Reduced Peripheral Conversion of Thyroxine to Triiodothyronine in Patients with Hepatic Cirrhosis

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ABSTRACT The role of liver in the peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3) was studied in normal subjects and patients with alcoholic liver disease by measurement of thyrotrophin (TSH) and total and free T_4 and T_3 in random and serial serum samples. Also, T_4 to T_3 conversion rates and T_3 disposal rates were compared by noncompartmental analysis. While the mean total serum T_4 values were similar for the two groups, 8.6 and 8.1 μg/dl, the mean free T_4 value was significantly higher in the cirrhotic patients (3.3 ng/dl) than in the normal subjects (2.1 ng/dl, $P < 0.001$). The mean serum T_3 value, 85 ng/dl, was significantly reduced in the hepatic patients as compared to a mean serum T_3 value of 126 ng/dl in the normal subjects ($P < 0.001$), while the free T_3 value was 0.28 ng/dl in both groups. The reduction of the serum total and free T_3 values were closely correlated with the degree of liver damage, as indicated by elevation of serum bilirubin ($r = -0.547$) and reduction of serum albumin ($r = 0.471$). The mean serum TSH level was 3.1 μU/ml in the normals and 7.1 μU/ml in the cirrhotic patients ($P < 0.001$). 15% of the hepatic patients had serum TSH values above 10 μU/ml, which, however, did not correlate with any of the four liver function tests studied. Serial blood sampling from two convalescing patients with alcoholic hepatitis showed a gradual normalization of serum TSH and T_3 levels as the liver function improved. After oral T_4 administration, 0.25 mg/day for 10 days, three of four cirrhotic patients studied failed to raise their serum T_3 values. The mean T_4 to T_3 conversion rate of seven normal subjects was 35.7%. The mean T_4 to T_3 conversion rate of four cirrhotic patients studied was significantly reduced to 15.6% ($P < 0.001$). The mean disposal rates of T_4 and T_3 of the normal subjects were 114 and 34 μg/day, respectively. The ratio of T_4 disposal to T_3 disposal was 3.5. In contrast, the mean T_4 disposal rate, 82 μg/day, and the mean T_3 disposal rate, 10 μg/day, were both reduced in the cirrhotic patients. Their ratio of T_4 disposal to T_3 disposal was 7.9. These findings suggest that impairment of T_4 conversion in patients with advanced hepatic cirrhosis may lead to reduced T_3 production and lowered serum T_3 level. Therefore, the liver is one of the major sites of T_4 conversion to T_3.

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INTRODUCTION

It is now well established that thyroxine (T_4) [1] is converted to triiodothyronine (T_3) in the peripheral tissues of man (1–4), rat (5), and sheep (6). The contribution of this pathway to the total T_3 production appears to be higher in man and sheep than in rat. T_3 can also be converted from T_4 in vitro by perfused rabbit liver (7) and rat heart (8), by slices of pituitary (9), kidney (10), and brain (11), and by tissue cultures of human fibroblast (12), kidney, and liver (13). Still, it is not known in what proportion the different organs contribute to the overall T_3 production in the intact animal under physiological circumstances. Several early studies suggest that liver plays a role in the metabolism of thyroid hormones (13–20). Cavalieri and Searle (17) estimated the hepatic volume of distribution for T_4 to be approximately 38% of the total T_4 volume of distribution. More recently, another laboratory as well as our own reported the observation of reduced T_3 and elevated thyrotropin (TSH) levels in the serum of

[1] *Abbreviations used in this paper:* MCR, metabolic clearance rate; T_3, triiodothyronine; T_4, thyroxine; TSH, thyrotropin.

