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Thyroid Hormone Metabolism and Thyroid Diseases in Chronic Renal Failure

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I. Introduction

END-STAGE renal disease (ESRD) is a relatively common nonthyroidal illness, which induces significant morbidity and mortality (1). In the United States, more than 220,000 patients were being dialyzed for ESRD in 1992, with an 8–9% annual increase in frequency over the last 10 years (1, 2). This rising incidence of ESRD reflects improved survival rates of ESRD patients and increasing age of the general population, with the greatest increase in ESRD frequency being in people over 64 yr of age (2). ESRD is a moderate to severe nonthyroidal illness and, as such, frequently alters thyroid hormone metabolism (3). In addition to metabolic and endocrine derangements induced by ESRD, these patients frequently have a multitude of nonrenal nonthyroidal disorders that affect thyroid hormone metabolism, including diabetes mellitus (1), infections (1), and malnutrition (4–6), and they are treated by a variety of pharmacological agents. Knowledge of alterations of thyroid hormone metabolism in euthyroid ESRD patients is required to accurately diagnose and treat concurrent hypothyroidism and hyperthyroidism. Furthermore, thyroid diseases including goiter, hypothyroidism, thyroid nodules, and thyroid cancer may occur more frequently in ESRD patients than in the general population and may be underdiagnosed due to limited clinical awareness. Although principles of therapy for thyroid diseases are not altered in ESRD patients, radioactive iodide dosages for follicular thyroid cancer and hyperthyroidism must be reduced to avoid radiation-related complications.

This review will focus on: 1) thyroid hormone metabolism in euthyroid patients with ESRD, compared with nonrenal nonthyroidal disorders, hypothyroidism, and hyperthyroidism; 2) effects of reduced iodide excretion by residual renal function and different dialysis regimens; and 3) frequency, diagnostic features, and specific treatment requirements of thyroid disorders in ESRD patients, compared with nonrenal patients.

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II. Thyroid Hormone Metabolism in Chronic Renal Failure

The hypothalamic-pituitary-thyroid hormone axis as well as peripheral thyroid hormone metabolism are altered in ESRD patients without concurrent thyroid disease. Similarities and differences in thyroid hormone metabolism in ESRD and nonrenal nonthyroidal disorders are compared with those of hypothyroidism and hyperthyroidism in Tables 1 and 2.

A. TSH

Basal serum TSH concentrations, diurnal variations, and glycosylation of TSH are altered in ESRD patients. In one study, basal serum TSH levels were above the normal range of 3.8 mU/liter in 12.5% of 40 euthyroid ESRD patients receiving chronic hemodialysis therapy, with the highest value being 5.4 mU/liter (7). In our study, 10.5% of 287 euthyroid ESRD patients had serum TSH values above 5 mU/liter, and 1% were above 10 mU/liter, in association with normal total T_4 and free T_4 index values (3). All euthyroid ESRD patients with TSH values between 10 and 20 mU/liter had repeat TSH values below 10 mU/liter (3). Transient TSH elevations, to above 20 mU/liter in some instances, also occur during recovery from acute nonrenal nonthyroidal illnesses (8–10), and then decrease in association with normal or rising total T_4 and free T_4 index values (8–11), suggesting relief of pituitary TSH suppression as illness severity decreases. In the general hospital population, serum TSH levels above 20 mU/liter are as frequently due to nonthyroidal illness (3.3%) as to primary hypothyroidism (3.3%), and TSH values between 6.8 and 20 mU/liter are more frequently due to nonthyroidal

illness (9.1%) than to primary hypothyroidism (1.5%) (10). Serum total T_4, free T_4 index, and free T_4 by equilibrium dialysis values are usually normal in euthyroid sick patients when serum TSH concentrations rise transiently (8–11). In contrast, sick patients with primary hypothyroidism have persistently elevated serum TSH values in association with persistently reduced total T_4, free T_4 index, and free T_4 levels by equilibrium dialysis (3, 8, 10, 11) (Table 1). Hypothalamic or pituitary lesions account for less than 5% of hypothyroidism and are usually associated with other endocrine deficiencies (including reduced cortisol, GH, and/or gonadotropin levels, and persistently reduced total and free T_4 levels) and TSH values below 15 mU/liter (12) and, therefore, are distinquishable from the transient changes due to nonthyroidal illnesses.

Reduced serum TSH levels have not been reported to date in euthyroid ESRD patients. Using an immunoradiometic TSH assay with a sensitivity limit of 0.06 mU/liter, none of 40 euthyroid ESRD patients undergoing regular maintenance hemodialysis therapy had serum TSH values below 0.4 mU/liter (7). However, hospitalized patients have serum TSH values below 0.1 mU/liter more frequently due to nonthyroidal illnesses (10.3%) than to hyperthyroidism (3.3%) in a second generation TSH assay, which by definition has a functional sensitivity limit of 0.1–0.2 mU/liter with a coefficient of variation of 20% in the clinical laboratory (10). Reduced serum TSH values could not be attributed to the dose or duration of glucocorticoid therapy in these hospitalized patients (10). However, high doses of exogenous glucocorticoids and intravenous dopamine therapy may reduce serum TSH values in euthyroid and hypothyroid patients (13–15). Seventy-two percent of serum TSH values below 0.10 mU/liter in euthyroid hospitalized patients with nonthyroidal illnesses were above 0.01 mU/liter using a third generation TSH assay (sensitivity limit of 0.01–0.02 mU/liter), with normal TSH responses to TRH, while all sick hyperthyroid patients had TSH values persistently below 0.01 mU/liter with absent TSH responses to TRH (16). Further, 73% of serum TSH values below 0.01 mU/liter in hospitalized patients, using a third generation assay, were due to hyperthyroidism while the remaining 27% were secondary to nonthyroidal illnesses (16). Interestingly, the highest frequency of abnormal TSH values in 504 newly hospitalized patients occurred in the most severely ill patients, with approximately 15% having reduced total T_4 and total T_3 levels as well as decreased serum TSH values using a second generation assay (17). Further studies using second or third generation TSH assays must be conducted to define the frequency of reduced serum TSH values in euthyroid ESRD patients.

Serum TSH responses to exogenous TRH are typically blunted in euthyroid ESRD patients before as well as after maintenance dialysis therapy, as in nonrenal nonthyroidal illnesses and with caloric deprivation (18–22). Further, increases in serum total T_4 concentrations after exogenous TSH administration may be diminished compared with normal subjects, while increments in serum T_3 concentrations are normal or blunted (18, 22). Despite these findings, steady state thyroidal T_4 production rates are normal in ESRD patients (19, 23). Further, pharmacokinetics of exogenously administered TRH are altered in ESRD patients receiving maintenance hemodialysis, with increased peak serum values (2.6 times), prolonged half-life (2.5 times), and reduced clearance rates (71% of normal) (21). These findings may indicate impaired exogenous TRH degradation and elimination in ESRD patients (21) that may alter the TSH response to endogenous as well as to exogenous TRH.

Normal serum TSH diurnal rhythm, characterized by peak levels in the late evening or early morning and pulsatile release, is altered in ESRD patients. In 10 chronically hemodialyzed ESRD patients, TSH periodicity was shorter, pulse amplitude was smaller, and evening TSH rise was diminished or absent (24). The nocturnal TSH surge was also absent in 90% of 20 euthyroid ESRD patients on maintenance hemofiltration, while basal morning serum TSH concentrations were normal (25) (Fig. 1). Interestingly, TSH clearance rates are reduced to 57% of normal in renal failure patients (26), which may reflect reduced renal clearance (27), smooth out TSH variations, and contribute to reduced TSH pulse amplitude in ESRD patients (24). However, the nocturnal TSH

TABLE 1. Serum thyroid hormone levels in thyroidal and nonthyroidal disorders

	TT_4	Free T_4 index	Free T_4[a]	T_4 Binding capacity	TT_3	Free T_3 index	TrT_3	Free rT_3	TSH	TSH Response to TRH
High TT_4 state of NTI	I	I	I	N, D	N, D	N, D	I	I	N, I	N, D
High TBG states	I	N, I	N	I	I	N	I	N	N	N
Hyperthyroidism	I	I	I	N, D	I	I	I	I	D	Absent
Normal TT_4 state										
of nonrenal NTI	N	N, I	N, I	N, D	N, D	N, D	I	I	N, I	N, D
of ESRD	N	N, I	N, I	N, D	N, D	N, D	N	I	N, I	N, D
Low TT_4 state										
of nonrenal NTI	D	D	N	D	D	D	I	I	D, N, I	N, D
of ESRD	D	D	N	D	D	D	N	I	N, I	N, D
Low TBG states	D	N, D	N	D	D	N	D	N	N	N
Primary hypothyroidism	D	D	D	I	N, D	N, D	D	D	I	I
Central hypothyroidism	D	D	D	–	D	D	D	D	N, I	N, D

I, increased; D, decreased; N, normal; –, no data, TT_4, total T_4; TT_3, total T_3; TrT_3, total reverse T_3, NTI, nonthyroidal illness. [Adapted from E. M. Kaptein: Thyroid hormone metabolism in illness. In: Hennemann G. (ed) Thyroid Hormone Metabolism, Basic and Clinical Endocrinology Series, Volume 8, Marcel-Dekker Inc., New York, NY, vol 8:297–333, 1986; (23) and E. M. Kaptein *et al:* Thyroid hormone metabolism: a comparative evaluation. In: Ferguson DC (ed) The Veterinary Clinics of North America: Small Animal Practice: Thyroid Disorders, WB Saunders, Philadelphia, vol 24:431–466, 1994 (128).]

[a] Free T_4 by direct equilibrium dialysis.

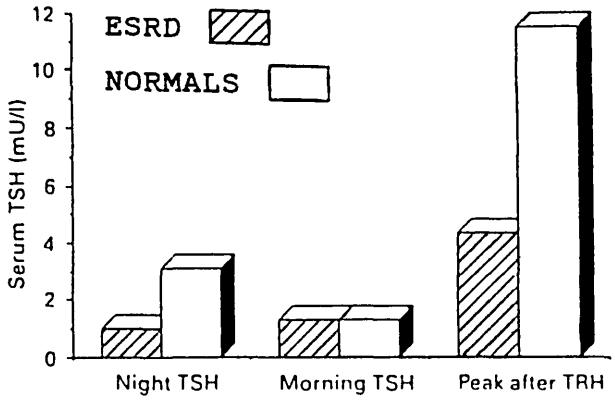

FIG. 1. Serum TSH levels at night and in the morning, and peak TSH values after TRH administration in ESRD patients and normal controls. [Reproduced with permission from L. Bartalena *et al.*: *Clin Nephrol* 34:30–34, 1990 (25).]

rise is also diminished in patients with nonrenal nonthyroidal illnesses and during fasting (17), suggesting a predominance of nonrenal factors. However, this central TSH dysregulation does not reduce thyroidal T_4 production rates (23).

TSH glycosylation is altered in euthyroid patients with severe nonthyroidal illnesses, including ESRD (28, 29), and altered glycosylation may change the plasma half-life of TSH (12). In addition, α-subunit levels are 14 times higher in euthyroid ESRD patients than in healthy euthyroid subjects, while TSH and α-subunit response to exogenous TRH are normal or impaired (30). *In vitro* bioactivity of extracted TSH determined by cAMP release from cultured rat thyroid (FRTL-5) cells (detection limit of 1.0 mU/liter) was highly correlated with immunoreactive TSH in both hemodialyzed ESRD patients and normal subjects (31) (Fig. 2). However, in patients with central hypothyroidism, *in vitro* bioactivity of TSH is normal while *in vivo* bioactivity, as determined by the ratio of increments in serum T_3 to those in serum TSH after TRH, are reduced (12) (Fig. 3). *In vivo* bioactivity of TSH in ESRD patients may also be reduced since the ratio of increases in serum T_3 to those in serum TSH after TRH are only 46% of the normal ratio (18).

