a re-evaluation of the results of tracer study analyses,[13,14] reversed the notion that thyroxine, because of its greater concentration in the serum, is the most important thyroid hormone.

The physiologic interrelationships of T_3 and T_4 are summarized in Table I.

Table I—Comparison of triiodothyronine (T_3) and thyroxine (T_4) values

Variable	T_3	T_4
Serum total, ng/dl (mean)	126	8 400
Serum free, % (mean)	0.340	0.030
Serum absolute free, ng/dl (mean)	0.375	2.80
Serum total T_4/T_3 ratio	1	67
Thyroidal vein total T_4/T_3 ratio	1	19
Biologic half-life, days (range)	1-2	6-7
Distribution space, litres (range)	26-35	10-12
Turnover per day, % (range)	52-77	18-27
Production rate, μg/d (range)	23-30	87-90
Biologic potency ratio	3-4	1
T_4 to T_3 peripheral conversion, %	—	60-80

The total circulating concentration of T_3 in the serum is approximately 70 times less than that of T_4 but the percentage of free T_3 (not bound to plasma protein) is higher than the percentage of free T_4, so that the absolute free concentration of T_4 is only sevenfold higher than that of T_3. Owing to its mainly intracellular location, T_3 has a two- to threefold larger distribution space than T_4. Also, T_3 has a more rapid turnover and hence a shorter biologic half-life. Thyroidal production accounts for only a small proportion of the total T_3 production; the thyroid gland secretes three times as much T_4 as T_3. Recent observations have supported the view that in euthyroid subjects the predominant source of circulating T_3 is provided by monodeiodination of T_4 to T_3 in peripheral tissues.[15] On the basis of clinical and experimental evidence[16-19] it is estimated that this peripheral conversion accounts for approximately 60 to 80% of the circulating serum T_3. This conclusion is also supported by the fact that thyroxine alone given to athyrotic patients will result in normal circulating concentrations of T_3.[15,16] Since the metabolic activity of T_4 can be almost completely accounted for on the basis of its peripheral conversion to the biologically more potent T_3,[17] it has been proposed that T_4 is primarily a prohormone.[17-19] However, Chopra and colleagues[20,21] have provided some evidence to support the view that T_4 also has intrinsic hormonal activity.

Measurement of total serum T_3 and T_4 concentrations in assessment of thyroid function

At present the test most frequently used to assess thyroid function is the measurement of total serum or plasma hormone concentration, which includes both the amount of hormone bound to plasma proteins and the tiny amount that is in the free aqueous form. Owing to their nonspecificity for measurement of thyroxine, serum protein-bound iodine (PBI) and "T_4 by column" methods have been replaced by more specific techniques — the competitive protein-binding method of Murphy and Pattee[22] and the more recently developed radioimmunoassay, which uses specific antiserum to T_4.[23]

The measurement of total T_3 serum concentration has been facilitated by the development of the radioimmunoassay procedure of Gharib, Mayberry and Ryan,[8] subsequently modified by others,[9-12] which uses a specific antibody to T_3 made by injecting rabbits with a T_3–albumin conjugate. Direct measurement of T_3 in unextracted serum is facilitated by the addition of chemicals that saturate thyroxine-binding globulin (TBG) sites, such as diphenylhydantoin,[11] salicylate[9] or, more commonly, 8-anilino-l-naphthalene-sulfonic acid.[10,12] Serum free of T_4 and T_3 is prepared for addition to the tubes containing the hormone reference standards to simulate plasma protein concentrations of the unknown serum samples. "Normal" ranges have been shown to vary considerably between laboratories,[24] depending on such factors as specificity of the antisera for T_3, purity of the reference hormone used for the standard curve, and geographic differences in iodine intake. The normal T_3 range (in ng/dl) in the euthyroid individual may vary from a low of 60 to a high of 350; the range most frequently reported by laboratories is approximately 80 to 220, and the mean value, 130.

