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Physiological variations in thyroid hormones: physiological and pathophysiological considerations

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Thyroid hormone production is regulated via pituitary thyrotropin (TSH) modulation of thyroxine (T_4) prohormone secretion by the thyroid gland and regulation of active triiodothyronine (T_3) production in peripheral tissues via metabolic events influencing activities of the iodothyronine monodeiodinase enzyme systems. Control at both levels is developmentally regulated and modified in serious nonthyroidal illness (trauma, infection, cancer, metabolic diseases). Racial and gender differences are of little significance except for the effects of placental estrogens and chorionic gonadotropin during pregnancy. There is a circadian rhythm of TSH secretion, with peak values at the onset of sleep and nadir concentrations during the afternoon hours. Peak and nadir concentrations differ by ~±50%. The effect on circulating T_4 and T_3 concentrations is not significant because of the large size of the extrathyroidal T_4 pool. In healthy subjects there is no significant impact of body weight, physical training, body habitus, posture, immobilization, exercise, or ambulatory status on thyroid function, and no significant geographic environmental variation. Nutrition also has a minimal impact except for variation in iodine intake. Subthreshold concentrations of iodine intake are associated with increased TSH secretion, goiter, increased thyroid iodine uptake, decreased T_4 production, an increased T_3/T_4 secretion ratio, and an increased ratio of circulating T_3/T_4 concentrations. Excessive iodine intake can block thyroid hormone biosynthesis by inhibiting the enzymes involved in the biosynthetic process, resulting in reduced T_4 secretion, increased TSH concentrations, goiter, and hypothyroidism if the iodine excess is chronic.

INDEXING TERMS: thyrotropin • triiodothyronine • thyroxine • hormone regulation

Thyroid gland function is regulated by thyrotropin (TSH) secretion from the pituitary gland *[1]*.[1] TSH secretion in turn is largely regulated by hypothalamic thyroliberin (TRH) secreted into the pituitary portal vascular system to stimulate pituitary gland TSH release, and by a feedback-inhibiting loop whereby free thyroxine (FT_4) acts at both the pituitary and hypothalamic levels [where it is converted to the active hormone triiodothyronine (T_3)] to inhibit TSH and TRH production, respectively. TSH stimulates the synthesis and secretion of the prohormone T_4, which circulates bound to binding proteins in serum. The most important of these binding proteins is thyroxine-binding globulin (TBG), but transthyretin (prealbumin) and albumin play secondary roles. T_4 is distributed to peripheral tissues, where it is metabolized by deiodination to T_3 by the iodothyronine monodeiodinases (MDIs) type I and type II *[2]*. Most of the circulating T_3 appears to be derived via hepatic monodeiodination of T_4 by type I MDI. Type II MDI produces T_3 for local action in brain, pituitary, and brown adipose tissue. T_4 also is deiodinated to inactive "reverse" T_3 (rT_3) by a type III MDI in most nonhepatic tissues, and T_4 can be sulfoconjugated, glucuronide conjugated, and (or) deaminated to the thyroacetic and thyropropionic acid derivatives. Of all the metabolites, only T_3 and triiodothyroacetic acid manifest bioactivity.

All of the hormones can be measured in peripheral blood. However, measurements of TRH, the sulfate and glucuronide conjugates, and triiodothyroacetic acid have little or no clinical application at the present time. The most important in vitro measurements for routine clinical use include TSH and a direct or indirect measurement of FT_4. The latter include the T_3 resin uptake and variations. Other measurements include T_3, free T_3 (FT_3), rT_3, TBG, and thyroglobulin.

PHYSIOLOGICAL VARIATIONS WITH GENDER, RACE, AND AGE

There are marked variations in thyroid function with age, evident in all of the in vitro hormone and protein measurements. These variations are summarized in Table 1 *[3–6]*. Thyroid

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[1] Nonstandard abbreviations: TSH, thyrotropin; TRH, thyroliberin; T_4, thyroxine; T_3, triiodothyronine; TBG, thyroxine-binding globulin; MDI, iodothyronine monodeiodinase; rT_3, reverse T_3; FT_4 (or FT_3), free T_4 (or free T_3); and hCG, human chorionic gonadotropin.