B. T_4

Serum total T_4 concentrations, T_4 binding to serum carrier proteins, and serum free T_4 estimates by some methods may be reduced in euthyroid patients with ESRD, as they are in other nonthyroidal illnesses, despite normal T_4 production rates (Table 1). Total T_4 and free T_4 index values were decreased in 21% and 13%, respectively, of 287 euthyroid ESRD patients, unrelated to presence or duration of dialysis therapy (3). Serum albumin levels were significantly lower in dialysis patients with subnormal than in those with normal total T_4 concentrations (3). Serum albumin levels correlate with morbidity and mortality in ESRD patients receiving hemodialysis or chronic ambulatory peritoneal dialysis (CAPD) therapy (1, 4, 5), suggesting reduced total T_4 values may relate to severity of malnutrition and nonthyroidal illness in ESRD patients, as in nonrenal nonthyroidal illnesses (17, 23).

Low total T_4 values in ESRD patients are primarily related to impaired T_4 binding to serum carrier proteins (Table 1). Free fractions of T_4 by tracer equilibrium dialysis are normal (32, 33) or increased in ESRD patients (34), T_4-binding globulin (TBG) concentrations are normal (33–38) or increased (32, 39), and transthyretin concentrations are normal (34), while serum albumin levels may be reduced (32, 34, 35). Inhibitors of T_4 binding to serum carrier proteins in euthyroid uremic patients may include elevated serum levels of 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF), indoxyl sulfate, and hippuric acid in uremic serum (17, 40), as well as increased serum levels of interleukin-1β (IL-1β), tumor necrosis factor (TNF-α), and their respective specific inhibitors (41). In nonuremic patients, elevated levels of oleic acid (42), interleukin-6 (IL-6) (43), and TNF-α (44) may reduce T_4 binding to serum carrier proteins, as may elevated bilirubin and nonesterified fatty acids in association with hypoalbuminemia in hepatic failure (45). In addition, exogenous inhibitors of T_4 binding to serum carrier proteins, such as furosemide, nonsteroidal antiinflammatory drugs, and heparin, may play a role (46). Sera from sick patients also inhibit *in vitro* T_4 binding to solid matrices in assays (47), with T_4 binding to charcoal matrix being impaired to a greater

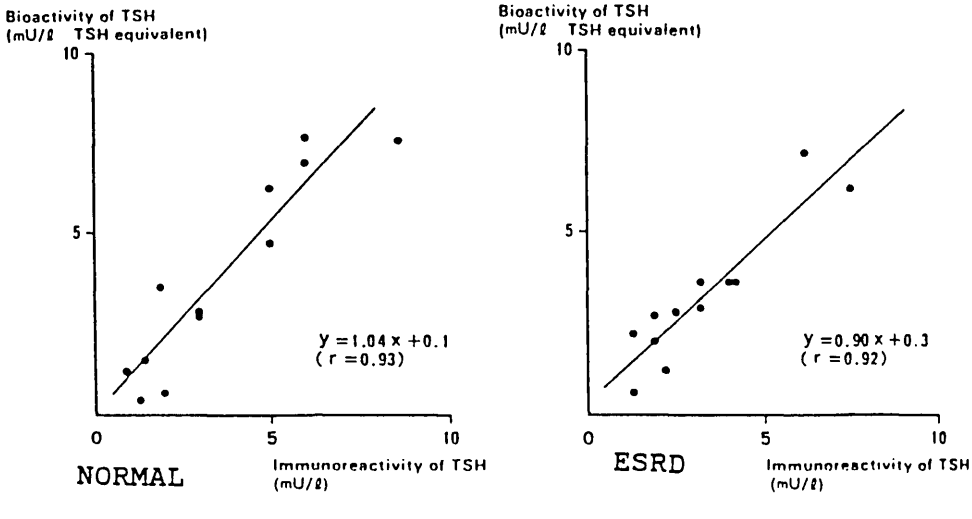

FIG. 2. Relationship between bioactivity and immunoreactivity of TSH in normal subjects and in ESRD patients. [Reproduced with permission from M. Horimoto *et al.*: *Acta Endocrinol (Copenh)* 121:191–196, 1989 (31).]

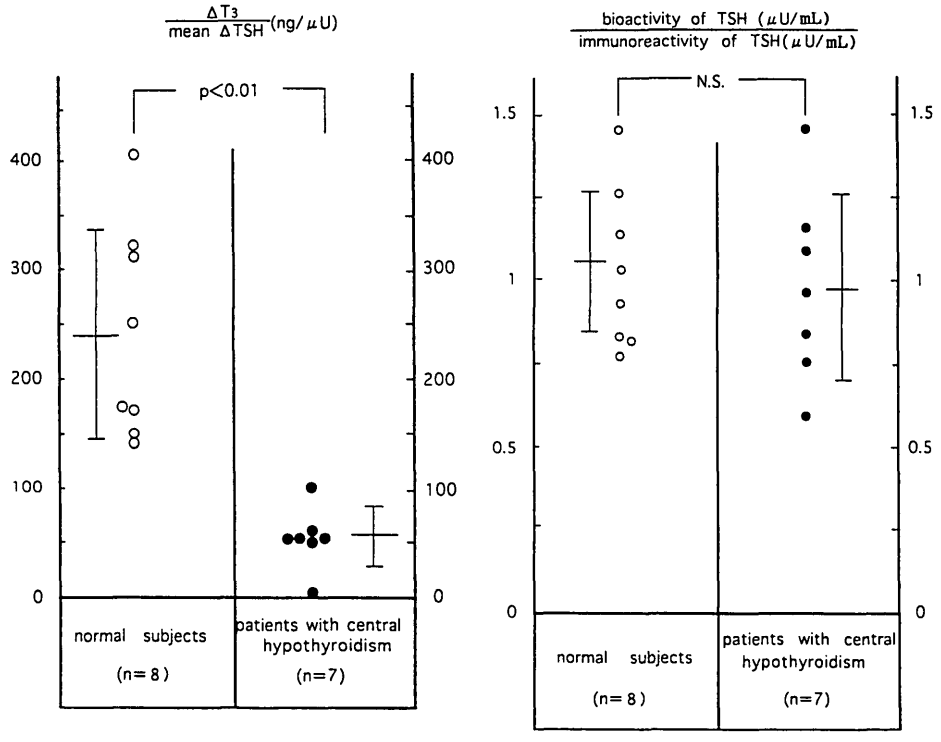

FIG. 3. *Left, In vivo* bioactivity of TSH determined as ratios of serum T_3 increases to mean serum TSH increases 30, 60, and 90 min after exogenous TRH administration in normal subjects and in patients with central hypothyroidism. *Right*, Ratios of *in vitro* TSH bioactivity to TSH immunoactivity in normal subjects and in patients with central hypothyroidism. N.S., Nonsignificant. [Reproduced with permission from M. Horimoto *et al.*: *J Clin Endocrinol Metab* 80:1124–1128, 1995 (12). © The Endocrine Society.]

extent than T_3 binding (48). The latter may partially explain the high frequency of reduced free T_4 index values, determined using T_3 tracer binding to an *in vitro* matrix, in sera from patients with nonthyroidal illnesses including ESRD (3).

In addition to inhibiting T_4 binding to serum carrier proteins, CMPF, hippuric acid, and indoxyl sulfate in uremic sera and bilirubin and nonesterified fatty acids in nonuremic sera inhibit T_4 uptake by rat hepatocytes *in vitro* (17, 40, 45, 49). Circulating inhibitors from sera of other sick patients also interfere with uptake of T_4 by rat hepatocytes (47) and cultured human hepatoma cells (50). *In vivo*, these findings may correspond to reduced fractional rates of T_4 transport from serum to tissues in ESRD, nonrenal illnesses, and caloric deprivation (11, 23) (Table 2).

When serum protein-binding capacity and/or affinity for thyroid hormones is altered, total but not free thyroid hormone levels are affected during steady-state conditions. Circulating free T_4 concentrations are most likely to be normal in euthyroid ESRD patients since T_4 production rates (23, 25, 32, 34) and rT_3 production rates from T_4 are normal in these patients (23, 32, 34), as in nonrenal nonthyroidal illnesses (23) (Table 2). In contrast, serum free T_4 estimates by all methods as well as T_4 and rT_3 production from T_4 are reduced in patients with hypothyroidism (23) (Table 2).

A variety of *in vitro* methods are available to estimate free

TABLE 2. Thyroid hormone metabolism in thyroidal and nonthyroidal disorders

	T_4				T_3				rT_3			
	Binding capacity	FTR	PR	MCR	Binding Capacity	FTR	PR	MCR	Binding capacity	FTR	PR	MCR
High TT_4 state of NTI	N, D	D	N, D	D	N, D	–	D	N	N, D	–	N	D
High TBG states	I	D	N	D	I	–	N	D	I	–	N	D
Hyperthyroidism	N, D	I	I	I	?N, D	–	I	I	?N, D	–	I	I
Normal TT_4 state												
of nonrenal NTI	N, D	D	N	N	N, D	N, D	D	N, D	N, D	N, D	N	D
of ESRD	N, D	D	N	N	?N, D	–	D	N, D	N, D	I	N	N, I
Low TT_4 state												
of nonrenal NTI	D	D	N, D	I	D	D	D	I	D	D	N	D
of ESRD	D	–	N	I	D	–	D	N	D	I	N	N, I
Low TBG states	D	I	N	I	D	–	N	I	D	–	N	I
Primary hypothyroidism	I	–	D	N, D	?I	–	D	D	?I	–	D	D

FTR, Relative fractional transfer rates of hormone from serum to extravascular sites; PR, production rates; ?, most likely but no data, –, no data. [Adapted from E. M. Kaptein: Thyroid hormone metabolism in illness. In: Hennemann G. (ed) Thyroid Hormone Metabolism, Basic and Clinical Endocrinology Series, Volume 8, Marcel-Dekker Inc., New York, NY, vol 8:297–333, 1986; (23) and E. M. Kaptein *et al.*: Thyroid hormone metabolism: a comparative evaluation. In: Ferguson DC (ed) The Veterinary Clinics of North America: Small Animal Practice: Thyroid Disorders, WB Saunders, Philadelphia, vol 24:431–466, 1994 (128).]

T_4 values in serum; however, in patients with nonthyroidal illnesses their performance varies (51). Direct equilibrium dialysis, tracer equilibrium dialysis, and ultrafiltration methods use minimally diluted serum and separate free from bound T_4 across a semipermeable membrane; the direct equilibrium dialysis method is commercially available. Free T_4 index methods correct total T_4 values directly or indirectly for altered serum concentrations of TBG. Immunoextraction or RIA methods estimate free T_4 by either a T_4 analog or two-step-back-titration with a solid phase T_4 antibody, without use of semipermeable membranes to separate free from bound hormone. By design, all free T_4 methods provide normal values for healthy euthyroid subjects with modestly increased or decreased TBG concentrations (low levels in hypothyroidism and high values in hyperthyroidism) in otherwise well patients (51). However, in patients with significant reductions of serum T_4 binding to serum carrier proteins, such as in nonthyroidal illnesses, all but the direct equilibrium dialysis method may provide spurious results (51).