Effect of thyroid hormone protein-binding on total serum T_3 and T_4 values

The above assays measure total (bound plus free) circulating serum concentrations of T_4 and T_3, and since there is usually a consistent parallel relation between the total and the free concentrations, the total values reflect the thyroid status in over 90% of individuals tested. However, alterations in plasma protein binding can change the percentage of free hormone available to the peripheral tissues, so that the total circulating hormone concentration may not accurately reflect the free T_4 concentration and, hence, thyroid status. T_4 is bound to TBG and thyroxine-binding prealbumin (TBPA), while T_3 is bound mainly to TBG and albumin. Hence, the most reliable assessment of thyroid function should include not only measurement of total hormone concentration but also evaluation of protein binding. A highly accurate measurement of the free hormone concentration can be obtained by a cumbersome and therefore less practical equilibrium dialysis technique, with the observed free percentage being multiplied by the total hormone concentration to obtain the absolute free concentration. A simpler but indirect method for assessing protein binding is the T_3 resin uptake test, which indicates the distribution of added labelled T_3 between serum binding proteins and resin sponge. Since there is an inverse relation between the amount of TBG and the T_3 resin uptake value, a free T_4 or T_3 index can be obtained by multiplying the total hormone concentration by the T_3 resin uptake value.[25]

Congenital and acquired conditions commonly affecting thyroid hormone protein-binding capacity are summarized in Table II. The changes obtained in the T_3 resin uptake test indicate the inverse relation that results from alterations in protein binding. However, calculation of a free T_3 or T_4 index by multiplying the observed serum T_4 or T_3 value by the resulting T_3 resin uptake value produces a normal free index value, thereby indicating indirectly the probable normal free hormone concentration influencing thyroid status and the metabolic rate in peripheral tissues.

Factors influencing assessment of thyroid status from serum T_3 values

Factors influencing serum T_3 concentrations include methods of measurement as well as variations in iodine intake and geographic location, so each laboratory must establish its own "normal" range of values. Neither an influence of sex on the normal serum concentration of T_3 nor a diurnal variation in concentration has been demonstrated consistently.[26] Variations in serum T_3 concentration with age have been noted; for example, values in the fetus and newborn are low but they increase greatly within the first several hours after birth then decrease during the first 3 days of life to normal values for adults.[27-29] Total T_3 values have been noted to be higher in infants 4 to 12

Table II—Conditions inducing alterations in thyroid hormone protein-binding capacity

Binding capacity	Condition
Increased (↑ serum T_4 and T_3 with ↓ T_3 resin uptake)	Pregnancy
	Drug therapy
	Estrogen (especially oral contraceptives)
	Perphenazine
	Infectious hepatitis
	Acute intermittent porphyria
	Congenital hyper-TBG-emia
Decreased (↓ serum T_4 and T_3 with ↑ T_3 resin uptake)	Drug therapy
	Androgens
	Corticosteroids
	Diphenylhydantoin and primidone
	Salicylates (high dosage)
	Major illness
	Nephrotic syndrome
	Congenital hypo-TBG-emia

weeks old than in adults; the reason is unknown.[30,31] In early childhood, serum T_3 values have been reported to be similar to adult values[32] and to be higher than adult values.[31] A decrease of 5 ng/dl per decade in the mean normal serum T_3 concentration after age 30 has been reported by Rubenstein, Butler and Werner.[31]

Serum T_3 concentration will be increased within several hours of administration of preparations containing T_3, such as pure T_3 or desiccated thyroid, or synthetic preparations containing both T_3 and T_4.[26,33] In agreement with the observations of Braverman, Ingbar and Sterling,[15] Surks, Schadlow and Oppenheimer[26] have reported that the adequacy of L-thyroxine therapy in athyrotic subjects in whom there is no interference with the peripheral conversion of T_4 to T_3 can be assessed from serum T_3 values; however, this should not be done until 4 to 6 weeks after initiating a change in T_4 dosage, to ensure that a new steady state of equilibrium in T_4 peripheral conversion to T_3 has been reached.

