

Euthyroid Sick Syndrome

A. Sattar, N. Asif, M. M. Dawood, T. Rafi, Z. Rehman*, M. Aamir

Departments of Chemical Pathology and Endocrinology and Haematology*, Armed Forces Institute of Pathology, Rawalpindi.

Introduction

Abnormalities in the circulating thyroid hormone concentration, without associated pituitary or thyroid disease, are seen in a variety of nonthyroidal illnesses (NIH). These abnormalities may be low plasma triiodothyronine (T3), low thyroxine (T4) or a combination of both, with an inappropriately normal plasma thyrotropin (TSH). These could be because of various factors acting on monodeiodinase, a key enzyme for the conversion of T4 to T3, or on transport system for thyroid hormones. Role of cytokines and other inflammatory mediators through their actions on hypothalamus, pituitary or thyroid gland has been extensively investigated, but their real action in vivo remains unclear. Knowledge of these hormone abnormalities is necessary to avoid errors in the diagnosis of thyroid disease. Whether the hormone responses in euthyroid sick syndrome represent part of an adaptive response, which lowers tissue energy requirement in systemic illness, or is a maladaptive response inducing damage to tissues in hypothyroidism, remains unclear. The thyroid function disturbances correlate with the disease severity, and low levels of thyroid hormones predict a poor prognosis in severe illness. The use of thyroid hormone therapy is still controversial in such illnesses, as few controlled trials have shown conflicting results for treatment with T3.

Abnormalities in the circulating levels of thyroid hormones, without evidence of coexisting thyroid or pituitary gland disease, are commonly seen in a wide variety of systemic nonthyroidal illnesses. Interpreting the test results and knowing what to do with the results when there is no evidence of thyroid dysfunction can be a challenge.¹ The term "euthyroid sick syndrome" is used to describe these abnormalities in thyroid function tests. It is the most common biochemical abnormality of endocrine function among medical inpatients; the incidence may be as high as 70%.² The observed thyroid hormone abnormalities do not indicate thyroid disease, but seem to represent a response to the underlying illness, as these invariably disappear with

recovery from underlying illness. The term "nonthyroidal illness syndrome" (NTIS) seems more appropriate alternative designation, as it does not presume the metabolic status of the patient.³

Appropriate and timely recognition of abnormalities of thyroid function in various nonthyroidal systemic illnesses has paramount importance because of three main reasons: (a) Abnormal results of thyroid function tests can sometimes mimic or at other times mask the biochemical changes observed in patients with intrinsic thyroid disease.⁴ (b) The hormonal response in euthyroid sick syndrome represents the part of an adaptive response to illness, so the treatment of these systemic illnesses with thyroxine is not of much help.⁵ (c) The severity and nature of changes in thyroid function tests have implications on the prognosis in such cases.⁶

Patterns of Euthyroid Sick Syndrome

Various patterns of thyroid hormone and TSH concentrations have been reported in euthyroid sick syndrome, reflecting the type and severity of illness.³ Chopra et al.⁷ have divided these patterns into following four major types:

1. Low T3 Syndrome

This is the most common abnormality, observed in about 70% of the hospitalized patients. Serum concentration of total triiodothyronine (T3) falls rapidly and progressively within 30 min to 24 hours of the onset of the causative illness. The degree of fall reflects the severity of disease process.⁸ Levels vary from undetectable to normal, and the mean value is approximately 40% of the normal level. Whenever measured, the concentration of serum free T3 (fT3) is low normal or slightly decreased.⁹ The daily production of T3 is decreased, while its clearance remains unchanged. The decreased conversion of thyroxine (T4) to T3 results from the inhibition of enzyme 5'-monodeiodinase (5'-MDI) activity, which catalyzes the deiodination of T4 to T3.¹⁰ Serum total T4 and free T4 (fT4) are normal in patients with low T3 syndrome.¹¹

Generally serum TSH concentration and its response to thyrotropin releasing hormone (TRH) are normal. However

Generally serum TSH concentration and its response to thyrotropin releasing hormone (TRH) are normal. However TSH level may increase slightly, but returning to normal with recovery.¹² The serum concentration of reverse T3 (rT3) is increased except in renal failure¹³ and traumatic brain injury.¹⁴ Daily production rate of rT3 is normal. The increase in the serum rT3 level is mainly due to its reduced metabolic clearance.¹⁵

2. Low T3 and T4 syndrome

The low T3 and T4 syndrome is observed in severely ill, moribund patients admitted to medical intensive care units. About 30-50% of patients have subnormal levels of T3 and T4. The T4 concentration falls over a period of 24-48 hours. However the fT4 values are frequently within normal limits. This disparity between low T4 values and normal fT4 levels is partly due to decreased T4 binding. Kinetic studies have shown reduced hepatic uptake and clearance of T4. The fall in circulating thyroid hormone concentration coupled with reduced clearance implies substantially low thyroidal production rates.¹⁶