Table 1. Changes in thyroid-function indicators with age.[a]

	Serum conc							
	T_4, nmol/L	FT_4, pmol/L	TSH, mIU/L	TBG, mg/L	T_3, nmol/L	rT_3, nmol/L	Tg, μg/L	T_4 utilization, μg/kg per day
Fetus								
12–20 weeks	5–50	0–50	1–8	2–23	0.5	—	—	1
21–30 weeks	35–100	5–12	1.9–8.8	8–33	0.10–0.75	—	6–230	2
31–40 weeks	70–180	12–22	3–12	15–50	0.2–1.5	1.5–7.7	2–54	5
Infant								
1–4 days	142–277	28–68	1–39	22–42	1.5–11.4	—	2–110	10
1–4 weeks	106–221	12–30	1.7–9.1	—	1.6–5.3	0.4–4.5	—	7
1–12 months	76–210	10–23	0.8–8.2	16–36	1.6–3.8	0.17–2.0	—	6
Child								
1–5 years	94–193	10–27	0.7–5.7	12–28	1.6–4.1	0.23–1.1	2–65	5
6–10 years	82–171	13–27	0.7–5.7	12–28	1.4–3.7	0.26–1.2	2–65	4
11–15 years	71–151	10–26	0.7–5.7	14–30	1.3–3.3	0.29–1.3	2–36	3
16–20 years	54–152	10–26	0.7–5.7	14–30	1.2–3.2	0.39–1.2	2–36	2
Adult								
21–50 years	55–161	12–32	0.4–4.2	17–36	1.1–3.1	0.46–1.2	2–25	1.5
51–80 years	55–160	12–32	0.4–4.2	17–36	0.6–2.8	0.46–1.2	2–25	1.5

[a]Data from refs. *3–6* and Corning Nichols Institute Clinical Correlations Division.
Values are 2 SD range.

function in the fetus matures progressively to maximum levels of thyroid hormone production and utilization (per kilogram of body weight) in early infancy *[3, 4]*. T_4, T_3, FT_4, FT_3, and TSH concentrations all are highest during this period, as are T_4 utilization and presumably production rate.

T_4 utilization rates decrease progressively with age after birth *[6]*; other indicators decrease more modestly. In adults ages 20 to 50 years there are no changes with age in serum T_4, FT_4, or TSH concentrations, but modest decreases in T_3 and T_4 utilization are observed *[7]*. In subjects >50 years, there are a variety of progressive changes in hypothalamic–pituitary thyroid axis function, as summarized in Table 2 *[7]*. The net effect of these changes on circulating thyroid T_4 and TSH concentrations is minimal. There is a modest, progressive decrease in serum T_3 concentrations.

Recent studies show little variation in serum TSH or FT_4 concentrations during the hormonal changes of puberty *[5]*. In general, thyroid-function indicators in healthy subjects show little or no clinically significant gender or racial variation. Estrogen increases serum TBG concentrations by enhancing hepatic sialylation of the molecule, which reduces metabolic clearance; androgens reduce circulating TBG concentrations *[2]*. However, these are predominantly pharmacologic effects manifest during drug administration (contraceptive or other therapeutic uses) or during pregnancy in women.

Table 2. Changes in thyroid function with aging.[a]

Decreased TRH secretion
Decreased TSH response to TRH
Decreased pituitary (negative) feedback sensitivity
Decreased T_4 secretion
Decreased T_4 disposal
Decreased (slight) T_4 monodeiodination
Decreased T_3 disposal
No change in serum TSH, T_4
Decreased (slight) serum T_3

[a]From ref. *7*.

