Hypermetabolic low triiodothyronine syndrome of burn injury

RICHARD A. BECKER, MD; GEORGE M. VAUGHAN, MD; MICHAEL G. ZIEGLER, MD; LEONARD G. SERAILE, MS; I. WILLIAM GOLDFARB, MD; ESBER H. MANSOUR, MD; WILLIAM F. McMANUS, MD; BASIL A. PRUITT, Jr., MD; ARTHUR D. MASON, Jr., MD

The free tetraiodothyronine index (FT$_4$I) and free triiodothyronine index (FT$_3$I) in burn patients represented the serum levels of free (dialyzable) T$_4$ and free T$_3$, respectively. FT$_4$I and FT$_3$I were lower with greater burn size and were lower in nonsurvivors than expected for the burn size. There was no compensatory elevation of basal or releasing hormone-stimulated thyrotrophin (TSH) concentrations. Reverse T$_3$ was higher with greater burn size. T$_3$ treatment restored FT$_3$I but did not affect mortality or resting metabolic rate (MR) measured in survivors, compared with placebo therapy. Whereas the hypermetabolic response to burn injury appeared to be independent of thyroid hormones, MR was correlated positively with burn size and with elevated plasma noradrenaline and epinephrine concentrations for several weeks after injury. Lack of augmented TSH concentrations, absence of low plasma reverse T$_3$, and presence of hypermetabolism suggest that the reduced plasma free T$_3$ does not indicate functional hypothyroidism, but may represent an adaptation to the assumption of metabolic control by the sympathetic nervous system.

Many nonthyroidal illnesses (NTI), such as starvation, infection, liver disease, kidney disease, malignancy, myocardial infarction, diabetes mellitus, and accidental burn injury are associated with a decrease in total and free T$_3$ concentration in plasma (low T$_3$ syndrome). Reduction in T$_3$ may signify a more critical severity of illness: among patients admitted to a medical intensive care facility, those with a low total T$_4$ had a subsequent releasing hormone (TRH) between postburn days (PBD) 5 and 20. Five burn patients survived (SURV) and 5 nonsurvivors (NSURV) expired later (Table 1). No patient received dopamine or corticosteroids before or during TRH stimulation. Serum samples were taken for TSH assay before and at intervals up to 90 min after TRH injection. The TSH-time curve integral (area under the curve) was computed. Analysis of variance and the Student-Newman-Keuls test were used to compare means.

PATIENTS AND METHODS

Study 1

Five nonburned healthy controls (CONT) and 10 burn patients received a single 250 mg iv bolus of thyrotropin-releasing hormone (TRH) between postburn days (PBD) 10 and 20. Five burn patients survived (SURV) and 5 nonsurvivors (NSURV) expired later (Table 1). No patient received dopamine or corticosteroids before or during TRH stimulation. Serum samples were taken for TSH assay before and at intervals up to 90 min after TRH injection. The TSH-time curve integral (area under the curve) was computed. Analysis of variance and the Student-Newman-Keuls test were used to compare means.

Study 2

Thirty-six men, aged 17-23 yr and burned in a single gasoline fire in a military camp, were entered into a prospective study of T$_3$ versus placebo administration on a protocol approved by the institutional committee monitoring ethical considerations of clinical studies. Eight of
these CONT patients had minimal injury. The remaining 28 had 2nd and 3rd degree total burn size (TBS) of 18–93% of body surface area and were randomly assigned in double blind fashion to treatment with either placebo or T4, 200 µg/day orally or by nasogastric tube in 4 divided doses until their wounds were healed. This dose of T4 was previously found to maintain normal T4 levels in burn patients. Because 4 deaths occurred during placebo (NSURV) and 4 during T4 treatment (NSURV-TX), the patients were assessed according to the 5 groups characterized in Table 2. We sampled blood for determination of thyroid hormones (serum) and catecholamines (plasma) beginning on PBD 3–5, and then approximately thrice weekly, when the patients were under basal conditions in the supine position between 0500–0700 h, just before their next dose of placebo or T4. At weekly intervals in the morning, after overnight recumbency and at least an 8-h period free of caloric intake, resting MR was measured in all surviving patients. Because of the large number of measurements to be made, priority was given to those who appeared the most stable clinically, and their MR was followed longitudinally. The others, whose MR was not measured, happened to be nonsurvivors. A record was kept of the total daily caloric intake and the separate intakes of carbohydrate, protein and fat.