Serum TSH concentration is frequently low, as measured with sensitive TSH assays and TRH responses are blunted.¹⁷ This blunted response is probably due to decrease in the enzyme activity responsible for TRH degradation, leading to impairment of TRH metabolism. TSH level rises with recovery, and may be transiently elevated until T3 and T4 levels are restored to normal.¹⁸ The rT3 synthesis diminishes due to the decreased availability of its precursor T4, but because of slow degradation rT3 concentrations are frequently increased.¹⁵

Several factors may contribute to low T3 and T4 levels. These include: (1) reduced binding proteins, e.g., thyroxine binding globulin (TBG), albumin and prealbumin especially in chronic liver disease¹⁹ and in renal dialysis²⁰, (2) abnormal TBG due to altered sialylation²¹, (3) circulating competitive binding inhibitors of T4 to serum protein, including drugs²² (furosemide in high doses²³), non-esterified fatty acids (NEFA) and metabolic products²⁴ and (4) decreased serum TSH, especially in patients treated with dopamine.²⁵

3. High T4 syndrome

This is an unusual variant of euthyroid sick syndrome, seen in approximately 1% of sick patients. High serum T4 level is seen in some systemic illnesses-notably acute intermittent porphyria²⁶, liver diseases such as chronic active hepatitis and primary biliary cirrhosis²⁷, acute psychiatric illness²⁸, and patients on certain drugs such as amiodarone²⁹, and radiocontrast agents like ipodate and iopanoic acid used for oral cholecystography.³⁰ The serum concentration of fT4 remains normal. The high serum T4 level is usually the result of increased serum TBG. Serum T3 may be normal or increased, but fT3 concentration is typically decreased. The serum concentration of rT3 is also increased in such patients, a finding related to both a high TBG concentration and a decreased metabolism of rT3. The serum TSH is usually very low or undetectable, and TRH response is blunted to absent.¹⁶

4. Other abnormalities

Studies have shown that there is decreased nocturnal TSH surge, unrelated to ambient circulating T4 and T3 levels, but probably related to hypothalamic

Table. Conditions associated with Euthyroid Sick Syndrome.

1. Medical	Acute myocardial infarction. ⁶⁸ Acute renal failure. ¹³ Pulmonary tuberculosis. ⁶⁹ Alcoholic liver disease. ⁷⁰ Hepatic cirrhosis. ¹⁹ Lymphomas, leukemia and during their chemotherapy. ⁷¹ Aplastic anemia. ⁷¹ Stroke. ⁷² Malignancy. ¹ Obstructive chronic bronchopneumopathy with acute respiratory failure. ⁷³ Diabetic ketoacidosis. ⁷³ Acute cerebral vasculopathies. ⁷³ Collagenopathies. ⁷³ Hodgkin disease. ⁷⁴ Chronic heart failure. ⁷⁵
2. Surgical	Acute and chronic spinal cord injury. ⁷⁶ Major trauma. ⁷⁷ Severe burn. ¹ After elective cholecystectomy. ⁷⁸ During and after cardiopulmonary bypass. ⁶⁷
3. Infections	Viral hepatitis type A. ⁷⁹ Advanced stages of HIV. ⁸⁰ Sepsis. ⁷³
4. Miscellaneous	Patients receiving antituberculosis treatment. ⁶⁹ Premature and sick infants. ⁸¹ Bone marrow transplantation. ⁸² Haemodialysis. ²⁰ Progressive systemic sclerosis. ⁸³ Extensive dermatitis. ⁸³ Malignant Mediterranean spotted fever. ⁷³ Acute psychiatric illness. ²⁸ Acute intermittent porphyria. ²⁶
5. Drugs	a) Inhibitors of T4 to T3 conversion Amiodarone. ²⁹ Glucocorticoids. ²² Propranolol in high doses. ¹⁹ Propylthiouracil. ²² Radiographic contrast agents. ³⁰ b) Augmentation of clearance of T4 (enzyme induction) Phenobarbital. ²² Phenytoin. ²² Rifampicin. ⁶⁹ Carbamazepine. ²²

c) Inhibitors of TSH secretion

Dopamine.²⁵
 L-Dopa.²²
 Somatostatin.²²

d) Inhibitors of thyroid hormone synthesis or release

Iodine.²²
 Lithium.²²

e) Inhibitors of binding of T4/T3 to serum proteins

Nonsteroidal anti-inflammatory agents.²²
 Salicylates.⁸⁴
 Heparin.⁸⁵
 Furosemide.²³

f) Increasing concentration of T4 binding proteins²²

Estrogen.
 Clofibrate.
 Opiates.
 Perphenazine.

g) Stimulators of TSH secretion²²

Haloperidol.
 Clomiphene.
 Dopaminergic antagonists.

