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# CLINICAL REVIEW 86

# Euthyroid Sick Syndrome: Is It a Misnomer?

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THE TERM euthyroid sick syndrome (ESS) identifies abnormalities in thyroid function tests observed in patients with systemic nonthyroidal illnesses (NTIs) and those undergoing surgery or fasting (1, 2). The term nonthyroidal illness syndrome (NTIS) has also been employed to describe these abnormalities (3). These abnormalities result from variable, usually reversible, disturbances in the hypothalamo-pituitary-thyroid axis, thyroid hormone binding to serum proteins, tissue uptake of thyroid hormones, and/or thyroid hormone metabolism. Several recent reviews have addressed these issues (3–6). I shall focus mainly on the clinical diagnosis, significance, and treatment of ESS.

*NTIS*

Abnormalities of thyroid function in NTIS have been classified as 1) low $T_3$ syndrome, 2) low $T_3$-low $T_4$ syndrome, 3) high $T_4$ syndrome, and 4) other abnormalities (7).

Although serum concentrations of total $T_3$ and $T_4$ are now measured routinely by similar RIAs, several methods have been employed for measurement of the small, biologically active, free fraction of $T_3$ and $T_4$ (8–14). Most workers in the field view the measurement of free thyroid hormones by equilibrium dialysis as the gold standard, and the ultrafiltration method is comparable or a close second. Until recently, tracer equilibrium dialysis was believed to be the most accurate procedure for measurement of free $T_3$ or $T_4$. This is expected to be increasingly replaced by the newer, more accurate, equilibrium dialysis/RIA (12, 14); reasonably priced kits are available commercially for free $T_4$ measurement by this procedure (Nichols Diagnostics, San Juan Capistrano, CA) and should be available soon for free $T_3$ measurement. A detailed discussion of methods of measurement of free thyroid hormones is beyond the scope of this minireview, and the reader is referred to several studies comparing available procedures (9, 10, 13). The analog methods for free thyroid hormone measurements are popular in several countries outside of the United States. These methods yield free thyroid hormone readings in NTI that are similar to those from the index method and different from those by the tracer equilibrium dialysis or equilibrium dialysis/RIA procedures (9, 10, 13). For this review, I have relied mainly on free thyroid hormone levels measured by the newer equilibrium dialysis/RIA procedure when data are available, or those measured by tracer dialysis and/or ultrafiltration procedures.

Low serum total $T_3$ is the most common abnormality in NTI. It is observed in about 70% of hospitalized patients. Serum total $T_3$ may vary from undetectable to normal in patients with systemic illness, and the mean value is approximately 40% of the normal level. The serum free $T_3$ concentration as measured by direct equilibrium dialysis/RIA [free $T_3$(D)] is also decreased, but less severely, and the mean value is approximately 60% that of normal (14). The serum free $T_3$ concentration measured by ultrafiltration is either normal or reduced (11). Low values were observed in patients given dopamine. It is curious that free $T_3$ was often low in NTI when measured by equilibrium dialysis (14) and typically normal when measured by ultrafiltration (11). The discrepancy is possibly explained by the lower total $T_3$ and more severe NTI in patients determined by equilibrium dialysis than by ultrafiltration. Free $T_3$ in systemic illness has also been measured by a variety of other techniques and has been found to be low, but the accuracy of these procedures is questionable in NTI patients (8, 10, 15). When measured, the daily production rate (PR) of $T_3$ is decreased in NTI (16, 17), which supports the finding in NTI of low free $T_3$(D). Serum total $T_4$ and free $T_4$(D) and, when measured, daily PR-$T_4$ are normal in the low $T_3$ syndrome (12, 16, 18, 19). A decreased serum free $T_3$(D) concentration and PR-$T_3$ at a time when the serum free $T_4$(D) concentration and PR-$T_4$ are normal reflect decreased conversion of $T_4$ to $T_3$ in NTI (12, 16, 18, 19). The serum concentration of $rT_3$ is increased in NTI, except in renal failure (20). However, daily PR-$rT_3$ is normal, and the increase in the serum $rT_3$ level is related mainly to the delayed MCR of $rT_3$, which is predominantly due to decreased activity of the type I iodothyronine 5′-monodeiodinase (5′-MDI) in tissues (16); 5′-MDI deiodinates $T_4$ to $T_3$ and $rT_3$ to 3,3′-diiodothyronine ($T_2$) (21).