DIETARY INFLUENCES, NUTRITION

Caloric restriction tends to reduce thyroid function, with effects at both the hypothalamic–pituitary and peripheral tissue levels. Basal and TRH-stimulated serum TSH concentrations are reduced somewhat and the type I MDI activities in peripheral tissues are reduced, with a concomitant reduction in T_4-to-T_3 conversion and a reduction in serum T_3 concentrations *[8]*. These effects are related to the extent and duration of the caloric deprivation. In severe and prolonged restriction, as in anorexia nervosa, increased cortisol secretion may contribute to the suppression of TSH release. The mechanism(s) mediating the decreased TSH secretion in response to caloric deprivation is not clear. Somatostatin antibody abolishes the decline in rats, suggesting increased somatostatin tone, and TRH does not reverse the acute decline in TSH during fasting *[8]*. T_4 and FT_4 concentrations are not usually altered significantly in association with caloric deprivation.

CIRCADIAN AND SEASONAL RHYTHMS

There is a clear circadian variation in circulating TSH concentrations in animals and in humans. TSH concentrations are low during the daytime, increase in the evening, and peak shortly before sleep *[9–11]*. Amounts decline slowly during sleep. Table 3 summarizes studies of mean, nadir, and peak serum TSH concentrations in 98 healthy children, ages 5–18 years, and in two cohorts of healthy adults, one younger group (20–27 years, n = 8) and one older (67–84 years, n = 8) *[9–11]*. TSH is

Table 3. Circadian variation in serum TSH.[a]

Study group and age, years	TSH conc, mIU/L (±SD)				Time	
	W	Mean	Nadir	Peak	Nadir	Peak
Children, 5–18	98	2.4 (±1.0)	1.6 (±1.0)	3.7 (±2.0)	1500	2300
Adults, 20–27	8	1.4 (±0.4)	0.9 (±0.3)	1.94 (±0.5)	1653	0356
Adults, 67–84	8	1.01 (±0.7)	0.73 (±0.6)	1.30 (±0.9)	1611	0215

[a]Data from refs. *9–10*.

secreted in a pulsatile fashion throughout the day, and the nocturnal TSH surge is associated with increased pulse frequency and pulse amplitude. The diurnal TSH rhythm is modulated by the circadian pacemaker in the suprachiasmatic nucleus, and the circadian rhythm can be advanced or delayed 1–2 h by exposure to light in the late or early part of the night, respectively *[11]*. Pharmacologic doses of glucocorticoids can inhibit basal TSH secretion and abolish the circadian TSH rhythm, but preventing the cortisol diurnal rhythm with metyrapone does not alter the TSH rhythm *[8]*. The nocturnal TSH increment is obtunded in nonthyroidal illness, hyperthyroidism, central hypothyroidism, syndromes of hypercortisolism, surgical stress, depressive states, and poorly controlled diabetes mellitus.

The diurnal variation in TSH concentration approximates ±50% (Table 3), so that time of day may influence the measured serum TSH concentration. However, the variation between 0900 and 1600 usually does not exceed 10% *[9–11]*. The circadian variation in TSH secretion has a minimal effect on serum T_4 concentrations, since the hourly T_4 secretion rate (3–5 μg) represents a very small fraction of the extrathyroidal T_4 pool (500–600 μg).

There is the known variation in total T_4 amount with the diurnal change in plasma protein concentration due to hemodilution, but there is no significant diurnal change in FT_4 concentration. There may be a seasonal variation in TSH concentrations, with a statistically higher T_4 concentration in winter vs summer, but this variation, too, is minimal *[8, 11, 12]*. This variation may be due to an effect of cold to accelerate the peripheral metabolism of thyroid hormone during the winter months. There are no data at present to suggest that normative values for serum TSH or T_4 should be seasonally altered.