dysregulation.³¹ In addition, evidence suggests that TSH has reduced biological activity in euthyroid sick patients due to some structural abnormality.³² Euthyroid sick syndrome is also associated with low serum total protein. Low albumin³³ and high sympathetic response like high cortisol and nor-epinephrine levels are also commonly seen in acutely ill patients.³⁴

Pathophysiology

The thyroid gland produces mainly two iodine-containing hormones, T4 and T3. One third of the circulating T4 is normally converted to T3 by deiodination and 45% is converted to rT3 in the peripheral tissues. Two different enzymes are involved in these conversions i.e., enzyme I, 5'-monodeiodinase (5'-MDI), catalyzing the formation of T3, and enzyme II, 5-monodeiodinase (5-MDI), catalyzing the formation of rT3. The T3 is approximately 4-5 times more potent than T4 whereas rT3 is biologically inactive. Most of the T4 and T3 circulate in reversibly bound form with various plasma proteins: thyroxine-binding globulin (TBG), transthyretin (thyroxine binding prealbumin) and albumin. Only about 0.03% of T4 and 0.3% of T3 circulate in free form.³⁵

The exact cause of changes in serum thyroid hormone and TSH concentration observed in euthyroid sick syndrome is not completely understood. Various mediators have been implicated for the observed abnormalities in thyroid hormones seen in different systemic diseases. Reduced T3 production in peripheral tissues may be related not only to a decreased 5'-MDI activity but also to decreased T4 transport into various tissues. A number of factors are responsible for these actions

(1) Transport of T4 into liver is regulated by intracellular adenosine triphosphate (ATP) and energy stores. Evidence indicates that the tissue content of ATP and high-energy phosphates is reduced in euthyroid sick syndrome. Decreased T4 tissue uptake has been documented during fasting, liver disease and critical illnesses. Substances such as 3-carboxy-3-methyl-5-propyl-2-furanpropanoic acid (CMPF), indoxyl-sulfate, free fatty acids³⁶, hippuric acid, and bilirubin³⁷, which are increased in various systemic illnesses are known to decrease T4 uptake into hepatocytes leading to reduced T3 generation.

(2) The enzyme I, 5'-monodeiodinase (5'-MDI) is a low affinity and high capacity enzyme located in the major organs including liver, kidney and thyroid. It is responsible for generation of bulk of circulating T3.³⁸ There are a number of factors, which suppress the activity of this enzyme:

(a) Compromised nutritional status: The enzyme 5'-MDI is sensitive to caloric intake especially the one derived from carbohydrates. Fasting and hypercaloric diets reduce T3 level resembling euthyroid sick syndrome.³⁹

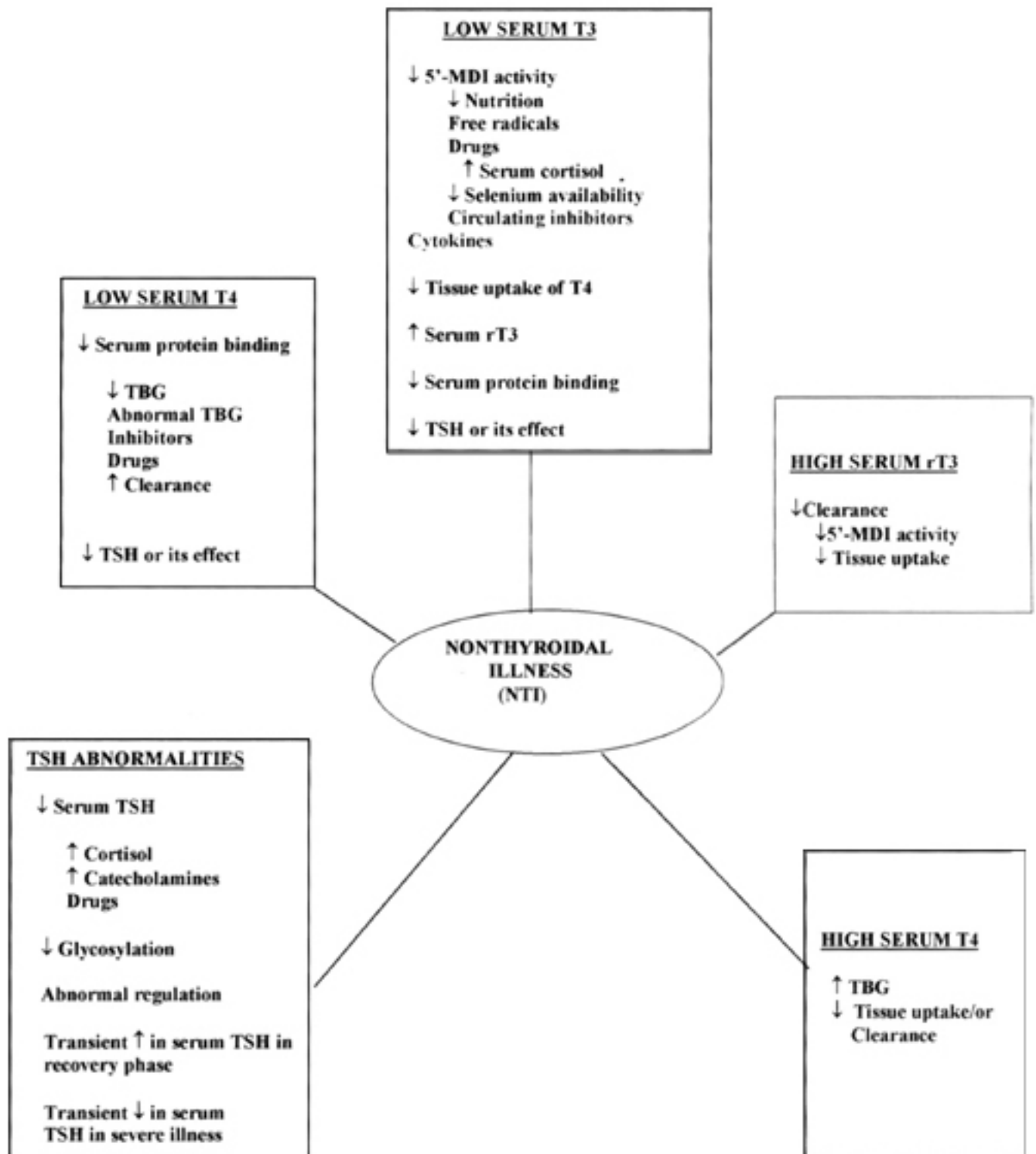
(b) Free radicals: Free radicals generated in the tissues also inhibit 5'-MDI activity. Moreover increased 5'-MDI activity has been observed in the presence of free radical scavengers.⁴⁰