The low $T_3$ and low $T_4$ syndrome is observed in severely ill, frequently moribund, patients, usually admitted to medical intensive care units. Low serum total $T_4$ correlates with a bad prognosis (22). The serum concentration of free $T_4$, as measured by equilibrium dialysis/RIA [free $T_4$(D)], is normal in most NTI patients with low total $T_4$ (12). Interestingly, total $T_4$ is often low in NTI patients even when their serum

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concentration of immunoassayable $T_4$-binding globulin (TBG) is clearly normal (8). However, the free $T_4$ index is frequently low in these patients (7, 9, 10). This combination of findings in NTI has been explained by the presence in the circulation of an inhibitor of serum (and resin) binding of thyroid hormones (15, 23). The nature of the inhibitor is not known. We and others have considered a role for nonesterified fatty acids in some cases, especially when serum albumin is low (15, 24, 25). An inhibitor of serum binding of thyroid hormones is present in tissues (26), and its nature or its leakage into the circulation are not known. Some investigators do not agree with the existence of such an inhibitor in the sera of NTI patients (27). On the basis of experiments involving mixing of normal sera with NTI sera, Mendel *et al.* (27) were unable to document the existence of an inhibitor in NTI. They suggested that diminished serum binding of $T_4$ in NTI patients with normal immunoassayable TBG is a result of high level of desialylated TBG (27). This may indeed be the case, but direct measurements of desialylated TBG were not performed. Interestingly, however, the researchers observed that desialylated TBG has markedly decreased avidity for $T_4$, but its avidity for $T_3$ remains unchanged (27). Therefore, the finding of clearly decreased serum binding of $T_3$, evidenced by a markedly elevated dialyzable fraction of $T_3$, in several NTI patients with normal immunoassayable TBG (8) supports the possibility of a thyroid hormone binding inhibitor in NTI. When present, a decreased serum concentration and/or affinity of thyroid hormone binding proteins, especially TBG, can explain the findings of low total $T_4$ and normal free $T_4$(D) in NTI. Decreased serum binding of $T_4$ in NTI is associated with an increased MCR, which, too, contributes to a decreased serum concentration of total $T_4$. Interestingly, however, the increase in the MCR of $T_4$ in NTI is not as much as expected from the degree of reduction in serum binding of thyroid hormones (4).

The serum free $T_4$ concentration is low in NTI patients treated with dopamine and corticosteroids, which decrease serum TSH levels (11, 28–30). Besides low TSH, factors that may contribute to the low $T_4$ of NTI include abnormalities in TSH secretion, decreased biological activity of TSH, and diminished thyroidal response to TSH (31, 32).

High serum total $T_4$ is seen in some NTI patients, who have elevated serum concentrations of TBG. Serum TBG is elevated in acute intermittent porphyria (33) and several liver diseases, including chronic hepatitis and primary biliary cirrhosis (34). The serum concentration of free $T_4$(D) is normal in these patients in the absence of thyroid disease. Serum total $T_3$ may be normal, but free $T_3$(D) or the free $T_3$ index is low normal or low as in other patients with NTI. The serum concentration of $rT_3$ is elevated in NTI patients with high $T_4$.