Free T_4 immunoassays depend upon serum protein-bound T_4 dissociation to stabilize free T_4 concentrations during assay perturbations (52). Consequently, reduced protein-bound T_4, induced by severe nonthyroidal illnesses, may result in inappropriately low serum free T_4 estimates (52). Underestimation of free T_4 due to protein-bound T_4 dependence has been demonstrated with a one-step labeled T_4 analog kit (Coat-a-Count, Diagnostic Products Corp., Los Angeles, CA), a one-step labeled T_4 antibody FT_4 kit (Amerlex-MAB, Eastman Kodak, Rochester, NY) and a two-step immunoextraction FT_4 assay kit (Clinical Assays GammaCoat Free T_4 Two-step, Incstar Corp., Stillwater, MN) (52). Free T_4 values paralleled concentrations of protein-bound T_4 in these nondialysis methods (52). As expected, free T_4 levels determined by direct equilibrium dialysis are minimally dependent upon protein-bound T_4 concentrations (52) and are normal or elevated in 96% of patients with severe nonthyroidal illnesses who have reduced serum total T_4 concentrations (53).

When compared with direct equilibrium dialysis, tracer equilibrium dialysis overestimates the free fraction of T_4 and free T_4 values in sera from normal and pregnant patients but not from patients with TBG deficiency or with the low total T_4 state of nonthyroidal illnesses, due to TBG and protein-bound T_4 dependency of the tracer equilibrium dialysis method (54). As a result, free T_4 values are lower than normal in severely ill patients with nonthyroidal illnesses when determined by tracer equilibrium dialysis but normal by direct equilibrium dialysis (54).

In vitro sequestration of free T_4, independent of serum-protein T_4 binding, occurs to a major extent in nondialysis free T_4 immunoassay methods (Clinical Assays GammaCoat Free T_4 Two-Step, Incstar; Stratus II Free T_4, Baxter Diagnostics, Deerfield, IL; AxSym Free T_4, Abbott Laboratories, Abbott Park, IL; IMx System Free T_4, Abbott Laboratories; Clinical Assays GammaCoat Free T_4 Direct One-Step, Incstar; ACS Free T_4, Ciba Corning Diagnostics Corp., Medfield MA; and Coat-a-Count Free T_4, Diagnostic Products Corp.) (55). In these free T_4 methods, T_4 is bound by high capacity, low affinity adsorption sites on solid surfaces, on proteins including T_4 antibodies, and on other materials in the assay that compete for the label (55). T_4 sequestration accounts for 26–99% of actual free T_4 required to obtain expected free T_4 measurements in standard solutions in nondialysis assays, contributing to the underestimation of free T_4 concentrations in low total T_4 states of nonthyroidal illnesses (55). T_4 sequestration also occurs in the direct equilibrium dialysis free T_4 assay during the dialysis procedure, due to T_4 adsorption onto solid surfaces, but to a much lesser extent than for the immunoassays (55). This *in vitro* sequestration in the direct equilibrium dialysis free T_4 method may account for the reduced free T_4 values by the direct equilibrium method in 4% of patients with the low total T_4 state of severe nonthyroidal illness (53).

In ESRD patients, serum free T_4 estimate values are method dependent, as in nonrenal nonthyroidal illnesses (51, 53). Circulating free T_4 levels were normal in 87–97% of euthyroid patients with ESRD by tracer equilibrium dialysis (32, 34, 56, 57), in all 21 patients by SPAC-ET FT_4 RIA kit method (BYK-Sangtec, Dietzenbach, Germany) (40), and in 79–97% of ESRD patients by Liso-phase free T_4 method (Lepetit-Sclavo, Milan, Italy) which utilizes column adsorption chromatography of free T_4 followed by T_4 RIA in the eluate (25, 58). Total T_4 concentrations were reduced in 24–83% of these ESRD patients (34, 56–58), or mean total T_4 values were normal (32) or reduced to 55–70% of normal mean values (25, 40). In contrast, free T_4 estimates were frequently decreased in sera from ESRD patients using free T_4 index (21–59% low) (3, 57), immunophase (75%) (57), or liquisol (31%) (57) methods, in association with reduced total T_4 levels in 31%-41% of these patients (3, 57). Normal *in vivo* production rates of T_4 (23, 34, 51) and of rT_3 from T_4 (23, 34, 51) in euthyroid ESRD patients (Table 2) indicate that circulating free T_4 levels are normal and low free T_4 estimates by some free T_4 methods are spurious.

In nonrenal nonthyroidal illnesses, free T_4 values by direct equilibrium dialysis, SPAC-ET free T_4 RIA kit (BYK-Sangtec, Dietzenbach, Germany), and Amerlite MAB free T_4 luminometric assay (Kodak Clinical Diagnostics Ltd., Cardiff, Wales, UK), were normal in 96–100% of euthyroid patients with low total T_4 levels, while free T_4 values determined by tracer equilibrium dialysis methods were only normal in 70–81% (53). Other free T_4 methods provided low free T_4 values in 10–100% of euthyroid sick patients with reduced total T_4 concentrations (53); for example, free T_4 index values were reduced in 50–80% (53). In the general population, free T_4 index values are reduced as frequently due to nonthyroidal illnesses (0.2–1.1%) as to primary hypothyroidism (0.6%-1.1%) (10), while in ESRD patients free T_4 index values are reduced more often due to nonthyroidal illness (20–33%) than to hypothyroidism (3%-8%) (3). Thus, interpretation of free T_4 values in sick patients requires knowledge of performance of a given free T_4 method in nonthyroidal illness to avoid misdiagnosis and inappropriate treatment.

In the general population, transiently elevated free T_4 index values without thyroid disease occur as frequently (0.2–0.9%) as hyperthyroidism (0.3%-0.5%) (10) and are associated with mild nonthyroidal illnesses and acute psychiatric disorders (23). Euthyroid ESRD patients rarely have elevated

total T_4, free T_4 index, free T_4 by tracer equilibrium (3, 32, 34, 59), or SPAC-ET methods (40), due to the severity of their nonthyroidal illnesses and malnutrition (23). In euthyroid patients with nonrenal nonthyroidal illnesses and normal total T_4 concentrations, free T_4 values by direct or tracer equilibrium dialysis methods, ultrafiltration methods, SPAC-ET free T_4 RIA kit (BYK-Sangtec, Dietzenbach, Germany), Amerlite MAB free T_4 luminometric assay (Kodak Clinical Diagnostics Ltd), Abbott TDX (Abbott Laboratories), and Clinical Assays 2-step methods (Incstar) were elevated in 24–56% (53). These elevated free T_4 values may relate to decreased T_4 clearance rates since T_4 production rates are normal or reduced (23) (Table 2). In contrast, serum total and free T_4 values are elevated in hyperthyroidism secondary to increased T_4 production rates by the thyroid gland or to excess thyroid hormone administration (Table 2).

C. T_3

Total and free T_3 concentrations are frequently reduced in patients with ESRD, as in other nonthyroidal illnesses (3, 20, 23) (Table 1). Of 287 euthyroid patients with ESRD, 76% had total T_3 levels below 100 ng/dl, and 66% had free T_3 index values under 100 (3). Reduced T_3 levels are due to decreased peripheral tissue conversion of T_4 to T_3, while thyroid gland production of T_3 is normal and T_3 clearance rates are normal or decreased, as in other nonthyroidal illnesses (19, 20, 23).

Impaired conversion of T_4 to T_3 may relate to concurrent nonthyroidal illnesses, malnutrition, and humoral factors including cytokines. Direct correlations between total T_3 and both serum albumin ($r = 0.57$) and transferrin ($r = 0.54$) levels in ESRD patients (3) support a role for malnutrition. CMPF, hippuric acid, and indoxyl sulfate in uremic human sera and bilirubin and nonesterified fatty acids in nonuremic human sera inhibit T_4 uptake and subsequent deiodination of T_4 by rat hepatocytes *in vitro* and may reduce T_3 production from T_4 *in vivo* (17, 40, 45, 49). Plasma levels of IL-1β, TNF-α, and their specific inhibitors are elevated in both undialyzed and dialyzed ESRD patients (41). In hospitalized patients, serum total T_3 levels correlate inversely with serum IL-6, free fatty acid-albumin ratios, and bilirubin-albumin ratios (43) and with TNF levels in nursing home residents (60). Further, TNF given to healthy subjects decreases serum T_3 and TSH levels and increases rT_3 levels (61).

Although T_3 is the most metabolically active thyroid hormone, ESRD patients with reduced serum free T_3 concentrations are clinically euthyroid (56). Tissue effects of T_3 are mediated by T_3 nuclear receptor proteins, which are encoded by c-*erb*-A α- and β-genes (62). In 12 euthyroid ESRD patients, six on hemodialysis and six on CAPD therapy, c-*erb*-A α and β mRNA levels in peripheral mononuclear cells were increased 9.5- and 12.5-fold, respectively, compared with normal subjects (62) (Fig. 4). In euthyroid chronic liver disease patients, c-*erb*-A α and β mRNA concentrations were increased 3- and 5-fold, respectively, in peripheral mononuclear cells, and 20- and 5.5-fold, respectively, in liver tissue (62) (Fig. 4). After liver transplantation, c-*erb*-A α mRNA levels were normal in peripheral mononuclear cells but elevated in posttransplant liver tissue compared with donor liver samples (62) (Fig. 4). In euthyroid critically ill patients,

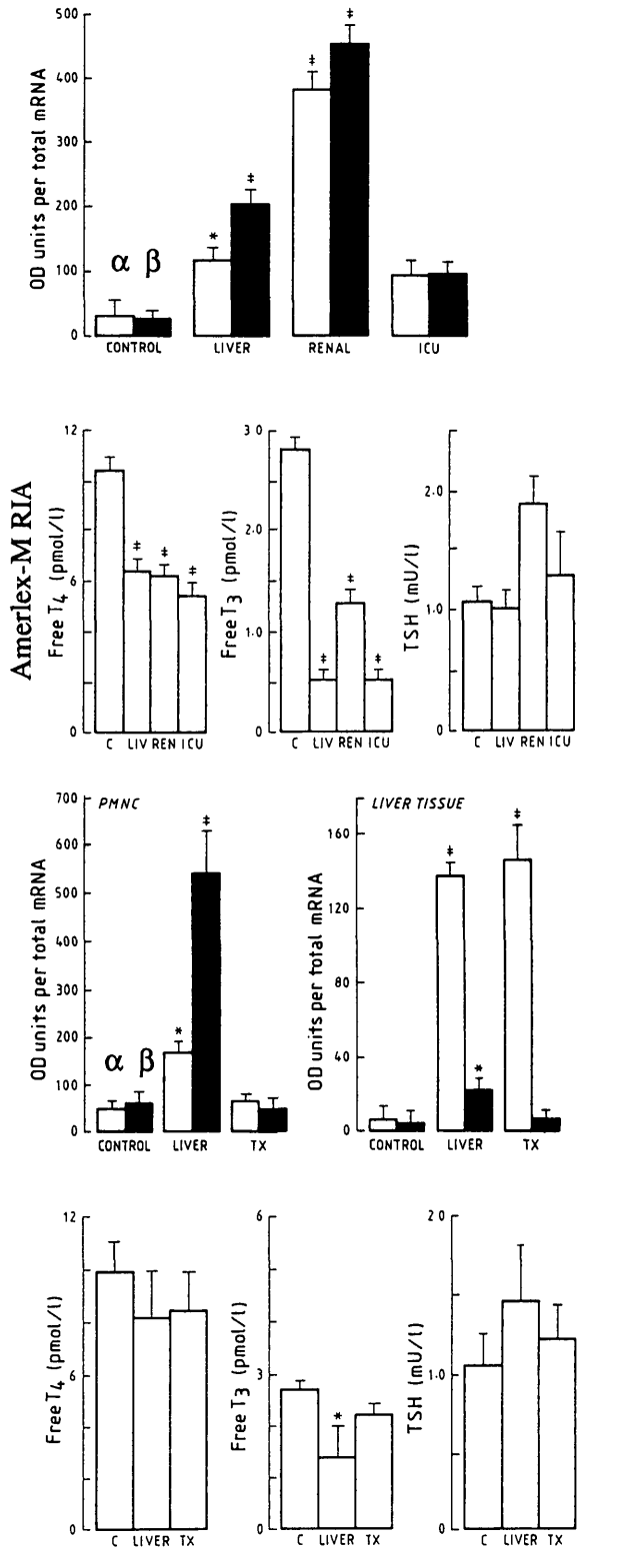

FIG. 4. *Top*, Thyroid hormone receptor mRNA levels in polymorphonuclear cells (PMNC), and serum free T_4, free T_3, and TSH values in control subjects and patients with chronic liver disease, chronic renal disease, or from intensive care unit (ICU). *Bottom*, Thyroid hormone receptor mRNA levels in PMNC and liver tissue, and serum free T_4, free T_3, and TSH values in control subjects and patients with chronic liver disease and post-liver transplantation (Tx). [Adapted with permission from G. R. Williams *et al.*: *Lancet* 2:1477–1481, 1989 (62). © The Lancet Ltd.]