(c) Alterations in selenium status: The enzyme 5'-MDI has selenocysteine at the active site of the enzyme. Selenium acts as a cofactor and thus is critical in T3 production. Selenium deficiency is associated with a progressive reduction of 5'-MDI activity in tissues and is restored by selenium supplements.

(3) Certain toxic metals such as cadmium⁴², mercury⁴³, and lead⁴⁴, and compounds such as carbon tetrachloride⁴⁵ have been associated with impaired 5'-MDI activity in animal models. Similarly vitamin B12 deficiency⁴⁶ and zinc deficiency⁴⁷ are associated with slight reduction in this enzyme activity, thus reducing T3 level. Nicotinic acid⁴⁸, lipoic acid⁴⁹, organophosphate compounds⁵⁰ and hyperglucagonemia⁵¹ all decrease serum thyroid hormone concentration while maintaining a euthyroid state.

Various clinical conditions and drugs associated with euthyroid sick syndrome have been summarized in Table.

VARIOUS PATTERNS OF EUTHYROID SICK SYNDROME



Cytokines

Recently, particular attention has been focused on the role of cytokines in the pathogenesis of euthyroid sick syndrome. Cytokines are multifunctional molecules with different biological effects on target cells. These can have autocrine, paracrine or endocrine actions. Cytokines may have a physiological or pathophysiological role contributing to development of euthyroid sick syndrome.⁵²

Among the different cytokines studied, tumor necrosis factor- α (TNF- α) is perhaps the most promising and best-studied candidate for a mediator of euthyroid sick syndrome. Infusion of TNF- α in man produces a decrease in serum T3, T4 and TSH levels and a rise in rT3.⁵³ The infusion of interleukin-1 (IL-1)⁵⁴, interleukin-6 (IL-6)⁵⁵, and interferon- α (IFN- α)⁵⁶ also produce the similar results. It has been shown that IL-1 and TNF- α both can induce the release of IL-6, suggesting that IL-6 may be the mediator of cytokine induced thyroid hormone changes. Several studies have been done to find the role of interferon- γ , IL-2, IL-8, and IL-10 in patients with euthyroid sick syndrome, but no evidence for their pathogenic role have been found.^{57,58}

Thus, it seems certain that nonthyroidal illness (NTI) is associated with an increased production and release of cytokines but the degree of cytokines involvement and their specific role in the pathogenesis remain controversial and undermined.⁵² One possibility is that NTI per se causes an increase in cytokine production and which is the only factor responsible for changes in euthyroid sick syndrome. A second possibility is that through incompletely understood mechanisms, the illness produces both an increase in cytokine levels and changes in thyroid function tests, the latter being totally independent of cytokine variations. The third and more likely model relates changes in thyroid parameters to both a direct effect of disease and the illness-related increase in cytokine production and release. This model best fits with available data indicating that in addition to the effects of cytokines, other substances, such as 3-carboxy-3-methyl-5-propyl-2-furan-propanoic acid (CMPF), indoxyl-sulfate, bilirubin, and FFA^{36,37} probably participate in the pathogenesis of euthyroid sick syndrome by reducing thyroid hormone transport into cells and thereby decreasing peripheral T3 production. Various biochemical changes associated with euthyroid sick syndrome have been summarized in Figure.