Both serum total and free $T_4$(D) concentrations are often increased in NTI patients treated with amiodarone and iodinated radiocontrast agents, *e.g.* iopanoic acid and ipodate used for oral cholecystography (13, 35, 36). These agents decrease hepatic uptake of $T_4$ and 5′-monodeiodination of $T_4$ (to $T_3$) and, in addition, may precipitate hyperthyroidism in patients with autonomous thyroid nodules by invoking the Jod Basedow phenomenon (37, 38). The effect of a single dose of oral cholecystography agents on serum $T_4$ typically lasts less than 24 h (36, 37, 39). NTI patients with high total and free $T_4$(D), especially those who have ingested iodine-containing agents, should be followed carefully for the appearance of typical hyperthyroidism (38). Serum $T_3$ may be normal or even low initially because of the effects of the drug and/or NTI on peripheral conversion of $T_4$ to $T_3$, and it may increase dramatically during follow-up.

The serum concentration of free $T_4$(D) is elevated in NTI patients given heparin (40). This is an *in vitro* artifact explained by displacement of $T_4$ from binding proteins by fatty acids generated from the action of lipase(s) on plasma triglycerides. Total $T_4$ and the free $T_4$ index are normal in these patients, who are clinically euthyroid.

Infection with human immunodeficiency virus (HIV) produces unusual alterations in thyroid function, including increases in $T_4$ and TBG, paradoxical decreases in $rT_3$ and the $rT_3/T_4$ ratio, and the maintenance of a normal $T_3$ and $T_3/T_4$ ratio even in severely ill patients. Serum $T_3$ decreases, however, in critically ill patients with HIV and pneumocystis infection (41). The basis for the differences in thyroid hormone abnormalities in HIV compared to those in other NTIs is not known.

### *Pathogenesis of the NTIS*

Some factors that may contribute to major abnormalities of the NTIS are listed in Fig. 1. They have recently been critically reviewed (3–6). There is evidence for decreased conversion of $T_4$ to $T_3$ in extrathyroidal tissues in the NTIS (16–19), and this may, in turn, be related to decreased activity and/or concentration of 5′-MDI (42). 5′-MDI has now been cloned in

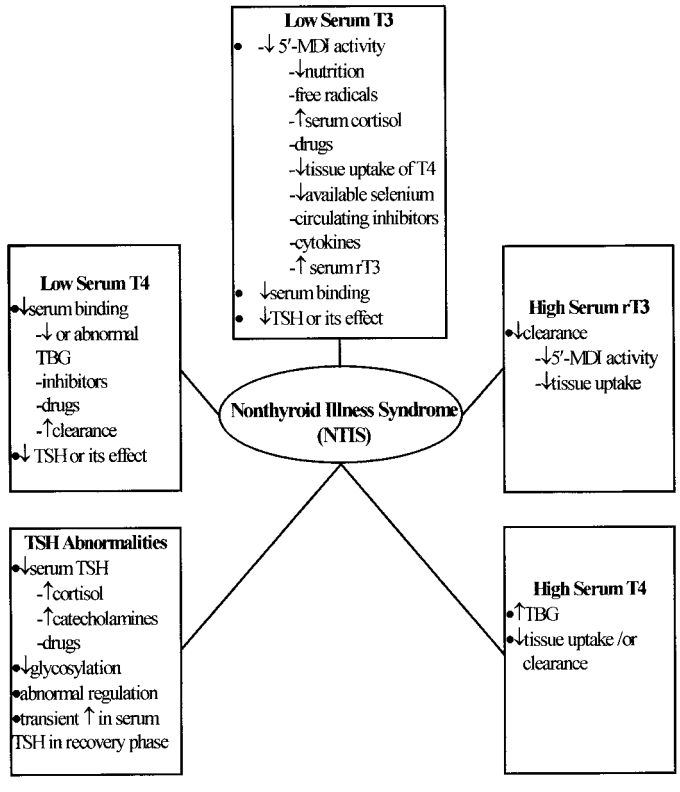


FIG. 1. Some factors that may contribute to major abnormalities of NTIS. The reader is referred to previous reviews (3–6) for detailed discussion of these factors.