In Study 2, the period of PBD 3–26 was chosen for analysis, because the major decrement in catecholamines and MR occurred by PBD 26, the CONT patients were available for varying periods up to this time, and all survivors received placebo or T4 treatment during this time (Table 2). All values sampled within 24 h of dopamine or corticosteroid administration were discarded from analysis. In one analysis the variables were considered as the mean value for each patient. But, because major changes in most variables took place over time, the time factor was accounted in separate analyses using individual values of variables in a standard stepwise multiple linear regression program (BMDP, UCLA) performed on a PDP 11/40 computer. For a given dependent variable, the program chose only those independent variables (from the ones entered) which significantly (p < 0.05) reduced the residual variance of the dependent variable about the values predicted from the other chosen independent variables. To test for possible dependent variation related to TBS and PBD, both of these and their respective squared values were entered as possible independent variables into most of the multiple regression analyses. Additional possible independent variables were also entered to determine whether they would account for dependent variation better than would TBS and PBD. In some analyses, death or T4 treatment was entered as the additional independent variable. In other analyses involving several hormones as the additional possible independent variables, the relevant dependent and independent variables are identified under “Results” and in Table 3.

In both of these studies (1 and 2), no patient received iodine or iodine-containing compounds topically or systemically. All patients received initial vigorous fluid resuscitation followed by administration of calories, mainly by the enteral route, to approach the estimated metabolic requirement. Wounds were treated with open topical applications of mafenide acetate or silver sulfadiazine and excision and grafting when appropriate. Systemic antibiotics were administered for sepsis or infection.

**Assays**

Determination of T4, T3 (Ortho), reverse T3 (rT3, Serono) and TSH (Diagnostic Products) were made by radioimmunoassays with kits obtained from the manufacturer. Least detectable concentrations were 0.2 µg/dl for T4, 10 ng/dl for T3, 2 ng/dl for rT3, and 0.5 µU/ml for TSH. Pooled hypothyroid, normal, and hyperthyroid sera yielded respective mean values (and interassay coefficients of variation) as follows: for T4, 4.7 (7.4%), 9.5 (7.1%), and 17.1 µg/dl (7.6%); for T3, 60 (8.3%).
TABLE 3. Regression analyses of hormonal variables and MR

<table>
<thead>
<tr>
<th>Analysis</th>
<th>n</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT&lt;sub&gt;3&lt;/sub&gt;&lt;sup&gt;L&lt;/sup&gt; = 7.34 - 0.0003 TBS&lt;sup&gt;2&lt;/sup&gt; - 0.002 DA + 0.001</td>
<td>143</td>
<td>0.344</td>
</tr>
<tr>
<td>PBD&lt;sup&gt;L&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FT&lt;sub&gt;3&lt;/sub&gt;&lt;sup&gt;L&lt;/sup&gt; = 98.6 - 0.568 TBS + 0.046 PBD - 0.035</td>
<td>143</td>
<td>0.417</td>
</tr>
<tr>
<td>DA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rT&lt;sub&gt;3&lt;/sub&gt; = 44.2 - 3.75 PBD + 0.094 PBD&lt;sup&gt;2&lt;/sup&gt; + 0.255</td>
<td>143</td>
<td>0.540</td>
</tr>
<tr>
<td>TBS = 0.002 TBS&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH = 1.69 + 0.005 PBD</td>
<td>141</td>
<td>0.129</td>
</tr>
<tr>
<td>NE = 1425 + 22.7 TBS - 122 PBD - 0.186</td>
<td>142</td>
<td>0.639</td>
</tr>
<tr>
<td>TBS + 2.92 PBD - 58.2 FT&lt;sub&gt;L&lt;/sub&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPI = 143 + 3.0 TBS - 8.75 PBD</td>
<td>142</td>
<td>0.397</td>
</tr>
<tr>
<td>DA = 208 + 0.026 TBS - 1.23 FT&lt;sub&gt;L&lt;/sub&gt;</td>
<td>142</td>
<td>0.290</td>
</tr>
<tr>
<td>DBH/P = 90.1 - 0.306 FT&lt;sub&gt;L&lt;/sub&gt;</td>
<td>141</td>
<td>0.037</td>
</tr>
<tr>
<td>MR = 120 + 0.243 TBS + 0.017 NE - 1.74 TSH + 0.041 DBH/P</td>
<td>36</td>
<td>0.827</td>
</tr>
<tr>
<td>MR&lt;sup&gt;L&lt;/sup&gt; = 35.2 + 0.022 NE + 0.036 EPI</td>
<td>37</td>
<td>0.576</td>
</tr>
</tbody>
</table>