T_3-toxicosis syndrome

While in most cases of hyperthyroidism both serum T_4 and T_3 values are increased, it has recently been noted that occasionally there is a dissociation in this relationship, resulting in the syndrome of T_3-toxicosis.[34-36] Characteristically, T_3 values are increased, perhaps as the earliest manifestation of hyperthyroidism, particularly in relapsing cases.[37] In comparison, serum T_4 values may be normal in the early stages of hyperthyroidism but increase later. The clinical and laboratory features that have been described for the T_3-toxicosis syndrome by Hollander, Mitsuma and Nihei[35] are as follows:

- Clinical signs and symptoms of hyperthyroidism.
- Normal values for total and free T_4.
- Normal or increased uptake of ^{131}I by the thyroid with no suppression response to exogenous T_3 administration.
- Increased values for total and free serum T_3.
- Cause of hyperthyroidism: toxic diffuse goitre (Graves' disease), toxic adenoma or toxic multinodular goitre.
- Estimated proportion of persons with hyperthyroidism who have this syndrome: 4 to 12.5%, depending on geographic location and iodine intake.
- Elevated serum T_3 values as possible premonitory or early manifestations of hyperthyroidism.

The T_3-toxicosis syndrome may occur in all forms of hyperthyroidism; no type has been reported to be consistently more frequent.[34-36] The prevalence of this syndrome as a cause of hyperthyroidism varies according to geographic location, from as low as 4% in some North American locations to as high as 12.5% in regions where goitre due to iodine deficiency is endemic.[36]

While in most cases of hyperthyroidism the increase in serum T_3 concentration is proportionately greater than the increase in T_4 concentration, less commonly "T_4-toxicosis" may occur when the T_4 concentration is increased and the T_3 concentration is normal. This situation can result from several conditions: hyperthyroidism with coexistent nonthyroidal diseases that have impaired peripheral conversion of T_4 to T_3; hyperthyroidism that has been inadvertently treated with iodine or thionamides; and subacute thyroiditis resolving from a previous hyperthyroid phase.

Conditions other than hyperthyroidism associated with increased serum T_3 concentrations are summarized in Table III.

Table III—Causes of increased serum T_3 concentration in relation to serum T_4 concentration

Serum T_4 concentration	Condition
Increased	Hyperthyroidism due to toxic diffuse goitre (Graves' disease), toxic adenoma, toxic multinodular goitre
	Factitious hyperthyroidism due to excess T_4 or combined $T_3 - T_4$ therapy
	Transient hyperthyroidism due to subacute thyroiditis
	Euthyroid hyper-TBG-emia, congenital or acquired
Normal or decreased	Hyperthyroidism due to T_3-toxicosis or premonitory subclinical hyperthyroidism
	Hyperthyroidism with hypo-TBG-emia
	Factitious hyperthyroidism (euthyroid with transient T_3 elevations) due to T_3 or combined $T_3 - T_4$ therapy

Table IV—Causes of decreased serum T_3 concentration in relation to serum T_4 concentration

Serum T_4 concentration	Condition
Decreased	Hypothyroidism, primary or secondary
	Euthyroid hypo-TBG-emia, congenital or acquired
Normal or increased	Fetus at term and neonate
	Senescence
	Nonthyroidal illness: hepatic and renal disorders, cachexia, malignant disease, starvation, protein-calorie malnutrition, carbohydrate deprivation, corticosteroid therapy, surgery

T_3-euthyroidism syndrome (compensated hypothyroidism)

Sterling and colleagues[32] initially recognized and reported the syndrome of T_3-euthyroidism, which is associated with impaired biosynthesis in the thyroid gland, such that more T_3 than T_4 is secreted. This occurs in goitrous hypothyroidism secondary to inborn errors of biosynthesis, chronic thyroiditis, ingestion of goitrogens and athyrotic hypothyroidism (idiopathic, postsurgical or after ^{131}I therapy for hyperthyroidism). The patients' clinical status is euthyroid, which correlates with their normal T_3 serum values (both total and free) but is at variance with their low T_4 serum values (both total and free). Their ^{131}I uptake by the thyroid is low or normal. Serum thyrotropin (TSH) concentrations are usually increased, resulting in stimulation of the impaired residual functioning thyroid tissue to secrete T_3 selectively; hence, secretion of T_3 is relatively increased and becomes a greater source of circulating serum T_3 than in the normal state, when T_3 is derived principally from the peripheral monodeiodination of T_4.[18,19] However, thyroidal responses to exogenously administered TSH and thyrotropin releasing hormone stimuli are usually impaired. Usually no definite subjective clinical benefit is noted from therapy with T_4 because these patients are euthyroid in spite of impaired thyroid gland biosynthesis and reserve.