the rat and man, and it turns out that it belongs to a small group of selenocysteine-containing proteins (43, 44). No data are available on the tissue content of the 5′-MDI protein or its messenger ribonucleic acid in human NTIS. However, the hepatic content of 5′-MDI protein was decreased in the fasting rat, studied as a model of NTIS (42). Diminution in the uptake of $T_4$ by tissues can also explain the decreased generation of $T_3$ in tissues (5). However, this abnormality should be associated with an elevated serum concentration of free $T_4$(D), which is clearly not the case (see above) (45). One could argue that decreased $T_4$ to $T_3$ conversion in NTI should also be associated with increased free $T_4$(D). However, $T_4$ is metabolized not just by 5′-MDI, but also by type III iodothyronine deiodinase, conjugation and side-chain alteration (21, 46); these alternate routes of $T_4$ metabolism are not known to be impaired in NTI and may compensate for $T_4$ not metabolized by 5′-MDI.

Alterations in serum binding of thyroid hormones is clearly an important factor contributing to changes in thyroid hormone levels in NTI (see above). Serum albumin binds compounds, *e.g.* fatty acids, that are capable of displacing thyroid hormones from TBG. The fall in serum albumin in NTI enhances the activity of such low affinity competitors of $T_4$ on TBG (15, 24, 25). Additionally, much has been written on abnormalities in the synthesis, secretion, structure, regulation, and effectiveness of TSH in NTI (3–6, 31, 32).

There has been much interest recently in the roles of cytokines in the pathogenesis of the NTI (3). However, their significance remains unclear. Proinflammatory cytokines [tumor necrosis factor-$\alpha$ (TNF$\alpha$), interleukins (*e.g.* IL-1 and IL-6), and interferon-$\gamma$], when administered to man or experimental animals, have caused changes in thyroid function tests that resemble NTIS (47–50). However, humans or animals so treated manifest substantial systemic illness, and it is unclear whether the thyroid hormone changes observed are due to the sickness induced by cytokines or the cytokines *per se*. In this respect, it is curious that lipopolysaccharide-induced NTIS in mice, although associated with increases in circulating TNF$\alpha$ and IL-6, was not prevented by immunoneutralization of IL-1 receptor, TNF$\alpha$, IL-6, or interferon-$\gamma$ (51) (Wiersinga, W. M., personal communication).

### *Clinical significance of NTIS*

Abnormal thyroid function tests are observed at least as frequently in systemic NTIS as in thyroid diseases (4, 52, 53). Thyroid function abnormalities in NTI may at times mimic and at other times mask the biochemical abnormalities observed in true thyroid disease. Furthermore, the severity and the nature of changes in thyroid function test have implications for the prognosis of the systemic illness. Thus, a low serum $T_3$ level predicts increased mortality form liver cirrhosis, advanced congestive heart failure (54, 55), and possibly several other systemic illnesses. Similarly, low total $T_4$ is associated with increased mortality from systemic illness, and those patients with low $T_4$ who have very low serum $T_3$ levels have the worst prognosis (22, 55, 56). Previous studies have suggested that there exist tissue factors that can inhibit the binding of thyroid hormones to serum proteins and the ability of polymorphonuclear leukocytes to phagocytose *Escherichia coli* (26, 57). However, it is not known whether the two effects are due to the same or even similar factors and whether the thyroid hormone binding inhibitor considered above in serum is similar to that extracted from tissues. In any case, leakage of tissue elements in the circulation in systemic illnesses may explain the correlation between the fall in serum $T_4$ and the increased mortality in NTI; this requires further study.