* In each analysis, all variables (except MR) were entered, together with TBS and PBD and their squared values, as possible independent variables with the following exceptions:
  1. If a thyroid hormone (FT<sub>3</sub>, FT<sub>4</sub>, or rT<sub>3</sub>) was the dependent variable, none of these was entered as an independent variable.
  2. If a catecholamine-related measurement was the dependent variable (NE, EPI, DA, or DBH/P), none of these was entered as an independent variable.
  3. In this analysis, only NE, EPI, and DA were entered as possible independent variables. The proportion of MR variability (r<sup>L</sup>) associated with NE alone was 0.50, and the inclusion of EPI accounted for an additional 0.076.

In Study 2, 4 of 14 T<sub>3</sub>-treated and 4 of 14 placebo-treated patients died with sepsis or pneumonia. There were a total of 16 patients with TBS > 50% (to include

(3.3%), and 298 ng/dl (4.48%); and for TSH, 36.4 (9.1%), 3.3 (10.7%), and 1.5 µU/ml (35%). For rT<sub>3</sub>, pooled hypothyroid and normal sera yielded respective means (and interassay coefficients of variation) of 11.8 (8.3%) and 22.3 ng/dl (13.9%). Indices of free thyroid hormone concentration (FT<sub>3</sub> and FT<sub>4</sub>) were calculated as the product of the total T<sub>4</sub> or T<sub>3</sub> and the resin T<sub>3</sub> uptake (T<sub>3</sub>U) divided by the normal calibrator T<sub>3</sub>U provided in the kit (Ortho). The FT<sub>3</sub> and FT<sub>4</sub> in 100 representative samples from burn patients (Fig. 1) were validated as indices of free hormone levels by comparison with the respective free T<sub>3</sub> and free T<sub>4</sub> concentration based on the dialyzable fraction which was also determined (Nichols Institute, San Pedro, CA). These samples were taken from patients with various burn sizes, including some with nearly healed wounds and normal thyroid hormone levels. In a group of 49 normal adults, mean FT<sub>3</sub> was 7.48 (range 5.1-11.1) and mean FT<sub>4</sub> was 125 (range 69-273). These index values have no assigned units. Plasma norepinephrine (NE), epinephrine (EPI) and dopamine (DA) were determined by radioenzymatic assay<sup>16</sup> as was dopamine beta-hydroxylase (DBH).<sup>17</sup> Total plasma protein was determined according to the method of Lowry et al.<sup>18</sup> Resting MR was measured at ambient 31°C by indirect calorimetry based on O<sub>2</sub> consumption measured for successive 2-min intervals using a head canopy with continuous air flow.<sup>19</sup> The lowest value for a 30-min period, usually when the patient was asleep, was taken for the MR measurement.

**RESULTS**

Figure 1 shows the comparison of FT<sub>3</sub>L and FT<sub>4</sub>L with the free hormone levels by dialysis (FT<sub>3</sub> and FT<sub>4</sub>, respectively) in 100 representative samples from burn patients. The close correlations indicate that low FT<sub>3</sub> and FT<sub>4</sub> are associated with proportionately low FT<sub>3</sub>L and FT<sub>4</sub>L, respectively.

In Study 1 (Table 1 and Fig. 2), TRH stimulation in SURV did not produce an exaggerated TSH response, though 4 out of 5 had basal FT<sub>3</sub>L below the lowest value for healthy controls. The response was blunted and delayed in NSURV, whose TSH concentration was higher at 60 than at 30 min after injection in every case. In contrast, TSH was lower at 60 than at 30 min after TRH injection in all CONT and SURV.