MENSTRUAL CYCLE, PREGNANCY

There is some evidence that estrogens can increase and androgens reduce the TSH response to TRH, but there is no apparent sex-related difference in the magnitude of the diurnal variation in serum TSH *[8]*. Additionally, as already discussed, estrogens increase and androgens tend to reduce the circulating amount of TBG. The responses of TSH and prolactin to exogenous TRH are greater in women than in men and greater during the preovulatory than in the luteal phase of the menstrual cycle *[13]*. Women, when hypothyroid, tend to have irregular, anovulatory menstrual cycles and excessive menstrual bleeding *[14]*. These effects appear related to an obtundation of the ovulatory lutropin surge. Thus, although there are interactions of gonadal and thyroid hormones across these endocrine systems, there are minimal and transient variations in thyroid- function indicators during the normal menstrual cycle. Total T_4 concentrations may fluctuate slightly because of the transient change in circulating estrogen concentrations and the effect on TBG concentration *[15]*.

In pregnant women, renal clearance of iodide increases because of an increase in the glomerular filtration rate and because of iodide and iodothyronine transfer to the fetus. Serum concentrations of inorganic iodide decrease, and women living in areas of marginal iodine intake (<50 μg per day) may manifest absolute or relative iodine deficiency and enlargement of the thyroid gland during pregnancy *[15]*. Serum concentrations of TBG increase during the first trimester as a result of reduced clearance mediated by an estrogen-induced increase in sialylation of TBG and an estrogen-stimulated increase in its synthesis *[15]*. The TBG concentration plateaus after 12 to 14 weeks of pregnancy, and there are parallel increases in serum total T_4 and T_3 concentrations. Serum FT_4 concentrations increase slightly during the first trimester, coincident with the first-trimester peak in human chorionic gonadotropin (hCG) concentrations. In general, however, they are lower than in nonpregnant controls. T_4 utilization increases during pregnancy by 25–50%, and increases in the T_4 dosage of this magnitude are necessary in women with hypothyroidism during pregnancy to maintain normal TSH concentrations. The reason for the increased T_4 utilization is not clear. The increase in TBG concentration is associated with an increase in the extrathyroidal pool of ~300 μg of T_4, but this increase is transient during the first trimester. Placental degradation of T_4, some maternal-to-fetal T_4 transfer, and an increase in maternal T_4 turnover probably are involved *[15]*.

Serum TSH concentrations remain within the normal range in most pregnant women. However, the placenta produces large amounts of hCG, which has some TSH-like bioactivity. hCG production by the placenta is maximal near the end of the first trimester, after which it declines. At the time of peak hCG concentrations there is a transient increase in maternal serum FT_4 concentrations and (or) a transient decrease in serum TSH concentrations *[15]*.

POSTURE, IMMOBILIZATION, EXERCISE, AMBULATORY STATUS

The hormonal response to exercise involves increased sympathoadrenal activity, increased somatotropin, corticotropin, β-endorphin, prolactin, vasopressin, and possibly TSH secretion *[16, 17]*. The increased epinephrine secretion inhibits insulin release, and the corticotropin increases cortisol secretion. The extent of these changes is related to training, nutrition, and state of health; all of the endocrine responses are reduced by exercise training. The thyroid axis aspects are of limited significance and have little impact with regard to thyroid-function testing. Immobilization, posture, and ambulatory status do not influence thyroid function significantly. Body weight and body habitus, in the absence of malnutrition, also are without effect on thyroid function.

GEOGRAPHIC AND ENVIRONMENTAL INFLUENCES

The geographic and environment factors influencing thyroid function include iodine intake and temperature. As mentioned earlier, the winter/summer effects on thyroid function are detectable in large studies but are modest in degree. It is not necessary to develop winter/summer calibrators for thyroid testing. There also may be minor variations in normative serum TSH/FT_4 concentrations in tropical vs colder geographic areas, but, again, these are minor in extent.

Subthreshold concentrations of iodine intake in geographic areas of endemic goiter are associated with a variety of alterations in thyroid-function indicators. These include reduced circulating inorganic iodine concentrations, increased thyroid iodine uptake, an increased T_3/T_4 secretion ratio, an increased serum T_3/T_4 concentration ratio, decreased total and FT_4 concentrations, increased serum TSH concentrations, and a tendency to goiter *[18]*. These changes are inversely related in degree to the prevailing iodine intake. Recommended amounts of iodine intake are shown in Table 4 *[6]*.