### *Diagnosis of thyroid disease in NTI*

It can be challenging to establish the diagnosis of thyroid disease in patients manifesting NTIS. The difficulty exists in hyperthyroid patients who may exhibit normal total $T_4$ and $T_3$ on account of a diminution in serum binding of thyroid hormones. However, serum free $T_4$ and free $T_3$ determinations by equilibrium dialysis/RIA (12) or ultrafiltration (45) should yield appropriately diagnostic elevated values. The free $T_4$ index and analog methods for free $T_4$ determination frequently yield low values in NTI and should be interpreted with caution. Serum TSH measured by the ultrasensitive RIA is typically undetectable ($<$0.10 mU/mL) in hyperthyroidism, whereas it is undetectable in less than 7% patients with NTI, usually those who have been treated with dopamine or corticosteroids (30). Definite diagnosis of hypothyroidism can also be difficult in the setting of NTI. However, primary hypothyroidism is a strong possibility if serum TSH is above 25–30 $\mu$U/mL. Serum TSH is supranormal in ~12% patients with NTI, and it is above 20 $\mu$U/mL in less than 3% of patients (30, 58). A subnormal free T4(D) concentration in the absence of treatment of NTI patients with TSH-suppressive drugs, *e.g.* dopamine, corticosteroids, and anticonvulsants (*e.g.* phenytoin and carbamozeprine) is strongly suggestive of hypothyroidism. As Hashimoto's thyroiditis is a common cause of hypothroidism in our patient population, findings of goiter and positive antithyroid antibodies (*e.g.* thyroid peroxidase and thyoglobulin autoantibodies) in serum are strong points favoring the diagnosis of primary hypothyroidism. An elevated serum $rT_3$ level argues against the diagnosis of hypothyroidism, when serum TSH is more than 10 $\mu$U/mL (59). As an individual test, serum $rT_3$ does not help in the diagnosis of hypothyroidism in NTI patients. Low, normal, and high serum $rT_3$ values are observed in patients with TSH values varying between low and 10 $\mu$U/mL (normal, 0.5–5.0 $\mu$U/mL). However, likely hypothyroid patients with serum TSH levels above 20 $\mu$U/mL do not demonstrate supranormal $rT_3$ (59). It is prudent not to rely solely on any one thyroid function test in the setting of NTI, and a combination of tests should be considered in separating primary hypothyroid from euthyroid patients with the NTIS. The diagnosis of secondary (or tertiary) hypothyroidism may require additional work-up. The serum TSH level may be low, normal, or minimally elevated in secondary hypothyroidism. Plasma cortisol is clearly elevated or high normal, whereas PRL and gonadotropin levels are typically normal in NTI without a specific pituitary or hypothalamic disease. On the other hand, decreased plasma cortisol and gonadotropin levels and elevated PRL levels support a diagnosis of a central (pituitary or hypothalamic) lesion as the basis for secondary hypothyroidism (60, 61). In

view of several above-mentioned complexities, it is often reasonable to wait for a week or so after recovery from an acute NTI before evaluating thyroid status.

*Are patients with NTIS hypothyroid?*

Many believe that patients with NTIS are metabolically euthyroid even though serum levels of the most active thyroid hormone, $T_3$, are clearly in the hypothyroid range. A normal serum TSH in most NTI patients is clearly an important element in this belief. However, several studies demonstrating abnormalities in the synthesis, secretion, glycosylation, regulation, and/or effectiveness of TSH in NTI (see above) lead one to question the normalcy of TSH in the face of low serum levels of active thyroid hormone ($T_3$) in NTI. The transient increase in serum TSH during recovery from NTI suggests that TSH is suppressed in an illness (62). Pituitary TSH suppression may be related to the stress of an illness, and the resulting elevated cortisol and catecholamine levels and associated caloric deprivation (4, 62, 63). The basis for the apparent euthyroid status in NTI remains unclear, but one or more of the following explanations may be considered: 1) a moderate degree and a short duration of reduction in thyroid hormone ($T_3$) levels, 2) insensitivity of the clinical diagnosis of (mild) hypothyroidism, and 3) increased sensitivity of body tissues to $T_3$. Although available data are limited and conflicting, a number of studies support the opposite viewpoint. Thus, oxygen consumption in response to $T_3$ has been found to be decreased (not increased) in fasting rats compared to fed rats (64). There is also information suggesting a decreased effect of low $T_3$ on TSH in fasting subjects with the low $T_3$ syndrome (65, 66). Similarly, there is a decrease (not an increase) in the binding of $T_3$ to nuclear receptors to $T_3$ in diabetes mellitus and fasting in the rat (67, 68). There is also evidence for a diminution in thyroid hormone effects at the postreceptor level (69). One study, however, has suggested an increase in $T_3$ receptor number and affinity in NTIS (70). Studies in the 1970s suggested low $T_3$ to be protective against protein breakdown in fasting (71, 72). However, a recent study was unable to document hypercatabolic effects of $T_3$ in fasting obese subjects (73). Finally, 4) there may exist in the sera of NTI patients high levels of thyromimetic compounds other than $T_3$. A high serum concentration of $T_3$ sulfate in NTI is of interest in this regard (74, 75). Increased exposure of body tissues to 3,5,3′-triiodothyroacetic acid has also been suggested in NTI (76).