Clinical Significance

Abnormal thyroid function tests are observed as frequently in systemic euthyroid sick syndrome as in intrinsic thyroid disease. These changes may mimic or mask the biochemical abnormalities of true thyroid disease.

It has been observed that the severity and nature of changes in thyroid function tests are related to prognosis of the systemic illness. The low serum T3 or T4 levels predict increased mortality from liver cirrhosis,¹⁹ advanced congestive heart failure⁵⁹, and several other systemic illnesses, thus indicating poor prognosis.

There is a suggestive evidence that tissue hypothyroidism occurs because of low supplies of T3 and T4. However many believe that patients with nonthyroidal illness syndrome (NTIS) are metabolically euthyroid, even in the presence of low serum T3 and T4. Recent studies have shown that tissues of patients dying of NTIS contain substantially lower levels of thyroid hormones (T3 and T4) than did tissues of control subjects dying suddenly.⁶⁰ In contrast, studies also suggest that there is an increase in T3 receptor number and binding affinity in NTIS, an indication of a possible increase in tissue sensitivity to T3 that may contribute to maintenance of euthyroid state, despite low serum T3.⁶¹

It remains unresolved whether the hormone responses in euthyroid sick syndrome represent part of an adaptive response to systemic illness, which lowers tissue energy requirements in face of systemic illness, or a maladaptive response, that impairs tissue function and makes recovery from life threatening illness less likely.³

Treatment

The vast majority of patients of euthyroid sick syndrome who recover from their underlying illnesses, have prompt recovery of the hypothalamic-pituitary-thyroid axis and therefore do not need any treatment. In case of more severe illness, showing evidence of tissue hypothyroidism, trials of intervention are certainly justified.

Several studies have examined the effect of treatment with thyroid hormones. Treatment with T4 is not beneficial as explained by diminished conversion of T4 to metabolically more active T3. It may not be useful even in patients with low free T4 values.⁶² However, there is difference of opinion on treatment with T3, regarding its benefits or otherwise in patient of NTIS. Limited studies have shown some beneficial effects of treatment with T3 in patients of dopamine dependent septic shock⁶³, brain injury,¹⁴ sepsis after pulmonary infarction⁶⁴, for recovery in organ recipients⁶⁵ and patients with hemorrhagic shock.⁶⁶ The T3 administration to patients undergoing thoracic surgery has shown benefits as measured by cardiac output and decreased systemic vascular resistance.⁶⁷ Other studies have demonstrated beneficial effects of T3 treatment in low cardiac output related to myocardial ischemia, heart transplantation and for patients with hyperlipidemia.⁶⁸ Clearly, the aforementioned benefits of treatment associated with sepsis, cardiopulmonary bypass, respiratory failure, or a surgical procedure suggest that there is a need for additional controlled studies to determine the scope of such treatment. Much more is required to be learnt about the dose-response ratio and possible adverse effects of T3 treatment.⁶²

Conclusion

Alterations in thyroid function tests are fairly common in patients with NTI. Multiple, complex and incompletely understood mechanisms are involved. Awareness of these alterations helps in avoiding errors in the diagnosis of thyroid disorders and inappropriate therapy. FT4 and fT3 are the investigations of choice to differentiate between euthyroid sick syndrome and intrinsic thyroid disease. Thyroid hormone alterations are seen in about 50-70% of the hospitalized patients, therefore investigations of hypothalamic-pituitary-thyroid axis may be tested after a week or so, after recovery.

References

1. Pauline MC, Arcot AD. Sick euthyroid syndrome: what to do when thyroid tests are abnormal in critically ill patients. *Postgrad Med* 1999;105:215-19.
2. The NHS in Scotland. Laboratory statistics 1999. Edinburgh: Information and Statistics Division, 1999.
3. Chopra IJ. Nonthyroidal illness syndrome or euthyroid sick syndrome? *Endocrinol* 1996;2:45-52.
4. Goichot B, Sapin R, Schlienger JL. Euthyroid sick syndrome: recent physiological findings. *Rev Med Intern* 1998;19:640-8.
5. Acker CG, Singh AR, Flick RP, et al. A trial of thyroxine in acute renal failure. *Kidney Int* 1998;7:293-8.
6. Philips RH, Valente WA, Caplan ES, et al. Circulating thyroid hormones in acute trauma: prognostic implications for clinical outcome. *J Trauma* 1984;24:1000-4.

