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 adrenaline 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) 1 and 20. Five burn patients received a single 250 µg 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 1

Five nonburned healthy controls (CONT) and 10 burn patients received a single 250 µg 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.13 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.

**Analysis**

Determinations 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%); 124

---

**Table 1. Basal FT₄ and FT₃ and TRH-stimulated TSH response in normal and burned subjects**

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yr)</th>
<th>N/Sex</th>
<th>TBS range (mean)</th>
<th>Days before death</th>
<th>FT₄</th>
<th>FT₃</th>
<th>TSH Integral (U·min/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONT</td>
<td>31-40</td>
<td>5/M</td>
<td>50-68</td>
<td>4-7</td>
<td>7.9±0.35</td>
<td>5.9±0.7</td>
<td>1245±208</td>
</tr>
<tr>
<td>SURV</td>
<td>19-54</td>
<td>5/M</td>
<td>(58)</td>
<td></td>
<td>153±9.5</td>
<td>95.0±2.10</td>
<td>1326±216</td>
</tr>
<tr>
<td>NSURV</td>
<td>18-63</td>
<td>4/M</td>
<td>28-68</td>
<td></td>
<td>2.9±0.6</td>
<td>25.0±6.0</td>
<td>579±109</td>
</tr>
<tr>
<td></td>
<td>1/F</td>
<td></td>
<td>(47)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05; p < 0.01; for SURV, comparison group is CONT; for NSURV, comparison group is SURV. Error terms are SEM.

---

**Table 2. Group characteristics of the T₄ treatment study**

<table>
<thead>
<tr>
<th>N</th>
<th>% TBS (mean)</th>
<th>% TBS (range)</th>
<th>Begin placebo</th>
<th>End placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONT</td>
<td>8</td>
<td>4.5</td>
<td>2-7.5</td>
<td>31-104</td>
</tr>
<tr>
<td>SURV</td>
<td>10</td>
<td>44.3</td>
<td>18-82</td>
<td>3</td>
</tr>
<tr>
<td>NSURV</td>
<td>4</td>
<td>68.4</td>
<td>55-93</td>
<td>3</td>
</tr>
<tr>
<td>SURV-TX</td>
<td>10</td>
<td>45.3</td>
<td>28-75</td>
<td>3</td>
</tr>
<tr>
<td>NSURV-TX</td>
<td>4</td>
<td>72.9</td>
<td>62-85</td>
<td>3</td>
</tr>
</tbody>
</table>

*p < 0.05; *p < 0.01; for SURV, comparison group is CONT; for NSURV, comparison group is SURV. Error terms are SEM.
Table 3. Regression analyses of hormonal variables and MR

<table>
<thead>
<tr>
<th>Analysis</th>
<th>n</th>
<th>r²</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT₄, = 7.34 - 0.0003 TBS² - 0.002 DA + 0.001</td>
<td>143</td>
<td>0.344</td>
</tr>
<tr>
<td>PBD²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FT₃, = 98.6 - 0.568 TBS + 0.046 PBD² - 0.035</td>
<td>143</td>
<td>0.417</td>
</tr>
<tr>
<td>DA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rT₄, = 44.2 - 3.75 PBD + 0.094 PBD² + 0.255</td>
<td>143</td>
<td>0.540</td>
</tr>
<tr>
<td>TBS - 0.002 TBS²</td>
<td>141</td>
<td>0.129</td>
</tr>
<tr>
<td>TSH = 1.69 + 0.085 PBD</td>
<td>142</td>
<td>0.639</td>
</tr>
<tr>
<td>NE = 1425 + 22.7 TBS - 122 PBD - 0.186</td>
<td>142</td>
<td>0.397</td>
</tr>
<tr>
<td>TBS + 2.92 PBD - 58.2 FT₄</td>
<td>142</td>
<td>0.290</td>
</tr>
<tr>
<td>EPI = 143 + 3.0 TBS - 8.75 PBD</td>
<td>141</td>
<td>0.037</td>
</tr>
<tr>
<td>T₄, + 0.026 TBS² - 1.23</td>
<td>142</td>
<td>0.540</td>
</tr>
<tr>
<td>DA = 208 + 0.026 TBS - 1.23 FT₄</td>
<td>142</td>
<td>0.827</td>
</tr>
<tr>
<td>DBH/P = 90.1 - 0.306 FT₄</td>
<td>141</td>
<td>0.576</td>
</tr>
<tr>
<td>MR = 35.1 + 0.243 TBS + 0.017 NE - 1.74 TSH</td>
<td>36</td>
<td>0.677</td>
</tr>
<tr>
<td>+ 0.041 DBH/P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR² = 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 (FT₄, FT₃, or rT₄) 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 (r²) associated with NE alone was 0.50, and the inclusion of EPI accounted for an additional 0.076.

In Study 1 (Table I and Fig. 2), TRH stimulation in SURV did not produce an exaggerated TSH response, though 4 out of 5 had basal FT₄ 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 T₄-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

Figure 1 shows the comparison of FT₄ and FT₃ with the free hormone levels by dialysis (FT₄ and FT₃, respectively) in 100 representative samples from burn patients. The close correlations indicate that low FT₄ and FT₃ are associated with proportionately low FT₄ and FT₃, respectively.

In Study I, the FT₃ concentrations were higher in burn patients than in healthy controls. In Study 2, the FT₃ concentrations were also higher in burn patients than in healthy controls. The close correlations indicate that low FT₃ are associated with proportionately low FT₃, respectively.

FT₄ and FT₃ concentrations were derived from the dialyzable fraction.