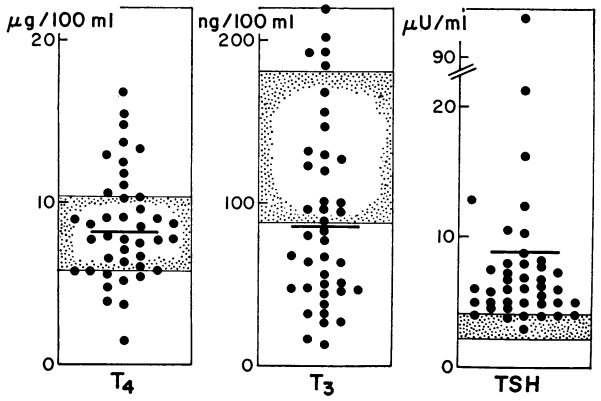

FIGURE 1 Random serum T_4, T_3, and TSH were assayed by radioimmunoassay in normal subjects and hepatic patients. The range of values obtained from normal subjects is shown as shaded area. The individual values from the liver patients are shown as dots while the group mean is shown as a horizontal bar.

hepatic patients (21, 22) that suggested possible failure of T_4 conversion. The present study was carried out to define the role of liver in the peripheral conversion of T_4 to T_3. Random and serial serum samples from normal subjects and hepatic patients were assayed for TSH, and total and free T_4 and T_3. The T_4 to T_3 conversion rate and the T_4 and T_3 disposal rates were estimated in both normal subjects and cirrhotic patients by noncompartmental analysis and were found to be markedly reduced in the cirrhotic patients. The results of these studies constitute the substance of the following report.

METHODS

Subjects. Normal volunteers were selected from the medical personnel for their good general health and absence of any thyroid or liver disorder. The hepatic patients were chosen from the hospitalized patients of two urban hospitals for advanced alcoholic liver disease, as documented by different combinations of hepatomegaly, icterus, ascites, abnormal serum proteins, and elevated bilirubin, alkaline phosphatase, and transaminase levels. The serum bilirubin, transaminase, and alkaline phosphatase were measured by AutoAnalyzer (Technicon Instruments Corporation, Ardsley, N. Y.) and the serum albumin was measured by electrophoresis in the hospital laboratories. Among the etiologies of the liver disorder were alcoholic cirrhosis, alcoholic hepatitis, and acute viral hepatitis. All subjects had given their informed consent for the present study.

Hormone assays. Serum TSH (23), T_4 (24), and T_3 (25) were assayed by the double-antibody technique of radioimmunoassay. Serum free T_4 and free T_3 were measured by dialysis, simultaneously, according to the method of Sterling and Brenner (26) with minor modifications. Human pituitary TSH standard 68/38 was a gift from the National Institute for Medical Research (Mill Hill, London). The purified human TSH for iodination was provided by the National Institute of Arthritis, Metabolism and Digestive Diseases (Bethesda, Md.). The T_4 and T_3 standards were purchased from Sigma Chemical Co. (St. Louis, Mo.). The anti-T_4 antiserum and the anti-T_3 antiserum were raised in our laboratory in rabbits immunized with bovine albumin conjugate of T_4 or T_3. The final dilution of anti-T_4 antiserum was 1:2,500 and that of anti-T_3 antiserum was 1:12,000. An anti-rabbit gammaglobulin antiserum from goat was used as the second antibody and was purchased from Antibodies, Inc. (Davis, Calif.). The interassay coefficients of variation for TSH, T_4, and T_3 assays were 7.9, 3.4, and 7.9%, respectively. The intra-assay coefficients of variation was 2.2% for TSH, 4.1% for T_4, and 3.9% for T_3. Each sample was run in triplicate. The random serum samples from normal subjects and hepatic patients were randomized and assayed together. In the longitudinal studies all sera from the same subject were assayed together. The least detectable concentration in the TSH assay varied between 1.5 to 2.1 μU/ml, calculated as the mean minus two standard deviations of the zero tube. Subjects with undetectable TSH level were routinely assigned a level half the respective least detectable concentration for the calculation of means. For the present study, no normal control had an undetectable TSH level.

Kinetic analysis. Radiothyroxine labeled with ^{125}I and radiotriiodothyronine labeled with ^{131}I, with a specific activity over 40 μCi/μg and 50 μCi/μg, respectively, were purchased from Amersham-Searle Corp. (Arlington Heights, Ill.). The purity of the radioactive hormones was 95–97%, as monitored by paper chromatography. They were diluted to the desired concentration with a 1% human albumin solution in normal saline and then passed through a Millipore filter (Swinnex 0.22 μm, Millipore Corp., Bedford, Mass.). The radioisotopes were assayed simultaneously in a well scintillation counter with a two-channel analyzer. The assay of ^{125}I activity was corrected for ^{131}I spillage.