In Study 2, 4 of 14 T<sub>3</sub>-treated and 4 of 14 placebo-treated patients died with sepsis or pneumonia. There were a total of 16 patients with TBS > 50% (to include

---

**FIG. 1. Correlation of FT<sub>3</sub>L and FT<sub>4</sub>L with respective free hormone concentrations derived from the dialyzable fraction.**
in FT₄ was proportional to burn size in patients not treated with T₃ (Fig. 3, upper left). Comparison of mean FT₄ and TSH suggests that the thyroid axis was similarly suppressed in NSURV and in T₃-treated patients (Fig. 3, upper right). An inverse relationship between rT₃ and FT₄ or FT₃ can also be seen in patients not treated with T₃ (Fig. 3, lower panels). Multiple regression analyses showed that T₃, T₄, FT₄, and FT₃ (<0.001) were inversely proportional to TBS or TBS² in placebo-treated patients. In these patients, T₃, T₄, FT₄, FT₃, and TSH were excessively low (p < 0.01) for burn size in the NSURV group. T₃ treatment raised T₃ and FT₃ in SURV-TX and NSURV-TX (<0.001) and suppressed T₃, FT₃, and TSH (p < 0.001) in survivors but not in nonsurvivors. Figure 3 (right panels) shows the corresponding results based on mean values for each patient for FT₃, TSH, and FT₃. Multiple regression analysis showed that in placebo-treated patients, higher rT₃ was associated with greater TBS (p < 0.01). T₃ treatment reduced rT₃ in SURV-TX (p < 0.001) but not in NSURV-TX patients (Fig. 3, lower panels).

Patients with more extensive burns had higher NE levels and MR, particularly in the first 3 weeks postinjury, and MR was positively correlated with NE (Fig. 4). NE and MR were both inversely correlated with FT₃ (p < 0.001, not shown) in placebo-treated patients. Multiple regression analysis showed that EPI (p < 0.001) and DA (p < 0.01) were also elevated in proportion to TBS and that NSURV had elevated plasma DA (p < 0.01) but not NE or EPI concentrations out of proportion

**Fig. 2.** TSH response to TRH in surviving (SURV) and nonsurviving (NSURV) burn patients and nonburned healthy controls (CONT). The number of patients is indicated in parentheses.

**Fig. 3.** Relationships among thyroid hormones, TBS, and TSH based on linear correlations of mean hormone values for each patient over PBD 3-26. In the upper right panel, location nearer the origin indicates suppression of the pituitary-thyroid axis, and the dashed line completely separates CONT and placebo-treated SURV from the others nearer the origin. The shaded areas (lower panels) include at least all points in the regressions for groups specified in the figure. In the lower left panel, the regression depicted (solid line) is positive, because nonsurvivors are excluded. If only T₃-treated patients are excluded, then the relationship between rT₃ and FT₄ (dotted line) is negative (r = -0.49, p < 0.05).
to TBS. Although SURV-TX had slightly lower NE values than did placebo-treated SURV for any given TBS and PBD ($p < 0.05$), NE levels were still markedly elevated in SURV-TX ($p < 0.001$). There was no detectable effect of T$_3$ treatment on EPI, DA, or MR.

Interrelationships among the measured values in untreated patients were defined by considering FT$_3$, FT$_4$, rT$_3$, TSH, NE, EPI, DA, DBH corrected for total serum protein (DBH/P), or MR as the dependent variable in separate multiple regression analyses. The remaining hormones (except those noted in Table 3) were entered together with TBS and PBD as possible independent variables. The resultant computer-chosen independent variables (Table 3) indicate that TSH has no correlation with thyroid hormones; thyroid hormones and catecholamines vary with burn size and time since the burn, and NE is inversely related to FT$_3$. MR was more closely related to NE than to EPI, in that the latter was not chosen as a predictor for MR from among the other variables. When TBS, PBD, and thyroid measurements were excluded from analysis, NE accounted for 50% of total MR variability, and inclusion of EPI accounted for another 7.6%. In analyses not shown, FT$_3$, FT$_4$, NE, and MR were not correlated with total or fractionated caloric intake among SURV, indicating that differences in nutrition did not influence the metabolic variables estimated in these patients. However, the mean total caloric intake for individual nonsurvivors was lower (NSURV, 609-1354; NSURV-TX, 537-1522 kcal/M$^2$.day) than for survivors (SURV, 1526-2192; SURV-TX, 1630-2256 kcal/M$^2$.day).