Low T_3-euthyroid syndrome in association with nonthyroidal conditions

In several clinical situations a low serum T_3 value is associated with either a normal or a high serum T_4 value in patients who are apparently clinically euthyroid (Table IV). In adults this occurs particularly in a variety of nonthyroidal illnesses,[21,38,39] including hepatic and renal failure, cachexia and malignant disease, chronic fasting by obese individuals,[39] and protein-calorie malnutrition,[40] as well as with senescence.[31] In these situations the decrease in serum T_3 values is out of proportion to that of T_4 values and cannot be ac-

counted for on the basis of reduced plasma protein binding alone.[21,38] Moreover, the free T_3 concentration is usually low, but the free T_4 concentration is either normal or slightly increased.[21,38] Further studies are required to elucidate the mechanisms responsible for the low T_3 concentrations and thus clarify their physiologic and therapeutic implications. Preliminary observations suggest that they may be accounted for on the basis of impaired peripheral conversion by monodeiodination of T_4 to T_3.[21] In fact, Vagenakis and colleagues[39] have recent evidence from studies during complete fasting in humans that peripheral T_4 metabolism is diverted from the formation of active L-T_3 to the inactive "reverse" T_3 degradation pathway. Similarly, an increase in formation of "reverse" T_3 and a reciprocal decrease in formation of active L-T_3 has been induced by reduction in carbohydrate content of the diet,[41] corticosteroid administration and surgical operations.[42]

Since the free hormone is generally regarded as the metabolically active fraction, serum T_4 concentrations appear to correlate better with thyroid status in these clinical situations than do serum T_3 concentrations; this supports further the view that T_4 has intrinsic hormonal activity in addition to its prohormone role.[20,21] It also must be concluded that the diagnosis of hypothyroidism on the basis of low serum T_3 values alone may be unreliable in clinical situations associated with the aforementioned nonthyroidal conditions.[38-42] As shown in Table IV, congenital or acquired hypo-TBG-emia conditions must also be excluded when both serum T_3 and T_4 values are low before a diagnosis of hypothyroidism can be confirmed.

Summary of clinical application of serum T_3 measurements

In spite of increasing recognition of the physiologic role of T_3 in health and disease, in most clinical situations the direction of changes in both serum T_3 and T_4 values is the same. Thus, the measurement of total circulating serum T_4 concentration, accompanied by an indirect assessment of plasma protein binding by a T_3 resin uptake test, will continue to be the mainstays in the laboratory assessment of thyroid status. However, radioassay of total serum T_3 appears to be indicated in clinical situations in which hyperthyroidism is suspected clinically but serum T_4 and T_3 resin uptake values are normal and the syndrome of T_4-toxicosis therefore requires exclusion. Also, when serum T_4 values are in the hypothyroid range, measurement of serum T_3 and TSH can lead to recognition of abnormalities in thyroid gland biosynthesis and an early stage of compensated hypothyroidism by demonstrating that serum T_3 values are still normal.

An awareness of the clinical conditions that induce alterations in thyroid hormone binding to plasma proteins, as indicated indirectly by T_3 resin uptake values, is required in the interpretation of moderately increased or decreased serum T_3 values. Commercial hormone preparations containing T_3 can produce transient, clinically misleading increases in T_3 concentration into the hyperthyroid range if the serum sample is taken between 2 and 8 hours after ingestion. Since nonthyroidal conditions can produce low serum T_3 values without hypothyroidism, secondary to alterations in protein binding or peripheral T_4 degradation pathways, the laboratory diagnosis of hypothyroidism on the basis of a low total serum T_3 value can be misleading.

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