In severe iodine-deficient areas (<50 μg of iodine intake/day in adults), there is an increased prevalence of goiter, congenital hypothyroidism, neurological and hypothyroid cretinism, and a reduction in mean population IQ *[18]*. Excessive iodine intake can block thyroid hormone biosynthesis by inhibiting the enzymes involved in the biosynthetic process (the Wolff–Chaikoff effect) *[19]*. The result is reduced efficiency of T_4 synthesis, reduced T_4 secretion, increased TSH concentrations, goiter, and hypothyroidism if the iodine excess is chronic. The chronic concentrations likely to produce these effects are variable with age (premature infants are most susceptible) and are summarized in Table 4. Most instances of iodine-excess hypothyroidism are due to individual dietary and drug effects, but there is some variation related to geographic availability of high-iodine foodstuffs such as seafood and kelp.

Excess iodine intake may produce a hyperthyroid state in individuals with subclinical autoimmune Graves disease in areas of borderline iodine deficiency *[20]*. In such instances the prevailing amount of iodine intake is such that the excessive thyroid gland stimulation is not sufficient to produce overt hyperthyroidism until the increased iodine substrate is provided. This phenomenon, referred to as "Jod-Basedow," is uncommon.

NONTHYROIDAL ILLNESSES

Systemic disease states, referred to as nonthyroidal illnesses, are associated with a variety of alterations in thyroid hormone metabolism *[19, 20]*. These include: (*a*) reduced serum total and FT_3; (*b*) increased serum rT_3; (*c*) low, normal, or increased serum T_4; and (*d*) normal or low serum TSH.

The changes in thyroid hormone metabolism are related to an inhibition of type I MDI activity, reduced conversion of T_4 to T_3 in peripheral tissues, reduced clearance of rT_3, and a decreased affinity of TBG for T_4, which is associated with reduced serum total T_4 but normal FT_4 in most subjects *[20]*. The normal FT_4 and TSH concentrations in most subjects and the transient nature of the disorder (as patients recover from their acute illness) have led to designation of the disorder as the "euthyroid sick syndrome." The extent of the disorder is related to the severity and duration of the illness. In severe disease there can be associated reductions in TSH and TBG concentrations, and total and free serum T_4 concentrations. Of patients in intensive care units, ~30–50% manifest low amounts of T_3 and T_4, and low serum T_4 is more frequently seen in severely ill, moribund patients *[20]*. In patients with certain liver diseases and in patients receiving certain drugs (amiodarone, radiocontrast agents), high serum T_4 concentrations can be seen—related to increased serum TBG concentrations or decreased T_4 metabolism, or both *[20]*.

Recent information has suggested that these thyroid system alterations in nonthyroidal illness are related, at least in part, to increased production of cytokines (including tumor necrosis factor and interleukins *[20]*), which have been shown to reduce TSH secretion, inhibit T_4 secretion, and inhibit hepatic gene expression of TBG *[20]*. Caloric deprivation and glucocorticoid hypersecretion may contribute significantly as pathogenetic factors *[20–22]*. The thyroid dysfunctions associated with nonthyroidal illness are generally considered secondary, adaptive effects, and the patients remain euthyroid. Treatment is focused on the underlying disease.

Table 4. Recommended dietary intakes of iodine and probable safe upper limits.[a]

	Dietary iodine intake, μg/kg per day	
Age	Recommended	Upper limit
Premature infants	30	100
Infants 0–6 months	15	150
Infants 0–12 months	7	140
Children 1–10 years	3	50
Adolescents/adults	2	30

[a]From ref. 6.

SURGERY, TRAUMA

Acute trauma, including surgery, also is associated with alterations in thyroid-function indicators. The changes are similar to those seen in nonthyroidal medical illness and the pathogenesis is similar, although the process is more acute and recovery may be more rapid *[20–24]*. Experimental studies are ongoing to determine whether T_3 replacement therapy in the low-T_3 syndrome associated with trauma or surgery may be beneficial.

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