only c-*erb*-A β mRNA was increased 2.3-fold (62). In patients with nonthyroidal illnesses, an increased synthesis of T_3 receptor in the face of reduced serum free T_3 levels was postulated to maintain a euthyroid status in target tissues, which may be tissue specific (62). In uremic rats, nuclear T_3 content was reduced in liver but unaltered in the pituitary gland, indicating tissue heterogeneity (63) and perhaps species differences.

D. rT_3

Patients with ESRD have normal total serum rT_3 levels rather than the elevated values observed in most nonrenal nonthyroidal disorders (20, 23, 32, 34) (Table 1). In ESRD, normal serum total rT_3 levels are associated with elevated free rT_3 concentrations, due to reduced free rT_3 clearance rates (23, 32). In addition, ESRD patients have normal total rT_3 clearance rates and rT_3 production rates from T_4, increased rT_3 fractional transfer rates from serum to tissue sites, and enhanced tissue rT_3 binding, suggesting a shift of rT_3 from vascular to extravascular sites (23, 32, 34) (Table 2). In contrast, patients with nonrenal nonthyroidal disorders and elevated total and free serum rT_3 levels have reduced serum total and free clearance rates (20, 23) (Table 2). Although serum total rT_3 levels are also normal with decreased serum T_3 concentrations in patients with acute renal failure, nephrotic syndrome with normal glomerular filtration rates, and primary hyperparathyroidism, alterations in rT_3 production, clearance, transfer, and tissue hormone binding differ among these disorders (11). In contrast, in hypothyroidism, rT_3 production from T_4 is reduced in association with low serum clearance rates (64) (Table 2). The clinical significance of these differences remains to be defined.

III. Effects of Therapy in Chronic Renal Failure

Medical therapy in ESRD patients may alter thyroid hormone metabolism. Treatment for uremia in ESRD includes hemodialysis in 56%, functioning renal transplants in 28%, and home peritoneal dialysis in 9% (2). In addition, effects of erythropoietin for treatment of anemia and of zinc and thyroid hormone replacement therapy will be discussed.

A. Dialysis

Dialysis therapy, as currently prescribed in the United States, does not significantly normalize thyroid hormone metabolism in ESRD patients. In 306 ESRD patients, serum total T_4 and T_3, free T_4 and free T_3 index, and TSH values were similar in nondialyzed patients and those receiving an average of 9 h of hemodialysis weekly (3) and were not altered by chronicity of hemodialysis therapy (3, 39). In contrast, in an Australian study (65), serum total T_4 and total T_3 concentrations were higher in patients receiving 27 h of hemodialysis per week than in those receiving 18 or 15 h per week, and total T_4 and T_3 levels correlated inversely with serum creatinine values in blood taken immediately before a dialysis treatment. Further, serum total T_4, free T_4 index, total T_3, TBG, and TSH levels, and TSH responses to TRH were similar in patients undergoing CAPD and hemodialysis therapy (58, 66–68), while serum TBG and albumin concentrations were lower in the CAPD patients (58), due to ongoing peritoneal losses.

B. Erythropoietin

ESRD patients frequently have anemia, primarily due to erythropoietin deficiency, and correction of anemia with recombinant erythropoietin reverses some of the endocrine alterations (22). In ESRD patients on maintenance hemodialysis therapy, blunted serum TSH responses to exogenous TRH normalized after correction of anemia with erythropoietin, while serum total T_4 and free T_4 and free T_3 (Amersham, Arlington Heights, IL) responses remained blunted (22) (Fig. 5). Anemia may induce relative tissue hypoxia, which decreases pituitary responsiveness to TRH, and is reversed by erythropoietin, or erythropoietin could have a direct trophic effect (22).

C. Zinc

Patients with renal failure commonly have zinc deficiency, which in turn has been associated with decreased serum T_4

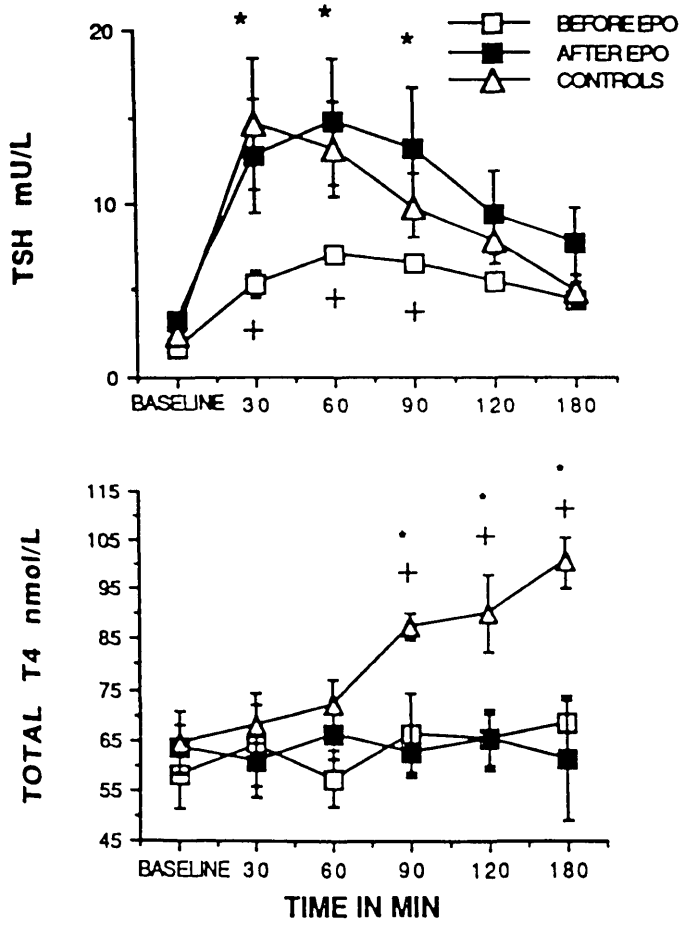

FIG. 5. Effects of correction of anemia with erythropoietin (EPO) on TSH and total T_4 responses to TRH in hemodialysis patients compared with normal volunteers. *, $P < 0.05$, post-TRH *vs.* baseline; +, $P < 0.05$, pre- and post-TRH patients compared with controls. [Reproduced with permission from G. Ramirez *et al.*: *J Clin Endocrinol Metab* 74:517–524, 1992 (22). © The Endocrine Society.]

and T_3 concentrations as well as blunted TSH response to TRH (38). Zinc supplementation to eight ESRD patients receiving intermittent peritoneal dialysis therapy increased low basal serum zinc levels toward normal, in association with normalization of serum total T_4 and T_3 concentrations (38) (Fig. 6). Changes in TSH, T_4, and T_3 values correlated directly with changes in serum zinc levels (38) (Fig. 6).

D. Thyroid hormone therapy

Decreased T_3 production from T_4 in ESRD may provide metabolic adaptation for energy conservation, as in nonrenal nonthyroidal illnesses and caloric deprivation (17, 20, 68, 69). Catabolism of protein stores, as indicated by increased nitrogen excretion and negative nitrogen balance, were induced by administration of near-physiological quantities of T_3 (50 μg/day for 9 days) to ESRD patients without concurrent thyroid disease (68) (Fig. 7). Conversely, when serum T_3 concentrations were reduced in these patients by Ipodate (1 g/day for 9 days), nitrogen excretion decreased (68) (Fig. 7). Nitrogen balance correlated inversely with serum total T_3 concentrations in these ESRD patients but not in control subjects (68) (Fig. 7). These findings indicate that thyroid hormone therapy should be reserved for ESRD patients with documented hypothyroidism (17, 69).

E. Renal transplantation

After successful renal transplantation, serum thyroid hormone levels may be affected by glucocorticoids, other pharmacological agents, and concurrent nonthyroidal disorders such as infections (20). In 11 patients treated with azathioprine and prednisone (unspecified dose) 6 months after successful renal transplantation, reduced serum total T_3 concentrations, T_3 production rates, and T_4 to T_3 conversion rates returned to normal (19). In 18 renal transplant patients, 24 months or more after renal function was stable on azathioprine, low dose prednisone (10 mg/day), and cyclosporine A, serum thyroid hormone levels were not different from normal; however, serum T_3 values correlated inversely ($r = -0.61$) with the prednisone dose (70). In 36 ESRD patients receiving prednisolone (15 mg/day) and azathioprine 2 to 98