![Figure 1](https://example.com/figure1.png)
The number significant approach, accounting for time since burn, showed a
independent variables in multiple regression analyses.
analyzed over this time period with PBD and TBS as
over PBD 3-26. Subsequently, individual values were
were first considered as the mean value for each patient
Because both time since burn and burn size were impor-
0.62 in SURV (p
FT
Student’s t-test) than in
(mean ± SE.) in SURV was slightly but not significantly
weeks. In NSURV, the values were initially lower and
values for these controls rather than to normal ranges in
all nonsurvivors), in which 4 of 8 T$_0$-treated and 4 of 8
placebo-treated patients died. The CONT group with a
very small injury (Table 2) known not to influence MR$^{12}$
consisted of particularly appropriate control subjects for
this study. They were homogeneous with the other pa-
tients with respect to age, sex, physical training, and
previous environment, and they were housed in the same
general ward area. Therefore, hormonal values for the
more extensively burned patients are better compared to
values for these controls rather than to normal ranges in
a heterogeneous population.
FT$_4$ and FT$_3$ in SURV were lowest initially (PBD
3-5) and generally returned to CONT levels over 3-4
weeks. In NSURV, the values were initially lower and
did not rise before death which occurred on PBD 6-54.
On PBD 5 (CONT samples not taken earlier), FT$_4$
(mean ± SE) in SURV was slightly but not significantly
lower (6.59 ± 0.46) than in CONT (7.62 ± 0.42), and
FT$_3$ in SURV (63.6 ± 3.9) was lower (p < 0.001.
Student’s t-test) than in CONT (99.8 ± 4.5). On PBD 3,
FT$_4$ in NSURV was 3.57 ± 0.63 compared to 7.11 ±
0.62 in SURV (p < 0.01) and FT$_3$ in NSURV was 26.5
± 7.38 compared to 69.8 ± 12.1 in SURV (p < 0.001).
Because both time since burn and burn size were impor-
tant variables, hormonal values in relation to burn size
were first considered as the mean value for each patient
over PBD 3-26. Subsequently, individual values were
analyzed over this time period with PBD and TBS as
independent variables in multiple regression analyses.
Because of variation with time and less variation of FT$_4$
than FT$_3$ with burn size, only the multiple regression
approach, accounting for time since burn, showed a
significant burn size-related suppression of FT$_4$ in
SURV.
Based on mean values for each patient, the reduction
in FT$_4$ was proportional to burn size in patients not
treated with T$_0$ (Fig. 3, upper left). Comparison of mean
FT$_4$ and TSH suggests that the thyroid axis was simi-
larly suppressed in NSURV and in T$_0$-treated patients
(Fig. 3, upper right). An inverse relationship between rT$_3$
and FT$_4$ or FT$_3$ can also be seen in patients not treated
with T$_0$ (Fig. 3, lower panels). Multiple regression anal-
yses showed that T$_0$, T$_3$, FT$_4$, and FT$_3$ (p < 0.001) were
inversely proportional to TBS or TBS$^2$ in placebo-treated
patients. In these patients, T$_0$, T$_3$, FT$_4$, FT$_3$, and TSH
were excessively low (p < 0.01) for burn size in the
NSURV group. T$_3$ treatment raised T$_3$ and FT$_3$ in
SURV-TX and NSURV-TX (p < 0.001) and suppressed
T$_0$, FT$_4$, and TSH (p < 0.001) in survivors but not in
nonsurvivors. Figure 3 (right panels) shows the corre-
sponding results based on mean values for each patient
for FT$_3$, TSH, and FT$_4$. Multiple regression analysis
showed that in placebo-treated patients, higher rT$_3$
was associated with greater TBS (p < 0.01). T$_3$ treatment
reduced rT$_3$ 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 postin-
jury, and MR was positively correlated with NE (Fig. 4).
NE and MR were both inversely correlated with FT$_4$
(p < 0.001, not shown) in placebo-treated patients. Mul-
tiple 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

![Diagram](attachment:image.png)

**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.

![Diagram](attachment:image2.png)

**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 T$_0$-treated patients are excluded, then the relationship
between rT$_3$ and FT$_4$ (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 \( T_i \) treatment on EPI, DA, or MR.

Interrelationships among the measured values in untreated patients were defined by considering FT, FT, 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, I. 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, FT, 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/M²·day) than for survivors (SURV, 1526-2192; SURV-TX, 1630-2256 kcal/M²·day).

**DISCUSSION**

In agreement with previous findings, 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. NSURV of burns had the lowest FT, and FT, 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. These results are compatible with failure of brain centers controlling the thyroid axis or with direct suppression of TSH release by elevated DA or cortisol. Whether the excessively low FT, FT, 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 \( T_i \) to \( T_2 \) and accumulation of the inactive \( rT_2 \) (the product of inner ring monodeiodination of \( T_i \) in the periphery) are features of other forms of NTI. Similarly, we found an inverse relationship of \( rT_2 \) to FT, and TSH values for SURV 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.

Burned patients are hypermetabolic, which again suggests the absence of functional hypothyroidism. Their hypermetabolism is blunted by propranolol, a \( \beta \)-blocker. Their urinary catecholamines are elevated in proportion to MR as are their plasma catecholamines as shown in the present study. MR was more closely correlated with NE than 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. 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, such as elevation of heart rate, cardiac output and core temperature. In our placebo-treated patients, larger burn size and lower FT, 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. \( T_i \) 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 trauma[13] and several types of febrile illnesses[14] are associated with hypermetabolism, and febrile illnesses are associated with elevated catecholamine secretion[15] and decreased T₃ levels.[15] Patients with extensive burns and probably patients with other non-thyroidal 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 Fehrman, and Jan Bullard for technical assistance and Sandy Hale for technical, editorial, and typing assistance.

REFERENCES