**DISCUSSION**

In agreement with previous findings,$^7$ we have confirmed that severe burns suppress free indices of thyroid hormone levels. Additionally, we now show that this is related to extent of injury and is without an augmentation of TRH-stimulated plasma TSH. An augmented TSH response is the expected normal result of even smaller decrements in thyroid hormones.$^{20}$ NSURV of burns had the lowest FT$_3$ and FT$_4$ and also exhibited a blunted and delayed TSH response to TRH. The altered regulation of TSH in burn patients resembles that found in other forms of NTI.$^1$ These results are compatible with failure of brain centers controlling the thyroid axis$^{22}$ or with direct suppression of TSH release by elevated DA$^{22}$ or cortisol.$^{23,24}$ Whether the excessively low FT$_3$, FT$_4$, and TSH values for NSURV burn patients are a result of sepsis, a deficient caloric intake, or other factors is yet to be determined. Though some unidentified factor also might interfere with hormone release from the thyroid, the thyroids from our patients at autopsy microscopically indicate lack of TSH stimulation.

Inhibited peripheral conversion of T$_3$ to T$_4$, and accumulation of the inactive rT$_3$ (the product of inner ring monodeiodination of T$_3$ in the periphery) are features of other forms of NTI.$^{1,2,6}$ Similarly, we found an inverse relationship of rT$_3$ to FT$_4$, in burn patients not treated with T$_3$. The presence of normal or high rT$_3$, may be evidence for lack of hypothyroidism in burn injury, in that such levels of rT$_3$ have also been used to distinguish other forms of NTI from classical hypothyroidism.$^{25}$

Burned patients are hypermetabolic, which again suggests the absence of functional hypothyroidism. Their hypermetabolism is blunted by propranolol.$^{27}$ a $\beta$-blocker. Their urinary catecholamines are elevated$^{25,26,27}$ in proportion to MR$^{27,28}$ as are their plasma catecholamines as shown in the present study. MR was more closely correlated with NE than with EPI, suggesting $\beta$-mediation of some of the hypermetabolism. Another study failed to find a correlation between plasma catecholamines and MR in children whose hypermetabolism and catecholamine levels were partially reduced by restricting heat loss with occlusive dressings.$^{26}$ Reduction in metabolic and sympathetic signals together with fewer measurements may have reduced the chance to observe a correlation in that study. Burn patients also exhibit other signs of elevated sympathetic activity,$^{12,13,28}$ such as elevation of heart rate, cardiac output and core temperature. In our placebo-treated patients, larger burn size and lower FT$_3$ were closely correlated with higher plasma NE and higher MR, and MR was inversely related to plasma TSH. Thus, downward adjustment of TSH secretion appears not to indicate central hypothyroidism, but perhaps is a response to the metabolic effect of catecholamines. T$_3$ treatment did not alter mortality in...
this study. Failure of T₃ replacement to alter the MR further indicates that the hypermetabolic response to injury is independent of stimulation by the thyroid axis. The fall in thyroid hormones may be an adaptation to the assumption of metabolic control by the sympathetic nervous system after severe injury.

The hypermetabolic low T₃ syndrome may occur in a variety of settings. Other types of trauma³ and several types of febrile illnesses⁴ are associated with hypermetabolism, and febrile illnesses are associated with elevated catecholamine excretion⁶ and decreased T₃ levels.⁵ Patients with extensive burns and probably patients with other nonthyroidal illnesses develop a hypermetabolic low T₃ syndrome. Their hypermetabolism is due, at least in part, to elevated catecholamine secretion. The syndrome in burn patients would appear potentially harmful in terms of extremely high levels of catecholamines or low levels of free thyroid hormones, but an attempt to alter it with T₃ administration did not greatly affect catecholamines, hypermetabolism, or mortality.

ACKNOWLEDGMENTS

We thank Jennifer Tucker, Arlene Masters, Steve Fahrman, and Jan Bullard for technical assistance and Sandy Hale for technical, editorial, and typing assistance.

REFERENCES