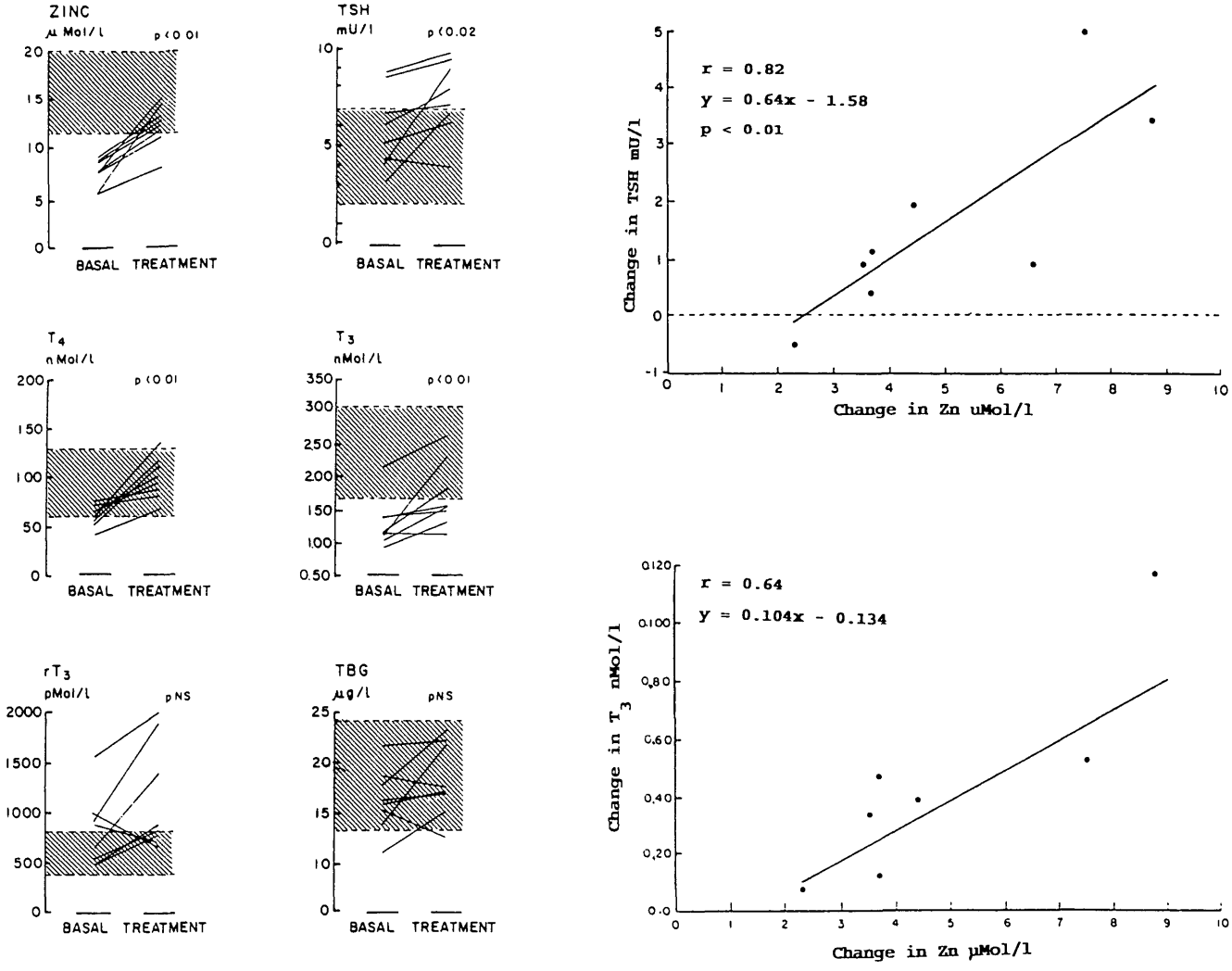

FIG. 6. *Left*, Serum thyroid hormone levels before and after 4 weeks of zinc therapy. ESRD patients received 28 peritoneal dialysis exchanges per week. *Right*, Correlation between changes in plasma levels of TSH, T_3, and zinc after 4 weeks of zinc therapy. [Reproduced with permission from F. Arreola *et al.*: *Horm Metab Res* 25:539–542, 1993 (38).]

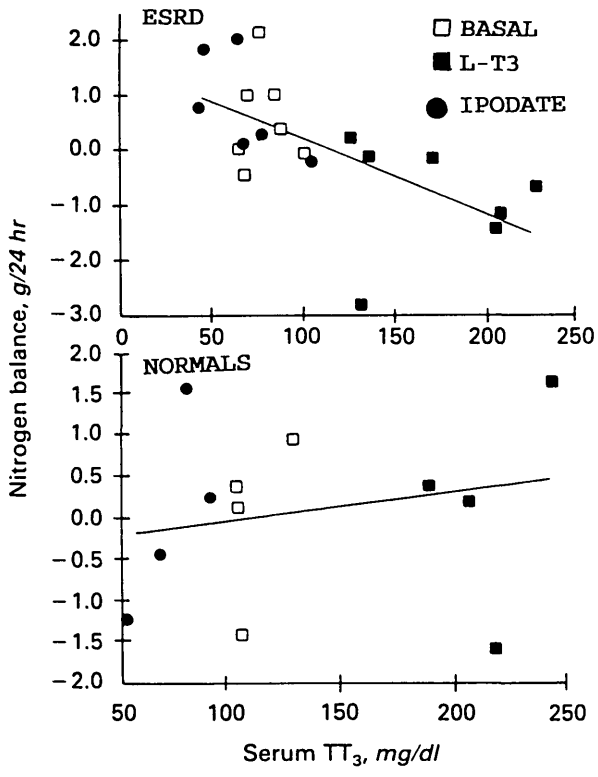

FIG. 7. Nitrogen balance in ESRD patients and normal subjects before (*open squares*) and after administration of L-T_3 (*closed squares*) or ipodate (*closed circles*). [Reproduced with permission from Blackwell Science, Inc., V. S. Lim *et al.*: *Kidney Int* 28:541–549, 1985 (68).]

months after renal transplantation, basal TSH values were normal, while TSH responses to TRH remained blunted in 12 patients (71). Patients with normal TSH response to TRH had normal serum total T_4 values, while total T_3 levels were reduced to 85% of normal, and those with blunted TSH response to TRH had total T_4 and T_3 concentrations reduced to 90% and 77% of normal, respectively (71). In these patients, TSH response to TRH and serum total T_3 values correlated inversely with prednisolone dose (71). In 10 ESRD patients studied before, and 1, 3, and 6 months after renal transplantation, serum total T_4 and T_3 concentrations were in the normal range before transplantation, followed by decreased total T_4 values to 59% of baseline at 1 month, 72% at 3 months, and 83% at 6 months and reduced total T_3 values to 64%, 88%, and 100% of baseline values, respectively, after transplantation (72). All patients received immunosuppressive therapy with cyclosporine A and azathioprine, while prednisone was tapered from 60 mg/day to 10 mg/day (72). In normal subjects, short-term administration of large doses of glucocorticoids (dexamethasone 2–8 mg/day or prednisolone 60 mg/day) suppresses the hypothalamic-pituitary-thyroid axis and reduces serum T_3 levels, by impairing T_4 to T_3 conversion (73–77), with changes being dose-dependent (78). Thus, low dose prednisone (10 mg/day) therapy in stable renal transplant recipients minimally affects T_4 to T_3 conversion or serum T_3 concentrations, while higher doses significantly change thyroid hormone metabolism.

IV. Inorganic Iodide Metabolism in Chronic Renal Failure

Iodide removal from the body occurs primarily by renal excretion (79). Urinary Na ^{131}I clearance rates are 25–35% of creatinine clearance rates in subjects with normal renal function (79–82) (Table 3). In patients with severe renal insufficiency (mean creatinine clearance rates of 4–11 ml/min), Na ^{131}I clearance rates average 50–57% of creatinine clearance rates (79, 80). However, with creatinine clearance rates below 6.3 ml/min, Na^{131}I clearance rates may exceed creatinine clearance rates (80). In subjects with normal renal function, 56% of a 10-mg iodide load is excreted in 24 h, compared with 11% excretion in patients with renal insufficiency (creatinine clearances <44 ml/min) (83).

Serum inorganic iodide levels are increased 4 to 9 times normal in ESRD patients, despite decreased dietary iodide intake, due to reduced renal excretion of iodide (<5 ml/min) (18, 79, 80). After dietary iodide restriction for 2–15 weeks in patients with creatinine clearance rates from 5–44 ml/min, serum iodide levels were still 3.5 times normal (83). Although inorganic iodide is removed by all forms of dialysis, serum iodide levels were elevated in 84% of patients receiving maintenance hemodialysis and in 92% of patients receiving CAPD therapy (84). Elevated serum iodide levels in some dialyzed ESRD patients may relate to ongoing use of povidone-iodine for disinfecting shunt and catheter sites. However, discontinuation of povidone-iodine for 3 months decreased serum iodide levels only modestly in CAPD patients and did not change serum iodide levels in hemodialysis patients (84). Thus, iodide from dietary and percutaneous

TABLE 3. Iodide clearance rates by dialysis in ESRD patients

	Duration of therapy (h/week)	Time per week (%)	Creatinine clearance (liters/week)	Iodide clearance (% of normal GFR)		Hours between ^{131}I and dialysis	Effective iodide half-life (h)
				Dialysis	Kidneys		
Normal	NA	NA	1008	NA	25–35	NA	8–10
HD	9–12	5–7	129	154	<5	0	20
						48	47
CIPD	36–48	21–29	–	25–35	<5	0	8–10
						168	>50
CCPD	56–70	33–42%	56	–	<5	–	–
CAPD	168	100	72	–	<5	0	60

HD, Chronic hemodialysis; CIPD, chronic intermittent peritoneal dialysis, consisting of 40 peritoneal fluid exchanges every 5 to 7 days; CCPD, chronic automatic nightly peritoneal dialysis; CAPD, Chronic ambulatory peritoneal dialysis consisting of four to six peritoneal fluid exchanges per day. NA, Not applicable; –, no data available.

sources frequently exceeds iodide removal by dialysis and residual renal function in ESRD patients. Increased total body inorganic iodide may induce goiter formation and/or reversible hypothyroidism in ESRD patients who cannot escape from the inhibition of iodide organification induced by iodide excess (the Wolff-Chaikoff effect) (83, 85–87).

Na ^{131}I clearance rates in ESRD patients depend upon the type, duration, and frequency of dialysis therapy, and, with intermittent dialysis, the interval between Na ^{131}I administration and the next dialysis procedure (Table 3). Clearance rates of Na ^{131}I during hemodialysis therapy average 154 ml/min (81, 88) compared with normal renal clearance rates of 25–35 ml/min (79–82) (Table 3). However, most ESRD patients only receive 3–4 h of hemodialysis therapy three times a week, resulting in rapid Na ^{131}I clearance by dialysis for only 5–7% of each week (Table 3). Na ^{131}I half-life between hemodialysis treatments depends upon residual renal function, resulting in Na ^{131}I clearance rates of less than 5 ml/min (82, 88) (Fig. 8). Due to rapid Na ^{131}I clearance during hemodialysis, effective Na ^{131}I half-life depends upon the interval between Na ^{131}I administration and the first hemodialysis procedure, being 20 h when hemodialysis was initiated immediately after the dosage (Fig. 8) and 47 h when hemodialysis was delayed 48 h (88), compared with an 8–10 h Na ^{131}I half-life in subjects with normal renal function (89, 90) (Table 3). Indeed, effective half-life of Na ^{131}I in a thyroid cancer patient was predicted to be 2½ times normal if the first 10 h hemodialysis was given 24 h after the dosage, and 4½ times normal if dialysis was delayed for 48 h (91). Data defining Na ^{131}I clearance rates by current hemodialysis techniques are limited to three case reports and require further definition to more accurately establish dosage guidelines.

Na ^{131}I clearance rates during 40 consecutive peritoneal dialysis exchanges were similar to normal renal iodide clearance rates (92). However, with chronic intermittent dialysis therapy, peritoneal dialysis removal of iodide only occurs for 36–48 h every 7 days, accounting for 21–29% of the total week (Table 3). Thus, Na ^{131}I removal rates would only be normal if ESRD patients received the radioiodide dosage immediately before peritoneal dialysis therapy. If the Na ^{131}I dosage were administered immediately after chronic intermittent peritoneal dialysis therapy, to minimize radiation exposure to personnel and limit cost, effective radioiodide half-life would be proportional to residual renal function, which is minimal in these patients (82, 88) (Table 3). In CAPD patients who received three to four peritoneal dialysis exchanges per day, average serum iodide half-life was 45 h compared to 9.7 h in patients with normal renal function (89). Na ^{131}I clearance data are not available for ESRD patients receiving chronic automatic nightly peritoneal dialysis (CCPD) for 8–10 h per day (33–42% of the week); however, their peritoneal creatinine clearance rates are similar to those of CAPD patients (93) and iodide clearance rates may also be similar (Table 3). Thus, peritoneal clearance rates of Na ^{131}I depend upon frequency and duration of peritoneal fluid exchanges and, in some instances, on the interval between Na ^{131}I dosage and the next dialysis therapy. Peritoneal membrane function and, therefore, iodide clearance rates may also vary among patients and over time.