Overall, it seems that although several patients with NTI may be euthyroid because of a short duration of NTIS, normal free $T_3$, and/or a contribution of non-$T_3$ thyroactive substances, there are others, especially those with a prolonged NTI (and those who manifest low free $T_4$ by dialysis), who may indeed be biochemically hypothyroid and may benefit from treatment with thyroid hormone. This idea is supported by data indicating that tissues of patients dying from NTI contain much decreased levels of thyroid hormones compared to tissues of control subjects who died suddenly, and that the degree of thyroid hormone deficiency varied from one organ to another (77). The issue of secondary hypothyroidism in NTI patients treated with dopamine has been noted above (13, 28, 29). Decreased levels of serum markers of thyroid hormone action, *e.g.* angiotensin-converting enzyme, have also been documented in NTI (78).

Some studies have examined the effects of thyroid hormone replacement in NTI. Treatment with $T_4$ was not beneficial (79). This may be explained by diminished conversion of $T_4$ to metabolically more active $T_3$ in NTI. For the same reason, treatment with $T_4$ may not be useful even in NTI patients with low free $T_4$(D) values. Studies evaluating treatment of NTI patients with $T_3$ have described either no benefit (80) or appreciable improvement (81–86). $T_3$ treatment of patients undergoing cardiothoracic or coronary bypass procedures showed benefits measured by cardiac output, decreased systemic vascular resistance, need for drugs for cardiac or inotropic support, and use of diuretics (87–94). These benefits have been related to restoration of aerobic metabolism in ischemic myocardium (88), increase in inotropy (95), increase in high energy phosphate stores (96), and increase in uptake of glucose in the plasma membrane (97). There has been no evidence of increased risk from replacement doses of $T_3$ (92–94, 98). Whether the observed effects of $T_3$ in the above-mentioned studies were pharmacological or physiological is not known. It is encouraging, however, that short term treatment with near-replacement doses of $T_3$ was associated with several beneficial effects in NTIS. Clearly, more should be learned about the appropriate patient population, dose-response issues, and any adverse effects of treatment of the NTIS with $T_3$.

*Summary*

Alterations in thyroid function tests are very common in patients with NTI. Multiple, complex, and incompletely understood mechanisms are involved in these abnormalities. Knowledge of these abnormalities is necessary to avoid errors in the diagnosis of thyroid disease. Measurement of serum TSH, free $T_4$, and free $T_3$ levels by direct equilibrium dialysis/RIA methods probably yield most useful (accurate) information in the setting of NTI. Patients with low free $T_4$ by these methods and normal or low TSH have secondary hypothyroidism. This may be due to NTI *per se*, drugs administered for treatment of NTI, or associated pituitary or hypothalamic disease; the latter consideration may require evaluation of cortisol reserve, PRL, and/or gonadotropins. A serum TSH level above 20–25 $\mu$U/mL probably reflects primary hypothyroidism; accompanying findings of goiter, low free $T_4$, and positive antithyroid antibodies help establish the diagnosis. An elevated serum concentration of $rT_3$ argues against hypothyroidism. Studies have demonstrated no discernible benefit of treatment of NTI patients with $T_4$. Some studies have shown a few benefits of treatment with $T_3$ in selected cases, but much more needs to be learned. There is no evidence of harm by treatment of NTI patients with up to replacement doses of $T_3$. As some NTI patients may indeed be hypothyroid, the term ESS should be replaced with NTIS.

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