7. Chopra IJ. Euthyroid sick syndrome: Is it a misnomer? *J Clin Endocrinol Metab* 1997;82:329-34.
8. Marechaud R. Low T3 syndrome. *Rev Prat* 1998;48:2018-22.
9. Chopra IJ, Taing P, Mikus L. Direct determination of free triiodothyronine (T3) in undiluted serum by equilibrium dialysis/radioimmunoassay. *Thyroid* 1996;6:255-9.
10. Moreno M, Berry MJ, Horst C. Activation and inactivation of thyroid hormone by type 1 iodothyronine deiodinase. *FEBS Lett* 1994;344:143-6.
11. Nelson JC, Tomei RT. Direct determination of free thyroxine undiluted serum by equilibrium dialysis/radio immunoassay. *Clin Chem* 1988;34:1737-44.
12. Adriaans R, Romijn JA, Brabant G, et al. Pulsatile thyrotropin secretion in non-thyroidal illness. *J Clin Endocrinol Metab* 1993;77:1313-17.
13. Spector DA, Davis PJ, Helderman H, et al. Thyroid function and metabolic state in renal failure. *Ann Intern Med* 1976;85:724-30.
14. Woolf PD, Lee LA, Hamill RW, et al. Thyroid test abnormalities in traumatic brain injury: correlation with neurologic impairment with sympathetic nervous system activation. *Am J Med* 1998;84:201-8.
15. Chopra IJ. An assessment of daily production and significance of thyroidal secretion of 3,3',5',5'-triiodothyronine (reverse T3) in man. *J Clin Invest* 1976;58:32-40.
16. Docter R, Krenning EP, de Jong M, et al. The sick euthyroid syndrome: changes in thyroid hormone serum parameters and hormone metabolism. *Clin Endocrinol* 1993;39:499-518.
17. Persani L. Hypothalamic thyrotropin-releasing hormone and thyrotropin biological activity. *Thyroid* 1998;8:941-5.
18. Duntas LH, Nguyen T, Keck FS, et al. Changes in metabolism of TRH in euthyroid sick syndrome. *Eur J Endocrinol* 1999;141:337-41.
19. Bernardi M, De Palma R, Trevisan F, et al. "Low T3 syndrome" in cirrhosis: effect of beta-blockade. *Am J Gastroenterol* 1989;84:727-31.
20. Kayima JK, Otieno LS, Gitau W, et al. Thyroid hormone profiles in patients with chronic renal failure on conservative management and regular haemodialysis. *East Afr Med J* 1992;69:333-6.
21. Mendel CM, Lauaghton CW, McMahon FA, et al. Inability to detect an inhibitor of thyroxine-serum protein binding in sera from patients with nonthyroidal illness. *Metabolism* 1991;40:491-502.
22. Green WL. Effects of drugs on thyroid hormone metabolism. In: Wu SY, ed. *Current issues in endocrinology and metabolism: thyroid hormone metabolism. Regulation and clinical implications*. Boston: Blackwell, 1991, pp. 239-45.
23. Stockigt JR, Lim CF, Barlo JW, et al. High concentrations of furosemide inhibit serum binding of thyroxine. *J Clin Endocrinol Metab* 1984;59:62-6.
24. Nicolson RE, Reilly CP, Pannal PR, et al. Do non-esterified fatty acids displace thyroxine from its plasma binding sites in severe non-thyroidal illnesses? *Clin Chem* 1989;35:931-4.
25. Van den Berghe G, de Zegher F, Lauwers P. Dopamine and the sick euthyroid syndrome in critical illness. *Clin Endocrinol* 1994;41:731-7.
26. Hollander TS, Scott RI, Tshudy DP, et al. Increase iodine and thyroxine binding in acute porphyria. *N Engl J Med* 1967;177:995-1000.
27. Caregato L, Alberino F, Amodio P, et al. Nutritional and prognostic significance of serum hypothyroxinemia in hospitalized patients with liver cirrhosis. *J Hepatol* 1998;28:115-21.
28. Sokolov ST, Kutcher SP, Joffe RT. Basal thyroid indices in adolescent depression and bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 1994;33:469-75.
29. Nademane K, Piwonka RW, Singh BN, et al. Amiodarone and thyroid function. *Prog Cardiovasc Dis* 1989;31:427-37.
30. Felicetta JV, Green WL, Nelp WB. Inhibition of hepatic binding of thyroxine by cholecystographic agents. *J Clin Invest* 1980;65:1032-40.
31. Romijn JA, Wiersinga WM. Decreased nocturnal surge of thyrotropin in non-thyroidal illness. *J Clin Endocrinol Metab* 1990;70:35-42.
32. Magner J, Roy P, Fainter L, et al. Transiently decreased sialylation of thyrotropin (TSH) in a patient with euthyroid sick syndrome. *Thyroid* 1997;7:55-61.
33. Langster W. Diagnosis of thyroid hormone transport protein anomalies: an overview. *Acta Med Austriaca* 1996;23:31-40.
34. Girvent M, Maestro S, Hernandez R, et al. Euthyroid sick syndrome: associated endocrine abnormalities and outcome in elderly patients undergoing emergency operation. *Surgery* 1998;123:560-7.
35. Visser TJ. Pathways of thyroid hormone metabolism. *Acta Med Austriaca* 1996;23:10-16.
36. Everts ME, Lim CE, Moerings EPCM, et al. Effects of a furan fatty acid and indoxyl sulfate on thyroid hormone uptake in cultured anterior pituitary cells. *Am J Physiol* 1995;268:E974-9.
37. Lim CF, Docter R, Visser TJ, et al. Inhibition of thyroxine transport into cultured rat hepatocytes by serum of non-uremic critically ill patients: effects of bilirubin and nonesterified fatty acids. *J Clin Endocrinol Metab* 1993;76:1165-72.
38. Berry MJ, Larsen PR. Molecular structure and biochemical characterization of type 1 iodothyronine deiodinase. In: *Molecular Biology and Alternate Pathways*. Boca Raton (FL): CRC Press 1994, pp. 1-22.
39. Lim CF, Docter R, Krenning EP, et al. Transport of thyroxine into cultured rat hepatocytes: effects of mild nonthyroidal illness and caloric restriction in obese subjects. *Clin Endocrinol* 1994;40:79-85.
40. Barregard-Slebozinska E, Pietras B. The protective role of some antioxidants and scavengers on the free radicals-induced inhibition of the liver iodothyronine 5'-monodeiodinase activity and thiols content. *J Physiol Pharmacol* 1997;48:451-9.
