Concordant Decreases of Thyroxine and Thyroxine Binding Protein Concentrations During Sepsis

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The principal thyroxine (T_4) binding proteins were measured in 8 septic patients and 8 controls to determine the extent to which a decrease in their concentration contributes to the decrease in serum T_4 in sepsis. T_4 binding globulin (TBG) evaluated by radioimmunoassay (RIA) and radial immunodiffusion (RID) was 61% and 66%, respectively, of the normal mean value in sera from septic patients. Decreases of albumin and transthyretin (TTR) to 55% and 29%, respectively, of the normal mean concentration contributed to the loss of T_4 binding power in these sera. Total serum binding of T_4, calculated from the normal contribution of each protein to T_4 binding and the reduction of its concentration in septic patients, was 55% of that in the normal controls. This decrease in the estimated protein binding of T_4 was proportional to the decrease of serum T_4 from a mean of 8.4 μg/dL in the normal controls to 4.7 μg/dL (56% of the control) in the septic patients. Because TBG binds most of the serum T_4, the decrease in the TBG concentration was the major factor in the decrease of total T_4 binding power. Since the concentration of the major T_4 binding proteins decreased sufficiently to account for the decrease in serum T_4, it is unnecessary to postulate the effects of additional factors such as binding inhibitors or modification of T_4 binding protein affinity.

APPARENT DISCREPANCIES between the increase in the free to bound thyroxine (T_4) ratio and the degree of decrease in T_4 binding globulin (TBG), transthyretin (TTR), and albumin in sera from patients with nonthyroidal illness[1,2] have led to the view that factors other than a decrease in T_4 binding proteins have a predominant role in the increase of free/bound T_4 and the decrease of total T_4 in these patients. Two recent reviews[3,4] discuss the diminished TBG binding of T_4 in nonthyroid illness mainly in terms of a competitive binding inhibitor or a decrease in affinity consequent to desialylation of the protein. It is our impression that serum TBG concentrations are sufficiently decreased in sera from patients with nonthyroidal illness to account for much, if not all, of the decrease in T_4 binding. Indeed, a review of one of the early articles proposing the existence of a binding inhibitor, reveals that the mean TBG concentration of 8 patients with nonthyroidal illness and low T_4 was 58% of the normal mean.[2]

To resolve the question of whether TBG decreases to a physiologically significant degree in nonthyroidal illness, we compared serum TBG and T_4 concentrations in 8 normal subjects and 8 septic patients. Albumin and TTR, which contribute to serum T_4 binding, were also evaluated.

SUBJECTS AND METHODS

The normal subjects (2 women and 6 men aged 37 ± 11 years, mean ± SD) were volunteers from the hospital staff. The sick patients (2 women and 6 men aged 64 ± 13 years) were hospitalized patients who were considered septic. They were febrile for at least 48 hours with a temperature over 102°F, tachycardia, and a white blood cell count greater than 12,000. All had a positive blood culture. The diagnoses were pneumococcal pneumonia (n = 5), empyema (n = 1), and gram-negative sepsis (n = 2). Test results for thyroid function were not known prior to the selection of subjects or controls. The methods for determining TBG and the standard thyroid function tests are described by our group in a separate report.[5] The protocol was approved by the institutional review board, and informed consent was obtained from the subjects (Table 1).

