A New Prognostic Index in Surgery and Parenteral Feeding: the Ratio of Triiodothyronine to Reverse Triiodothyronine in Serum (T₃/rT₃ ratio)

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ABSTRACT
Serum concentrations of albumin, triiodothyronine (T₃), and reverse triiodothyronine (rT₃) were measured in 46 patients on the first day after routine gastrointestinal surgery, and the molar ratio T₃/rT₃ was calculated. The median value of this ratio, but not of albumin, was significantly lower in 11 who subsequently suffered major septic complications than in the remainder. Measurement of the ratio correctly predicted the outcome of 80% of individuals.

The T₃/rT₃ ratio, midarm muscle circumference (MAMC), triceps skin fold (TSF) and serum concentrations of albumin and transferrin were measured in 23 patients at referral for parenteral feeding. Median values of T₃/rT₃ ratio, MAMC and transferrin, but not of the other parameters, were significantly lower in nine who died than in survivors. Measurements of the ratio, MAMC and transferrin correctly predicted the outcome of 87%, 78% and 74% of individuals, respectively.

INTRODUCTION
Following non-thyroidal surgery in euthyroid patients there is a fall in serum concentration of triiodothyronine (T₃), the main bioactive form of thyroid hormone, and a rise in serum concentration of reverse triiodothyronine (rT₃), its inactive stereo-isomer [1], resulting in a highly significant transient decrease in the molar ratio between their respective concentrations (T₃/rT₃) [2]. Similar changes occurring in fasting states [3], and in many serious diseases [4], are reversed upon recovery [4]. They appear to reflect the catabolic state accompanying illness [4], and the possibility of using them as a non specific index of the metabolic response to surgery has been suggested [2].

In a pilot study [5] in a small number of patients we confirmed that the post-operative fall in T₃/rT₃ ratio was significantly more profound and prolonged in those suffering post-operative complications than in those recovering normally. We have, therefore, extended our studies to clarify the role of the T₃/rT₃ ratio as a prognostic index. In our first study (A), we have determined the prognostic significance of T₃/rT₃ ratio and serum albumin concentration immediately following routine non-thyroidal surgery in terms of subsequent major septic complications. In a further group of patients (Study B) with various gastrointestinal conditions referred for parenteral feeding we have assessed, in terms of subsequent mortality, the prognostic values of T₃/rT₃ ratio, MAMC, TSF and serum concentration of albumin and transferrin.

PATIENTS AND METHODS
The patients in Study A were drawn from a series of unselected cases admitted to Greenwich District Hospital for major gastro-intestinal surgery from 46 of whom (19 female), blood was collected within 24 h of operation (Table 1). The only criterion for exclusion was the concurrent use of drugs known to produce...
changes in $T_3/rT_3$ ratio, namely, corticosteroids [6] and B-blocking agents [7]. All patients received routine post-operative care and monitoring according to the normal practice of the three general surgeons co-operating in the trial.

The patients in Study B were 23 cases (seven female) referred to the King’s College Hospital parenteral nutrition service, conforming to the same exclusion criteria (Table 2). Anthropometry was performed and blood taken for estimation of $T_3$, $rT_3$, albumin and transferrin concentrations at the time of referral.

Serum $T_3$ concentration was measured using a radioimmunoassay kit (Amersham Radiochemicals), $rT_3$ concentration by a modification of the method of Mathur et al. [8], and the molar ratio $T_3/rT_3$ was calculated from these results. Serum albumin was measured by a bromocresol green method and serum transferrin was measured by radial immuno-diffusion.

The prognostic ‘accuracy’ of each parameter studied is expressed as the percentage of total patients in whom the test correctly predicted the outcome. To determine ‘accuracy’ in Study A, post-operative values of the ratio $T_3/rT_3$ below 0.9 have been regarded as abnormal. In Study B values of serum transferrin concentration below 1.5 g/L, of the ratio $T_3/rT_3$ 1.0 and of MAMC below the fifth centile of age and sex matched normals [9], have been regarded as abnormal. These values were selected in each case from a random variety of possible cutoff points as they gave the highest ‘accuracy’. In statistical analysis of results, Wilcoxon’s unpaired rank sum test, Chi-square with Yates correction, and Fisher’s exact probability test, have been used, as appropriate.

**RESULTS**

**Study A**

Eleven patients (24%) suffered major sepsis following surgery (Table 3), including four in whom sepsis contributed to death. There was one death in the remaining 35. Those with sepsis showed a lower median value of $T_3/rT_3$ than the remainder, $p < 0.02$ (Fig. 1), though values of serum albumin did not differ significantly (Fig. 1) and were, therefore, not of prognostic value in this population. Sepsis occurred in nine of 16 with $T_3/rT_3$ ratio below 0.9, and in two of the remaining 30