41. Van Lante F, Daher R. Plasma selenium concentrations in patients with euthyroid sick syndrome. *Clin Chem* 1992;38:1885-8.
42. Gupta P, Kar A. Role of ascorbic acid in cadmium-induced thyroid dysfunction and oxidation. *J Appl Toxicol* 1998;18:317-20.
43. Barregard L, Lindstedt G, Schutz A, et al. Endocrine function in mercury exposed workers. *Occup Environ Med* 1994;51:536-40.
44. Chaurasia SS, Kar A. Protective effects of vitamin E against lead-induced deterioration of membrane associated type-1 iodothyronine 5'-monodeiodinase (5'MDI-1) activity in rat. *Toxicology* 1997;124:203-9.
45. Dhawan D, Goel A. Hepatoprotective effects of Liv-52 and its indirect influence on the metabolism of thyroid hormones in rat liver toxicity induced by carbon tetrachloride. *Res (Berl)* 1994;194:203-15.
46. Greg KD. Peripheral metabolism of thyroid hormones: a review. *Alter Med Rev* 2000;5:33.
47. Nishiyama S, Futagoishi-Suginohara Y, Matsukura M, et al. Zinc supplementation improves thyroid hormone metabolism in disabled patients with zinc deficiency. *J Am Coll Nutr* 1999;8:7.
48. Shakir KM, Kroll S, Aprill BS, et al. Nicotinic acid decreases serum thyroid hormone levels while maintaining a euthyroid state. *Mayo Clin Proc* 1995;70:556-8.
49. Segermann J, Hoots A, Ulrich H, et al. Effect of alpha-lipoic acid on the peripheral metabolism of thyroxine to triiodothyronine and on serum lipid, protein and glucose. *Arzneimittelforschung* 1991;41:1294-8.
50. Guven M, Bayram F, Unluhizarci K, et al. Endocrine changes in patients with organophosphate poisoning. *Humm Exp Toxicol* 1999;18:598-601.
51. Kabadi UM, Dragstedt LR. Glucagon-induced changes in plasma thyroid hormone concentrations in healthy dogs resemble euthyroid sick syndrome. *J Endocrinol* 1991;14:269-75.
52. Rasmussen AK. Cytokine actions on the thyroid gland. *Dan Med Bull* 2000;47:9.
53. Va der Poli T, Romijn JA, Wiersinga WM, et al. Tumor necrosis factor: a putative mediator of the sick euthyroid syndrome in man. *J Clin Endocrinol Metab* 1990;71:1567-72.
54. Hermus ARMM, Sweep CGJ, van der Meer MJM. Continuous infusion of interleukin-1 induces a non-thyroidal illness syndrome in the rat. *Endocrinology* 1992;131:2.
55. Bartalena L, Brogioni S, Grasso L, et al. Relationship of the increased serum interleukin-6 concentration to changes of thyroid function in nonthyroidal illness. *J Endocrinol* 1994;17:269-74.
56. Corssmit EPM, Heylingenberg R, Endert E, et al. Acute effects of interferon- α administration on thyroid hormone metabolism in humans. *J Clin Endocrinol Metab* 1994;79:134.
57. Panciera DL, Helfand SC, Soergel SA. Acute effects of continuous infusions of recombinant interleukin-2 on serum thyroid hormone concentrations in dogs. *Res (Berl)* 1995;58:96-7.
58. Boelen A, Platvoet-ter Schiphorst MC, Wiersinga WM. Relationship between serum triiodothyronine and serum interleukin-8, interleukin-10 or interferon- γ in patients with nonthyroidal illness. *J Endocrinol Invest* 1996;19:480-3.
59. Hamilton MA. Prevalence and clinical implications of abnormal thyroid hormone metabolism in advanced heart failure. *Ann Thorac Surg* 1993;56:S48-S52.
60. Arem R, Wiener GJ, Kaplan G, et al. Reduced thyroid hormone in failure of heart. *Metabolism* 1993;42:1102-8.
61. Erken Brack DE, Clemons GK. Modulation of thyroid hormone receptors by nonthyroidal illness. *J Recept Res* 1988;8:839-52.
62. Kaplan MM. Thyroid hormone therapy. What, when and how much. *Postgrad Med J* 1993;69:249-52.
63. Meyer T, Husch M, van den Berg E, et al. Treatment of dopamine-dependent shock with triiodothyronine: preliminary results. *Deutsch Med Wochenschr* 1979;104:1711-14.
64. Dulchavsky SA, Hendrick SR, Dutta S. Pulmonary biophysical effects of triiodothyronine augmentation during sepsis induced hypothyroidism. *J Trauma* 1993;35:104-9.
65. Novitzky D, Cooper DKC, Human PA, et al. Triiodothyronine therapy for heart failure. *J Heart Transplant* 1988;7:370-6.
66. Dulchavsky SA, Maitra SR, Maurer J, et al. Beneficial effects of thyroid hormone administration in metabolic and hemodynamic function in hemorrhagic shock. *FASEB J* 1990;4:104-7.
67. Klempner JD, Klein I, Gomez M, et al. Thyroid hormone treatment after coronary artery bypass surgery. *N Engl J Med* 1995;333:1522-7.
68. Gombert-Maitland M. Thyroid hormone and cardiovascular disease. *Am Heart J* 1998;136:96.
69. Post FA, Soule SG, Wilcox PA, et al. The spectrum of endocrine dysfunction in advanced pulmonary tuberculosis. *Clin Endocrinol (Oxf)* 1994;40:367-71.
70. Szilgyi A. Thyroid hormones and alcoholic liver disease. *J Clin Gastroenterol* 1993;17:93.
71. Nellen Hummel H, Gutierrez Escondido G, Talavera J, et al. Effect of chemotherapeutic agents on thyroid hormone concentration in patients with malignant hematologic diseases. *Res* 1997;28:215-17.
72. Liang DS. Stroke and thyroid hormones. *Chung Hua Shen ChingChingShen Ke Xue* 1991;24:352-4.
73. Di Napoli M, Reda G, Zannoni G, et al. The euthyroid sick syndrome. Its incidence and clinical significance in an internal medicine department. *Minerva Med* 1994;85:161-5.
74. Mohn A, Di Marzio A, Cerruto M, et al. Euthyroid sick syndrome in children with severe disease. *Pediatr Hematol Oncol* 2001;18:211-15.
75. Shanoudy H, Soliman A, Moe S, et al. Early manifestations of "sick euthyroid" syndrome in patients with compensated chronic heart failure. *J Card Fail* 2001;7:146-52.