The subjects were given T_4 by mouth, 0.25 mg daily, starting at least 2 wk before and 5 drops three times a day of Lugol's solution, starting just before study. At the start of study, the patients were given an intravenous injection of a combined dose of 60 μCi of ^{125}I-labeled T_4 and 100 μCi of ^{131}I-labeled T_3 in 1% sterile human albumin solution. Blood samples were taken at 0, 0.15, 1, and 2 h and then at 4-h intervals during the first 48 h and then at daily intervals up to 14 days. The serum was separated and an aliquot was stored at −20°C for radioimmunoassays later. The remaining aliquot was treated with propylthiouracil and sodium iodide, and precipitated with trichloroacetic acid as described elsewhere (3). The precipitate was extracted three times with three volumes of ethanol. The difference of radioactivity between the total precipitate and the extracted precipitate was assumed to represent the hormonal activity. The dose standard was added into the zero-time serum sample of each subject precipitated and extracted similarly. The recovery of radioactive T_4 and T_3 was 90% and 85%, respectively.

Calculation. The serum radioactivity (percentage of dose per liter) was plotted as a function of time.

The metabolic clearance rate, T_4 and T_3 disposal rates, and the conversion rate of T_4 to T_3 were estimated by the noncompartmental method of Tait (27) with minor modifications (28). The metabolic clearance rate (MCR), expressed in liters per day, was calculated from the area under the curve of the hormonal radioactivity disappearance from serum according to Simpson's rule.

TABLE I

Clinical Data of Consecutively Hospitalized Liver Patients

Subjects	Age	Bilirubin	SGOT	Alkaline phosphatase	Albumin	Remarks
	yr	*mg/dl*	*IU/liter*	*IU/liter*	*g/dl*	
Acute viral hepatitis						
1 J. M.	23	10.5	999	246	3.5	
2 G. B.	22	6.2	200	302	3.9	
3 B. H.	23	9.7	2,030	190	3.2	
4 *J. P.	39	22.5	1,500	140	4.2	
5 M. M.	26	7.4	1,300	160	4.4	
Alcoholic hepatitis and cirrhosis						
6 *P. W.	48	0.5	89	51	3.3	
7 J. P.	48	39.0	185	912	1.5	
8 D. J.	29	20.5	295	155	3.7	
9 D. M.	36	43.5	100	196	2.9	
10 C. W.	50	9.3	226	107	2.5	
11 A. S.	61	3.1	118	194	3.5	
12 L. M.	45	15.5	132	298	4.2	Ascites
13 S. M.	40	7.0	140	279	3.1	
14 W. W.	53	21.0	211	375		
15 G. H.	56	21.0	149	775	2.3	
16 A. H.	39	2.7	35	107		
17 C. P.	23	19.2	1,500	120	3.4	
18 B. D.	21	0.5	48	144	2.4	
19 E. G.	61	1.4	103	151	2.3	
20 E. W.	23	20.5	98	222	3.0	
21 T. J.	52		20	258		Ascites
22 S. B.	53	1.4		208	3.1	
23 L. D.	42	1.8	73	135	2.3	
24 E. B.	41	8.7	191	530	3.1	
25 T. H.	40	4.8	279	1,575	3.0	
26 C. R.	48	6.0	246	278	3.0	Ascites
27 D. D.	51	4.0	121	149	2.7	Ascites
28 C. B.	43	3.7	133	236	2.5	
29 W. R.	40	11.0	212	625	3.3	
30 P. S.	48	0.4	51	180	2.8	
31 E. W.	43	1.1	133	236	4.0	
32 J. C.	45	1.5	169	118	1.6	
33 E. W.	57	1.9	234	91	2.5	
34 B. H.	48	5.2	74	126	3.0	
35 J. H.	65	1.4	192	174	3.3	
36 S. F.	58	0.7	83	118	4.3	
37 W. A.	48	2.2	176	98	3.8	
38 J. F.	29	1.8	207	350	4.1	
39 W. S.	45	1.3	50	120	4.4	
40 T. B.	58	2.7	161	190	3.1	Ascites
41 E. L.	37	0.7	89	172	4.2	
Patients used in kinetic analysis						
42 C. R.	37	2.8	190	104	2.8	
43 R. J.	45	2.5	183	98	2.6	
44 W. T.	51	9.5	140	380	2.5	
45 J. D.	60	2.0	100	98	3.1	
Patient mean		8.2	295	261	3.2	
±SD		9.9	444	266	0.7	
Normal range		0.2–1.1	8–40	30–90	3.5–5.0	

All patients were men.