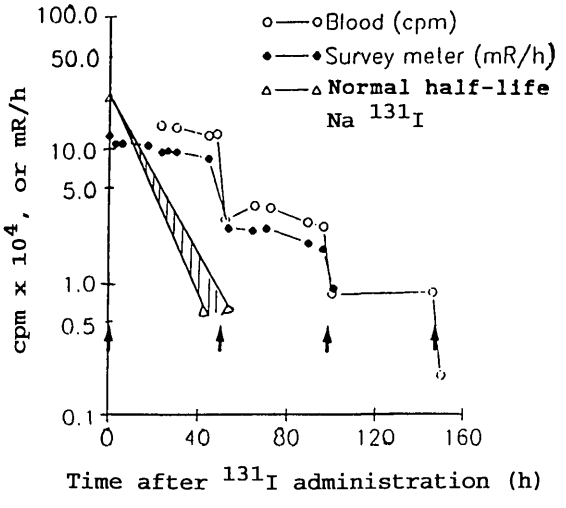

FIG. 8. Whole-body exposure rates (*closed circles*) and radioactivity in blood (*open circles*) after Na ^{131}I administration to an ESRD patient post thyroidectomy for papillary carcinoma. Hemodialysis therapy was given immediately after the dosage and repeated every 48 h as indicated by the *arrows*. The *hatched area* depicts normal serum and total body half-life of Na ^{131}I in subjects with normal renal function (89, 90). [Adapted with permission from D. W. Morrish *et al.*: *Cancer* 66:2509–2513, 1990 (88).]

V. Thyroid Diseases in Chronic Renal Failure and Renal Transplantation

ESRD patients may have a higher frequency of goiter, hypothyroidism, thyroid nodules, and thyroid carcinoma than the general population. The frequency of thyroid diseases in ESRD may be increased by older age, diabetes mellitus, and iodide retention. In 1991, 45% of ESRD patients were over the age of 65 yr, and 33% of ESRD was due to diabetes mellitus (1).

A. Goiter

Goiter prevalence in ESRD patients varies from 0% in Great Britain and Austria to 58% in Utah, suggesting geographic differences (3) (Table 4). Techniques for thyroid examination also play a role, since goiter frequency was 0% by palpation but 60% by ultrasonography in Denmark (3). In Los Angeles, 43% of ESRD patients had palpable goiters compared with 6.5% of hospitalized patients of similar age, gender, and racial background without renal disease (3) (Table 4). Goiter was more frequent (50%) in those receiving hemodialysis for more than 1 yr than in those dialyzed for less than 1 yr or not at all (39%) (3). The female-male ratio was 1.4:1 in ESRD patients with goiters compared with 2.8:1 in the control group, suggesting uremia-related factors may predominate (3). Goiter frequency in ESRD patients did not relate to age, race, diabetes mellitus, TSH or PTH levels, or to antimicrosomal antibody titers (3).

Goiter formation in some ESRD patients may reflect increased serum inorganic iodide levels since iodide excess may block thyroid hormone production in patients with preexisting thyroid gland abnormalities such as Hashimoto's thyroiditis, previously treated Graves' disease, or after hemithyroidectomy, as well as in patients

TABLE 4. Prevalence of goiter and antithyroid antibody titers in ESRD

Location	End-stage renal disease			Control population		
	No.	Goiter (%)	ATA titers (%)	No.	Goiter (%)	ATA titers (%)
Denmark	40	60[a]	7	40	0	–
Utah	53	58	0	–	8	–
California	306	43	7	139	6.5	1.4
Illinois	24	37	0	–	–	10
South Africa	85	32	–	–	–	–
Japan	60	30	–	224	6.7	–
Israel	46	24	–	–	–	–
Switzerland	50	20	–	–	–	–
Belgium	17	12	0	–	–	–
Maryland	38	8	0	–	–	–
Alberta	54	2	13	–	–	–
Great Britain	25	0	–	–	–	–
Austria	107	0	–	–	–	–

Abbreviations: ATA, Positive antithyroid antibody titers: No., number of patients studies. [Adapted from E. M. Kaptein *et al.*: *Medicine* 67:187–197, 1988 (3).]

[a] No thyroid enlargement clinically but increased thyroid gland volume using ultrasonography.

–, No data.

with apparently normal thyroid glands (86, 87). Thyroid gland size decreased significantly after 2–15 weeks of dietary iodine restriction of Japanese patients with reversible primary hypothyroidism due to an iodide organification defect and elevated nonhormonal iodide levels due to renal insufficiency (creatinine clearances from 4.7–43.5 ml/min) (83) (Fig. 9). In contrast, patients in the same study with irreversible hypothyroidism had no change in thyroid gland size after iodine restriction (83). In normal subjects without renal disease, 4 weeks of iodide administration (27 mg daily) increased thyroid gland volume by 16% from 16.5 to 19.1 g, as determined by high resolution ultrasound scanner (Fig. 10) (86). These subjects also had transient decreases in serum free T_4 values (enzyme-linked immunosorbent assay, Amersham, Aylesbury, Buckinghamshire, UK) with increases in mean serum TSH (0.95–2.43 mU/liter) (Fig. 10) and serum thyroglobulin (12.1 to 37.1 μg/liter) (86). These changes most likely reflected

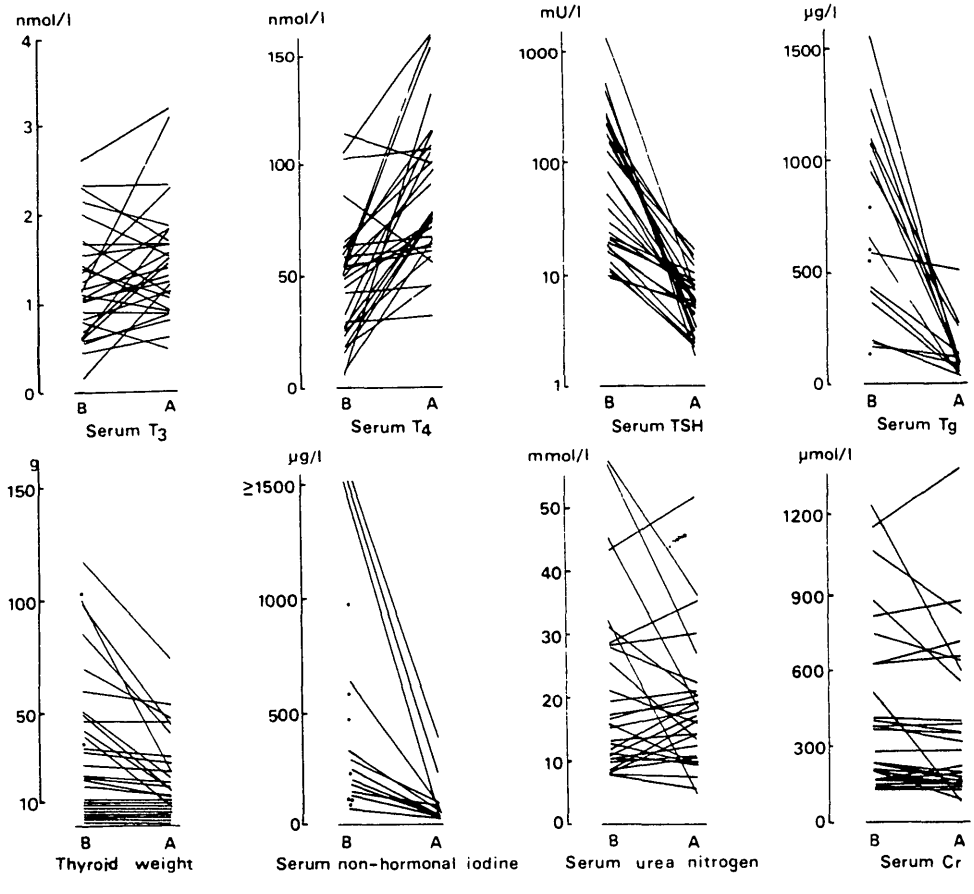

FIG. 9. Changes in renal function, nonhormonal iodide, thyroid weight, and serum thyroid hormone levels during 2–15 weeks of dietary iodide restriction in patients with reversible hypothyroidism and renal dysfunction. [Reproduced with permission from K. Sato *et al.*: *Acta Endocrinol (Copenh)* 126:253–259, 1992 (83).]

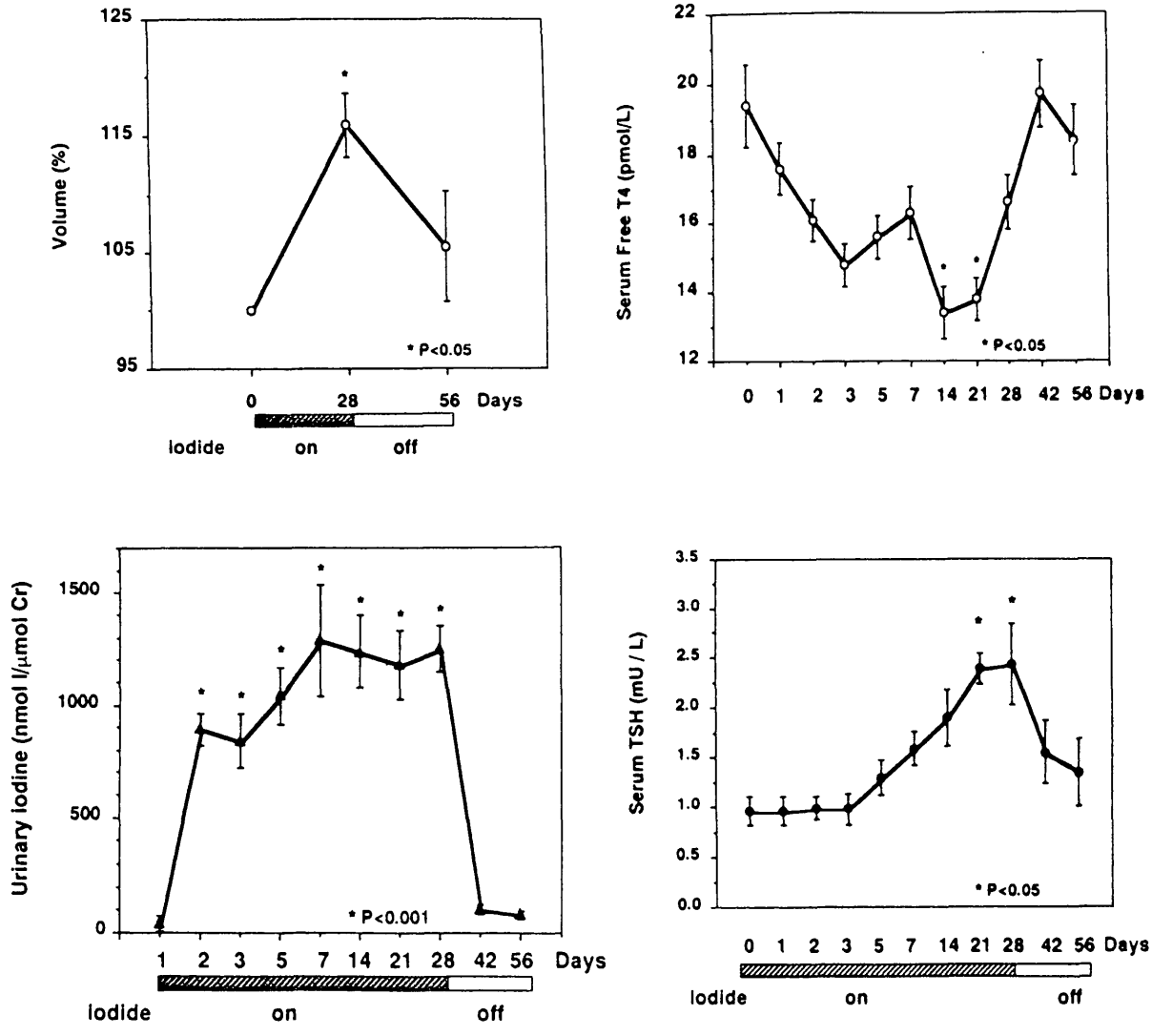

FIG. 10. Thyroid gland volume determined by ultrasound, urinary iodine, and serum free T_4 and TSH before, during, and after iodide administration in 10 normal subjects. [Reproduced with permission from H. Namba *et al.*: *J Clin Endocrinol Metab* 76:605–608, 1993 (86). © The Endocrine Society.]

transient iodide-induced inhibition of thyroid hormone synthesis and release by normal thyroid glands (86).