RESULTS AND DISCUSSION

The low total T_4 and triiodothyronine (T_3) and normal thyrotropin (TSH) are characteristic of nonthyroidal illness of moderate severity.[3] The increase in T_4 uptake is analogous to the increase in T_3 uptake found in nonthyroidal illness but reflects the effects of decreased TTR as well as albumin and TBG binding. Estimates of free T_4 in nonthyroidal illness have varied widely depending on the method used and the severity of illness.[6] The normal mean free T_4 concentration in these patients is consistent with free T_4 determinations in nonthyroidal illness by equilibrium dialysis/immunoassay[7] and with the conclusions of two reviews of nonthyroidal illness cited previously.[3,4] TBG was significantly lower in the septic patients versus the normal subjects, 1.66 versus 2.73 mg/dL (60.8%) by radioimmunoassay (RIA) and 1.46 versus 2.23 mg/dL (66.4%) by radial immunodiffusion (RID). Albumin and TTR, both of which are negative acute-phase reactants, were decreased to 55% and 29%, respectively, of their normal mean level. The decrease in TBG is the major factor in the decrease of T_4 because TBG accounts for most serum T_4 binding. Estimates of the relative contribution of the 3 major T_4 binding proteins previously obtained by sequential saturation[8] indicate that TBG normally accounts for 62%, albumin 23%, and TTR 15% of the total serum T_4 binding power (sum of the individual association constants and the corresponding unoccupied capacities).

To estimate the decrease in total serum T_4 binding power attributable to the decrease in T_4 binding protein in the septic patients, we added the product of the normal contribution of each T_4 binding protein multiplied by the fraction of its normal concentration present in the septic patients, ie, 62% × .608 for TBG + 23% × .545 for albumin + 15% × .285 for TTR = 55%. This estimate indicates that the decrease in serum T_4 binding power due to a decrease in the principal T_4 binding proteins is proportional to the decrease in serum T_4 in these septic patients (8.4 to 4.7 μg/dL, 56%). Thus, decreases in the T_4 binding protein concentration accounted for the observed decreases in serum T_4. This is at variance with previous

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Table 1. TBG, Albumin, and Thyroid Function in Sepsis

Parameter	Normal Range	Normal Subjects (n = 8)	Nonthyroidal Illness (n = 8)	P
TBG (mg/dL)				
RIA	1.3-3	2.73 ± .44	1.66 ± .34	<.001
RID	—	2.23 ± .48	1.46 ± .18	<.001
Albumin (g/dL)	2.8-5.7	4.7 ± 1.2	2.56 ± .66	<.001
TTR (mg/dL)	23-35	28.0 ± 1.8	8.0 ± 1.4	<.01
T_4 (μg/dL)	5.2-10.5	8.4 ± .14	4.71 ± 1.40	<.001
Free T_4 (ng/dL)	.71-1.85	1.29 ± .05	1.02 ± .32	NS
T_3 (ng/dL)	59-174	117 ± 14	46.7 ± 13	<.001
T_4U %	26-37	32 ± 2.6	46.0 ± 7.1	<.001
TSH (mIU/mL)	.38-4.7	1.36 ± .61	1.07 ± .70	NS

NOTE. Values are the mean ± SEM. A normal range was not available for the TBG by RID.

Abbreviation: NS, nonsignificant.

studies.[1,2,9] In our patients with acute sepsis, the postulated TBG binding competitors and changes in TBG affinity for T_4, if present, could have, at most, a minor effect on T_4 binding. These results in 8 septic patients do not exclude the possibility that endogenous binding inhibitors have significant effects in other circumstances such as the euthyroid sick syndrome associated with more chronic disease. However, our findings are consistent with the inability of Mendel et al[10] to detect an inhibitor of T_4 binding when mixing normal serum with sera obtained from 111 hospitalized patients with diverse diagnoses. The decreases in serum albumin and TTR we observed are known to occur during inflammation and appear to be explained by decreased synthesis due to rapid inhibition of transcription.[11]

A critical question is, what causes the decrease in the TBG concentration? In a model of the acute inflammatory response, we find that the decrease in TBG is too rapid to be accounted for by inhibition of synthesis.[5] Since TBG is a member of the serine protease inhibitor family[12] and is susceptible to cleavage by elastase,[13,14] we suspect that the decrease in the TBG concentration in inflammatory states such as sepsis is due to cleavage by inflammatory serine proteases such as elastase.[5] The decrease in total T_4 in sepsis is due to the combined effects of accelerated clearance and decreased production of T_4.[15]

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