76. Bauman WA, Spungen AM. Metabolic changes in persons after spinal cord injury. *Phys Med Rehabil Clin N Am* 2000;11:109-40.
77. Schilling JU, Zimmermann T, Albrecht S, et al. Low T3 syndrome in multiple trauma patients - a phenomenon or important pathogenetic factor? *Med Klin* 1999;94:66-9.
78. Langer P, Balazova E, Vician M, et al. Acute development of low T3 syndrome and changes in pituitary-adrenocortical function after elective cholecystectomy in women: some differences between young and elderly patients. *Scand J Clin Lab Invest* 1992; 52:215-20.
79. Tahirovic H, Maric D. Euthyroid sick syndrome in children with acute viral hepatitis A. *Acta Paediatr Hung* 1991;31:233-39.
80. Bonnyns M, Bourdoux P. Thyroid and AIDS. *Rev Med Brux* 1995;16:361-3.
81. Fisher DA. Euthyroid low thyroxine (T4) and triiodothyronine (T3) in premature and sick neonates. *Paediatr Clin North Am* 1990;37:1297-1312.
82. Kami M, Tanaka Y, Chiba S, et al. Thyroid function after bone marrow transplantation: possible association between immune-mediated thyrotoxicosis and hypothyroidism. *Transplantation*. 2001;71:406-11.
83. Molnar I, Czirjak L. Euthyroid sick syndrome and inhibitory effect of sera on the activity of thyroid 5'-deiodinase in systemic sclerosis. *Clin Exp Rheumatol* 2000;18:719-24.
84. Wang R, Nelson JC, Wilcox RB. Salsalate administration - a potential pharmacological model of the sick euthyroid syndrome. *J Clin Endocrinol Metab* 1998;83:3095-9.
85. Jaume JC, Mendel CM, Frost PH, et al. Extremely low doses of heparin release lipase activity into the plasma and can thereby cause artifactual elevations in the serum free thyroxine concentration as measured by equilibrium dialysis. *Thyroid* 1996;6:79-84.