B. Thyroid nodules

Thyroid nodules in Japanese ESRD patients may be more common than in the general population. Unsuspected thyroid nodules were found at parathyroidectomy in 64% of 11 hemodialyzed ESRD patients with secondary hyperparathyroidism (94). Further, thyroid nodules were present in 55% of 60 hemodialyzed female patients compared with 21% of 224 normal females, by a 10-MHz high frequency sonographic scanner (95). The presence of thyroid nodules did not relate to age, duration of hemodialysis, serum midportion-PTH , or TSH values (95). However, at neck exploration of 351 primary hyperparathyroid patients, 20% had thyroid nodules, of which 47% had prior radiation therapy for benign conditions of the head and neck (96). Thus, secondary hyperparathyroidism in ESRD patients could also play a role.

C. Thyroid carcinoma

Prevalence of thyroid carcinoma in ESRD patients may be increased and may relate to elevated serum PTH levels. Relative risk of thyroid malignancy (type unspecified) in 28,049 chronic dialysis patients in the United States was increased 2.9 times in females but not in males (1.2 times) (97). No risk factors were identified. In 913 renal transplant recipients in the United States with 799 preexisting nonskin cancers, 5.3% were thyroid carcinomas (98) compared with 1.2% in the general population (99). Of these thyroid carcinomas, 64% were papillary, 18% follicular, and 2.6% medullary; 15% were incidental findings during parathyroidectomy, and 7.7% recurred, resulting in one death (98). In the United Kingdom and parts of Europe (EDTA-ERA registry), thyroid cancer frequency was increased about 4–8 times in young female dialysis patients (ages 15–44 yr) and 2 times in older dialysis patients compared with the general population (100).

Thyroid carcinoma was also found in 36% of 11 ESRD patients from Japan with secondary hyperparathyroidism at surgery, compared with 11% in an autopsy control group, and serum C-terminal PTH levels were higher in those with thyroid carcinoma (94). In contrast, only 2.4% of of 123 ESRD patients undergoing surgery for severe secondary hyperpar athyroidism in the United Kingdom had thyroid carcinoma, all of which were papillary in type (101). Interestingly, 4.5% of 351 patients in the United States with primary hyperparathyroidism had thyroid carcinomas at neck exploration, of which 88% were papillary-follicular (96). Elevated PTH levels may have contributed in the 44% of thyroid cancer patients, without prior radiation exposure, who had primary hyperparathyroidism (96), as well as in ESRD patients with secondary hyperparathyroidism.

Risk of malignancy increases linearly with time after renal transplantation and may relate to immunosuppression therapy (102). Of 6353 renal transplant patients in Australia and New Zealand, 33% developed malignancies by 10 yr, 50% by 15 yr, and 60% by 19 yr with most being skin cancers (103). In another Australian study of 5879 patients, probability of developing cancer 20 yr after renal transplantation was 54% for skin cancers, 21% for nonskin cancers, and 63% overall (102).

Renal transplant recipients appear to have an increased frequency of thyroid malignancies. Risk of thyroid carcinoma in patients in Australia and New Zealand with a functioning renal transplant for 10 yr or more was estimated to be increased 322 times (103). In 876 patients in Cincinnati with renal transplants for a median of 49 months, 8.3% of nonskin cancers were papillary-follicular thyroid carcinomas (104), compared with 1.2% in the general population (99). In the Cincinnati Transplant Tumor Registry of 4899 *de novo* nonskin cancers in organ transplant recipients, including 85% with renal transplants, 2.0% were carcinomas of the thyroid (102). In 3468 Japanese renal transplant patients, 13% of malignancies were thyroid carcinoma (105). In the United Kingdom and parts of Europe (EDTA-ERA registry), thyroid cancer frequency was increased about 6.5 times in young female renal transplant recipients (ages 15–34 yr) compared with the general population (100).

When follicular thyroid malignancies are diagnosed, Na ^{131}I ablation of the thyroid remnant and metastases, and TSH suppression with L-T_4 may be required (106). Radiation dose to the thyroid remnant and functioning metastases, and to critical organs like bone marrow, depends upon Na ^{131}I uptake by target tissues and total body half-lives of iodinated compounds (90). Na ^{131}I uptake by the thyroid remnant and metastases may be reduced in ESRD patients due to increased total body iodide (19, 84). Iodide restriction before Na ^{131}I therapy should be attempted. However, stopping povidone-iodine use for 3 months was only modestly effective in CAPD and ineffective in hemodialysis patients (84). After Na ^{131}I administration, the majority of radioactivity in thyroid cancer patients is sodium iodide, even with functioning metastases (107). Effective Na ^{131}I half-life in ESRD patients depends upon residual renal function, type of dialysis, and, with intermittent dialysis, the interval between Na ^{131}I administration and the next dialysis therapy (Table 3) (Fig. 8). In ESRD patients, Na ^{131}I removal by native kidneys plus dialysis therapy is reduced compared with normal, effective total body half-life of Na ^{131}I is increased (Table 3), and, consequently, Na ^{131}I dosages must be decreased in proportion to prolongation of Na ^{131}I half-life to avoid excess radiation exposure to critical organs (106). CAPD patients receiving three to four peritoneal exchanges per day required a decrease in the Na ^{131}I dosage from 150 mCi to less than 30 mCi (89). In patients receiving hemodialysis, contamination of equipment with Na ^{131}I was minimal even after large dosages (88). However, Na ^{131}I should be given 48–72 h before the next hemodialysis (88, 91) to minimize radiation exposure to personnel and allow administration of less than 30 mCi of Na ^{131}I, a dose that can be given as an outpatient (106).

D. Hypothyroidism

Primary hypothyroidism may occur in up to 9.5% of ESRD patients compared with 0.6–1.1% of the general population (3) (Table 5). In Los Angeles, 2.6% of 306 ESRD patients had primary hypothyroidism, characterized by persistently elevated TSH values to above 20 mU/liter and reduced serum total T_4 and free T_4 index values (3). Eighty-eight percent of hypothyroid ESRD patients were female, 75% were over age 50 yr, 50% had elevated antimicrosomal antibody titers, 50% had goiter, and 50% had diabetes mellitus (3). No relationship between hypothyroidism and goiter or elevated antimicrosomal antibody titers was noted. However, nonuremic insulin-dependent diabetics have an increased frequency of elevated antimicrosomal antibody titers (17%), as well as of hypothyroidism (3%), as do the elderly (3, 108) and patients with systemic lupus erythematosus, suggesting an autoimmune component may be present.

Iodide excess may contribute to the increased frequency of hypothyroidism in ESRD patients, particularly those with an iodide organification defect (83, 109), concurrent Hashimoto's thyroiditis, previously treated Graves' disease, or after hemithyroidectomy. Povidone-iodine may induce hypothyroidism in some CAPD patients (110), and Amiodarone, an iodide-rich antiarrhythmic drug, induced reversible hypothyroidism in a hemodialysis patient (111). Further, hypothyroidism was reversed after 2–15 weeks of dietary iodine restriction in 83% of 245 Japanese patients with mild to severe renal dysfunction (creatinine clearances 4.7–43.5 ml/min) and elevated nonhormonal iodine levels, who had a thyroidal iodide organification defect (83) (Fig. 9). In these patients, serum iodide levels fell below 50 μg/liter in 93%, and mean TSH values dropped from 51 mU/liter to 5 mU/liter as total T_4 values rose from 56 nmol/liter to 88 nmol/liter (83) (Fig. 9). Antithyroid antibodies were present in 64% with reversible and 76% with irreversible hypothyroidism, suggesting autoimmune thyroiditis was not a factor (83). Likewise, three Japanese ESRD patients ingesting a high iodide diet had hypothyroidism, thyromegaly, and iodide organification defects, which reversed with iodide restriction (109). Further, the frequency of high urinary iodide levels in Japan correlated with that of thyroid autoantibody-negative hypothyroidism, but not with hyperthyroidism, supporting a role for iodide excess in inducing hypothyroidism (87) (Fig. 11).

In patients with ESRD, clinical and biochemical manifes-

TABLE 5. Prevalence of altered free T_4 index values due to thyroidal and nonthyroidal illnesses in ESRD

Location	No.	Free T_4 index			
		Reduced		Elevated	
		Hypothyroid (%)	Sick (%)	Hyperthyroid (%)	Sick (%)
End-stage renal failure					
Michigan	168	9.5	–	–	–
California	24[a]	8.3	33.3	0	0
Israel	46	6.5	19.6	0	0
Japan	93[b]	3.2	–	–	–
California	306	2.6	22.5	1.0	0
Maryland	38	0	–	–	–
Austria	107	0	–	–	–
Insulin-dependent diabetes mellitus					
Scotland	605	3.0	0.7	0	0
Great Britain	255	2.7	23.0	0	0
General population					
California	2122	1.1	1.1	0.3	0.9
California	2704	0.6	0.2	0.5	0.2

FT_4I, free T_4 index. [Adapted from E. M. Kaptein *et al.*: *Medicine* 67:187–197, 1988 (3).]
[a] Children.
[b] [Data from S.-I. Takeda *et al.*: *Nephron* 65:51–55, 1993 (109).]
–, No data available.

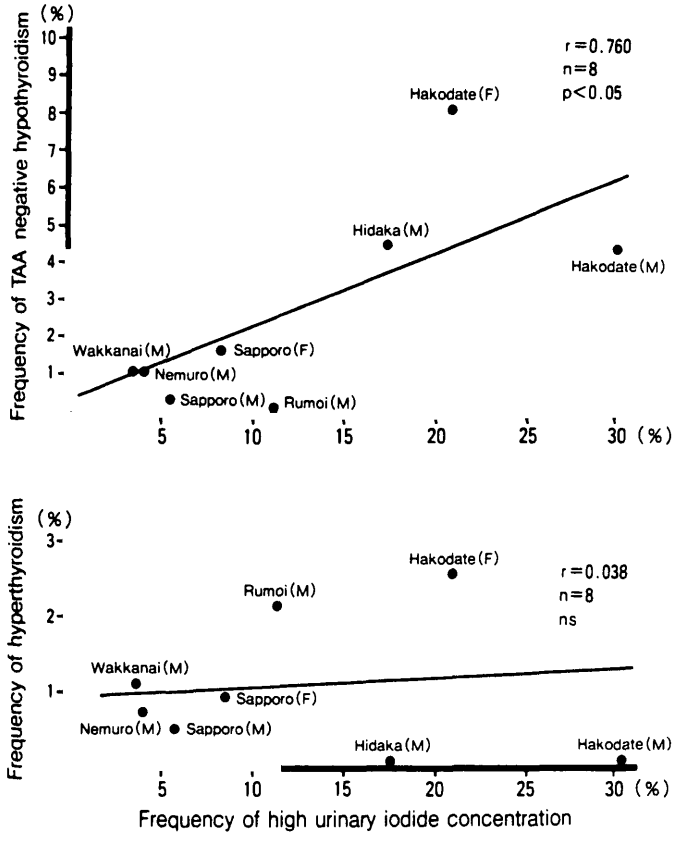

FIG. 11. Relationship between the frequency of high urinary iodide levels and thyroid autoantibody (TAA) negative hypothyroidism (*top*) and hyperthyroidism (*bottom*). [Reproduced with permission from N. Konno *et al.*: *J Clin Endocrinol Metab* 78:393–397, 1994 (87). © The Endocrine Society.]

tations of hypothyroidism are frequently mimicked or masked by concurrent ESRD (112), malnutrition, diabetes mellitus, and aging (108). Thus, a high index of suspicion for hypothyroidism must be present for patients at risk, and biochemical confirmation must be obtained before L-T_4 therapy (112). Biochemical features include persistently elevated TSH values to above 20 mU/liter and reduced serum total T_4 and free T_4 index values (3, 110–112).