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Patient details—Study B</th>
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</thead>
<tbody>
<tr>
<td>Non-Survivors $N = 9$</td>
<td>Survivors $N = 14$</td>
</tr>
<tr>
<td>Indications for parenteral feeding</td>
<td></td>
</tr>
<tr>
<td>Post-operative ileus ± sepsis</td>
<td>56</td>
</tr>
<tr>
<td>Malignant upper GI obstruction</td>
<td>11</td>
</tr>
<tr>
<td>Enterocutaneous fistula:</td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0</td>
</tr>
<tr>
<td>Mesenteric infarction</td>
<td>11</td>
</tr>
<tr>
<td>Ileus:</td>
<td></td>
</tr>
<tr>
<td>Cholangitis</td>
<td>11</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>11</td>
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</tbody>
</table>

**Table 3** Sites of sepsis in 11 patients—Study A

<table>
<thead>
<tr>
<th>Sepsis</th>
<th>Study A</th>
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</thead>
<tbody>
<tr>
<td>Deep wound abscess</td>
<td>5</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5</td>
</tr>
<tr>
<td>Septicaemia</td>
<td>2</td>
</tr>
<tr>
<td>Pericolic abscess</td>
<td>1</td>
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</table>
panied by a fall in concentration of thyroxine (T\textsubscript{4}), but there is no corresponding increase in basal TSH [13], indicating suppression of the pituitary thyroid axis. It is speculated that they may represent a pathophysiological adaptation to illness, producing a decrease in metabolic rate, and hence possibly exerting a protective effect in damaged and hypoxic tissues or limiting catabolism [10]. Indeed, muscle catabolism during fasting is increased by administration of physiological doses of T\textsubscript{3} [14].

The T\textsubscript{3}/rT\textsubscript{3} ratio has many of those features desirable in a surgical prognostic index. It is unaffected by changes in hepatic synthetic function and in total body water, which may produce spurious changes in plasma protein concentrations or, as we have reported [15], in anthropometric variables, and being the ratio between serum concentrations of two thyroxine metabolites, it is also independent of the rate of thyroxine secretion. Since both T\textsubscript{3} and rT\textsubscript{3} are measured by radioimmunoassay, results could be obtained within 24 h from a laboratory set up to provide an urgent service.

Results of this study confirm that in patients undergoing abdominal surgery, post operative measurement of the ratio is highly predictive of subsequent sepsis, which underlies the majority of major complications. The significant, and not unexpected, association between malignancy and sepsis makes it difficult to separate the relationship of these two variables to changes in the ratio. However, if the presence of malignancy were used to predict subsequent sepsis, the prognostic accuracy achieved would be only 70\textsubscript{o}, in this study population, and, in a survey of patients with benign disease, a strong relationship between post-operative values of the ratio and subsequent complications is being shown [16].

While it would be ideal to observe the association between values of the ratio, and sepsis, in a specific site, following a specific operation for a single disease in patients of comparable age, the numbers required are beyond the scope of this study. We have tried to approach this ideal by excluding patients having non-gastrointestinal surgery, and by studying only major sepsis, rather than all complications.

The obvious drawback of the ratio is that, as the changes seen occur in response to surgery or other severe illness, they can only be used to determine the need for subsequent intensive support, not in pre-operative assessment of routine surgical patients. In contrast, it has been suggested that pre-operative measurement of other indices such as handgrip dynamometry [17], or the Sheffield prognostic index [18], might lead to identification of a group who would benefit from pre-operative nutritional supplements. The role of such pre-operative measures is, however, far from established, and indeed, the Sheffield prognostic index may deteriorate further during such treatment [18]. Whilst Study A is not strictly comparable with those reporting pre-operative assessments, the 80\textsubscript{o}, accuracy of the T\textsubscript{3}/rT\textsubscript{3} ratio in predicting major sepsis is very similar to the best reported in predicting major complications with handgrip dynamometry [17], and slightly better than that found using the Sheffield prognostic index [19].
Results of Study B show that, in a heterogenous group of sick patients referred for nutritional support, the ratio was at least as accurate as the best of the other variables measured in predicting subsequent mortality. It appears to offer a non-specific but objective assessment of 'degree of illness', rather than of nutrition, and in this respect its closest equivalent may be post-operative handgrip dynamometry [20], an investigation which, unlike the ratio, is restricted to the conscious and co-operative patient.

The closest reported equivalent study investigated the association between various parameters of thyroid function and subsequent mortality in 195 unselected admissions to an intensive care unit [12]. Serum T₃ was found to be more strongly correlated than either T₃ or rT₃ alone, but achieved only 70% prognostic accuracy, compared with 87% achieved by T₃/rT₃ ratio in Study B. Furthermore, this was achieved by taking the lowest sequential value recorded, not that at the time of referral, and was therefore clinically less useful.

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REFERENCES


**Fig. 2** Study B. Values at time of referral of T₃/rT₃ (molar ratio), serum concentrations of albumin and transferrin (g/l), and of anthropometric variables (percentage of 50th centile for population of same age and sex†). Closed circles represent those dying. Open circles represent survivors. Horizontal bars are median values. (The 5th centile cutoff value of MAMC for each population approximates to 80%, of the 50th.)
[16] Calvey H Unpublished observations

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