A screening serum TSH concentration is most cost-effective for primary hypothyroidism since reduced total T_4 and free T_4 index values were present in 24% and 13%, respectively, of euthyroid ESRD patients while only 1% had TSH values above 10 mU/liter, and all TSH values between 10 and 20 mU/liter were transient (3). None of the ESRD patients with normal free T_4 index values were diagnosed to have overt hypothyroidism. A free T_4 estimate, preferably free T_4 by direct equilibrium dialysis, may play a confirmatory role (51). When a biochemical diagnosis of hypothyroid is established, a reversible cause such as iodide excess due to contrast agents, povidone or Amiodarone administration, should be sought. If hypothyroidism is irreversible, L-T_4 therapy should be initiated (113–115).

The absorption rate of L-T_4, which is normally 50–80%, is unaltered in ESRD and after renal transplantation (19). The initial dosage regimen for L-T_4 should be based on the cardiovascular status of the patient and adjusted to achieve euthyroidism as determined by clinical symptoms and signs and serum TSH levels. Since 10% of ESRD patients are euthyroid with serum TSH values between 5 and 10 mU/liter (3, 7), a conservative approach would be to adjust the dosage to attain TSH values in this range, unless otherwise indicated. Increasing the L-T_4 dosage until serum TSH values are within the normal range may induce mild hyperthyroidism and precipitate cardiac events in some ESRD patients, particularly those with diabetes mellitus, the elderly, and those with subclinical or overt ischemic heart disease. Total T_4 and most free T_4 estimates should not be relied upon to adjust the L-T_4 dosage since these values are frequently reduced in euthyroid ESRD patients (3).

Failure of serum TSH values to normalize in a patient receiving 1.6 μg/kg body weight L-T_4/day may indicate noncompliance with the dosage regimen, interference with intestinal absorption, or increased losses or degradation rates

of T_4 (113). T_4 and T_3 may be bound in the gastrointestinal tract by aluminum hydroxide, ferrous sulfate, cholestyramine, sucralfate, colestipol, activated charcoal, soya flour, food (113), and kayexylate (116). These agents may interrupt enterohepatic circulation of T_4 and T_3 and increase excretion rates from the body, even when agents are not given concurrently with L-T_4 (117). In addition, in ESRD patients receiving CAPD, T_4 losses in peritoneal fluid range from 8–29 μg/day (66, 110). Commonly administered pharmacological agents, including phenobarbital, phenytoin, carbamazepine, and rifampin, induce hepatic microsomal drug-metabolizing enzymes and increase rates of T_4 degradation by the body (113). These causes should be sought and corrected if possible when an ESRD patient requires more than predicted dosages of L-T_4 to attain euthyroidism.

E. Hyperthyroidism

In ESRD, hyperthyroidism may occur with a frequency similar to that of the general population (3). However, only 10 cases are reported in the medical literature (3, 118–124). Of these, all were female, five were over the age of 60 yr, and five were under the age of 40 yr. Eight of ten had goiter and three had diabetes mellitus. Hyperthyroidism was due to Graves' disease in eight and to multinodular toxic goiter in two patients. Clinical features in seven patients included palpitations (71%), weight loss (71%), weakness (43%), atrial fibrillation or flutter (43%), irritability (43%), tremor (29%), heat intolerance (29%), confusion (29%), and nervousness (14%). Five of seven patients had atypical presentations, three of whom were over the age of 60 yr, consistent with atypical clinical manifestations of hyperthyroidism in the elderly who may present primarily with anorexia, cardiovascular dysfunction, and weight loss (125). One elderly patient had recurrent atrial fibrillation, hypotension on hemodialysis, and sinus tachycardia (119), while another presented with cachexia and psychiatric symptoms (122), and one young woman had only weakness and severe weight loss (121). Thus, hyperthyroidism should be suspected in ESRD patients with unexplained symptoms and signs including weight loss, atrial fibrillation, angina pectoris, or congestive heart failure.

Biochemical manifestations of hyperthyroidism may be masked by changes due to nonthyroidal illnesses, including reduced T_4 binding to serum carrier proteins and impaired T_3 conversion from T_4. Nine of 10 hyperthyroid ESRD patients had elevated total and/or free T_4 levels and normal or increased T_3 values (118–124). Thus, normal or reduced T_3 values may not exclude hyperthyroidism since extrathyroidal T_3 production is reduced (20). Serum TSH values using second or third generation assays have not been reported in hyperthyroid ESRD patients, but TSH values were reduced to less than 0.01 mU/liter in association with an absent TSH response to TRH in all hospitalized hyperthyroid patients (16). Currently, a serum TSH concentration measured in a second- or third-generation assay is the most cost-effective screening test for hyperthyroidism in ESRD patients, with free T_4 and free T_3 estimates and TSH response to TRH as confirmatory tests (24).

When hyperthyroidism is diagnosed, the specific etiology should be determined and appropriate therapy initiated (126, 127). The dosages and efficacy of propylthiouracil and methimazole do not appear to be altered in hyperthyroid ESRD patients (121). However, methimazole is not protein-bound and should be administered after hemodialysis (121). If Na ^{131}I therapy is used, the dosage should be decreased in proportion to reduced radioiodide clearance rates by dialysis and residual renal function (Table 3). In contrast to athyreotic thyroid cancer patients, hyperthyroid patients have a functioning thyroid gland that incorporates ^{131}I into iodothyronines, primarily T_4 and T_3. Consequently, the ^{131}I half-life in blood of a hemodialyzed ESRD patient increased progressively with time, with a final physical half-life of 8.05 days from 9–15 days after administration (124) (Fig. 12), most likely reflecting the serum half-life of radiolabeled T_4.

Hyperthyroid hemodialysis patients reported in the literature received 7–24 mCi radioiodide (118–122, 124), a dosage similar to that of patients with normal renal function. In two cases, Na ^{131}I was administered 72 h before the next hemodialysis, at which time no radioactivity was detected in equipment or effluent (120, 124). Radiation doses to thyroid

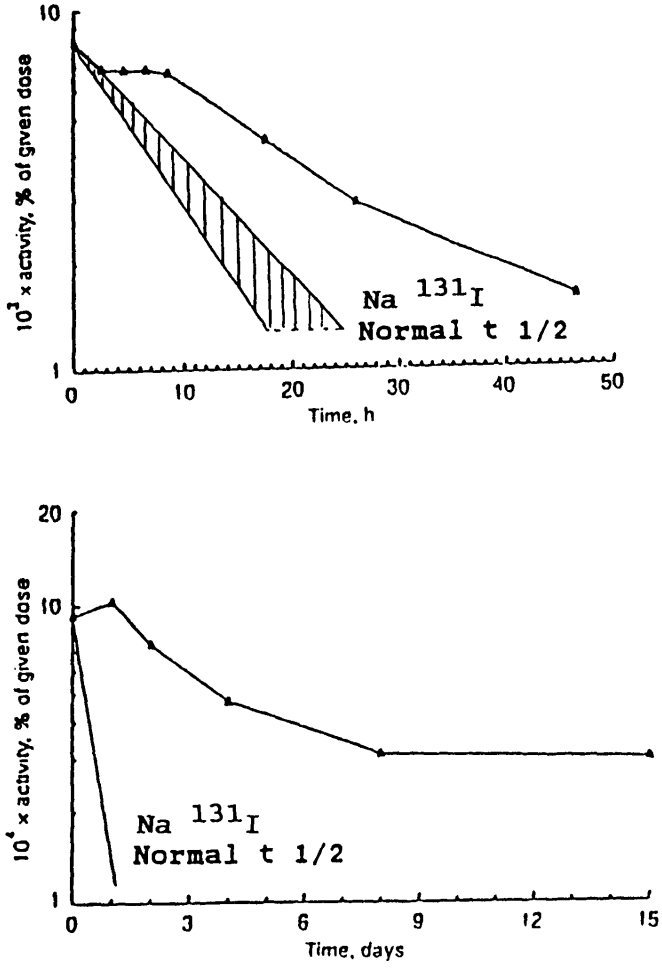

FIG. 12. Total serum ^{131}I activity, after correction for physical decay of ^{131}I, in a chronic hemodialysis patients with Graves' disease after an oral dose of Na-^{131}I. The *hatched area* (*top*) and the line labeled "Na ^{131}I Normal t1/2 " (*bottom*) are data from subjects with normal renal function (89, 90). [Reproduced with permission from J. R. Nibhanupudy *et al.*: *Am J Nephrol* 13:214–217, 1993 (124).]

and critical organs such as bone marrow in ESRD patients dialyzed 72 h after the Na ^{131}I dosage were probably 4- to 6-fold that of patients with normal renal function (91). To avoid risks of excess radiation exposure in hyperthyroid ESRD patients (106), Na ^{131}I dosages should be reduced in proportion to decreases in Na ^{131}I removal rates from the body, as determined by residual renal function and type, frequency, and duration of dialysis therapy, and should be given 48–72 h before the next hemodialysis (Table 3).

VI. Summary and Conclusions

Patients with ESRD have multiple alterations of thyroid hormone metabolism in the absence of concurrent thyroid disease. These may include elevated basal TSH values, which may transiently increase to greater than 10 mU/liter, blunted TSH response to TRH, diminished or absent TSH diurnal rhythm, altered TSH glycosylation, and impaired TSH and TRH clearance rates. In addition, serum total and free T_3 and T_4 values may be reduced, free rT_3 levels are elevated while total values are normal, serum binding protein concentrations may be altered, and disease-specific inhibitors reduce serum T_4 binding. Changes in T_4 and T_3 transfer, distribution, and metabolism resemble those of other nonthyroidal illnesses, while changes in rT_3 metabolism are disease specific. Dialysis therapy minimally affects thyroid hormone metabolism, while zinc and erythropoietin administration may partially reverse thyroid hormone abnormalities. Thyroid hormone metabolism normalizes with renal transplantation; however, glucocorticoid therapy may induce additional changes.

ESRD patients may have an increased frequency of goiter, thyroid nodules, thyroid carcinoma, and hypothyroidism. Goiter and hypothyroidism may be induced by iodide excess, due to reduced renal iodide excretion, and may be reversed with iodide restriction in some patients. The increased frequency of thyroid nodules and malignancies in ESRD may relate to secondary hyperparathyroidism. After renal transplantation, the higher frequency of thyroid malignancies may relate to the immunosuppressed state. Clinical symptoms and signs and biochemical features of hypothyroidism and hyperthyroidism may be altered by concurrent ESRD. ESRD patients with hyperthyroidism or follicular neoplasms require reduced dosages of Na ^{131}-I depending upon type, frequency, and duration of dialysis therapy.

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