* Deleted from calculation.

TABLE II

The Serum Thyroid Hormones in Patients with Alcoholic Hepatitis and/or Cirrhosis

Patients	T_4			T_3			TSH
	Total	Free fraction	Free	Total	Free fraction	Free	
	μg/dl	%	*ng/dl*	*μg/dl*	%	*ng/dl*	*μU/ml*
6*	1.5	0.027	0.4	13	0.285	0.04	93.1
7	3.9	0.077	3.0	16	0.483	0.08	5.7
8	3.7	0.075	2.8	27	0.490	0.13	6.3
9	6.7	0.053	3.6	32	0.395	0.13	7.9
10	8.5	0.053	4.5	31	0.443	0.14	4.9
11	5.6	0.042	2.4	38	0.404	0.15	3.7
12	5.4	0.049	2.6	44	0.390	0.17	16.4
13	8.7	0.066	5.7	46	0.494	0.23	12.4
14	5.4			46			12.4
15	5.8	0.082	4.8	47	0.582	0.27	5.1
16	5.7			47			4.1
17	7.7	0.050	3.9	48	0.352	0.17	5.9
18	6.3	0.085	5.4	50	0.600	0.30	3.0
19	7.1	0.037	2.6	51	0.279	0.14	7.5
20	7.9	0.045	3.6	56	0.344	0.19	8.8
21	7.5	0.033	2.5	64	0.331	0.21	4.1
22	8.9			64			4.0
23	6.5	0.037	2.4	67	0.309	0.21	6.8
24	6.0	0.069	4.1	68	0.496	0.34	5.0
25	11.0	0.025	2.8	77	0.210	0.16	7.3
26	8.6	0.041	3.5	80	0.351	0.28	10.4
27	9.0	0.042	3.8	83	0.362	0.30	6.8
28	7.7	0.031	2.4	89	0.270	0.24	6.0
29	10.3	0.032	3.3	95	0.320	0.30	21.3
30	4.7	0.032	1.5	96	0.311	0.30	4.4
31	13.3	0.028	3.7	100	0.238	0.24	6.0
32	5.7	0.034	1.9	101	0.303	0.31	4.0
33	13.7	0.029	4.0	120	0.260	0.31	4.9
34	9.6	0.048	4.6	123	0.390	0.48	10.2
35	10.6	0.029	3.0	127	0.270	0.34	7.2
36	9.1	0.027	2.5	132	0.297	0.39	7.9
37	12.9	0.026	3.4	147	0.218	0.32	5.0
38	7.8	0.030	2.3	156	0.270	0.42	5.6
39	7.7	0.032	2.5	184	0.261	0.48	5.1
40	9.0	0.034	3.1	193	0.286	0.55	7.7
41	14.8	0.024	3.6	219	0.224	0.49	4.2
Patient mean	8.1	0.044	3.3	85	0.351	0.27	7.1
±SD	2.7	0.016	0.9	50	0.103	0.52	3.8
Control mean	8.6	0.024	2.1	126	0.256	0.28	3.1
±SD	1.7	0.001	0.3	23	0.028	0.02	0.6
P	NS	<0.001	<0.001	<0.001	<0.005	NS	<0.001

* Data deleted from calculation.

RESULTS

Random serum samples from 33 normal medical personnel and 45 hepatic patients were assayed for TSH and total and free T_4 and T_3. The age range of the normal subjects was 22–48 yr. They were free of any thyroid or liver disease by history and physical examination. The hepatic patients were chosen from patients admitted consecutively to the medical wards with an admitting diagnosis of hepatitis or cirrhosis. All hepatic patients had hepatomegaly and many had icterus and ascites as well. Five of these patients had clinical features compatible with acute viral hepatitis while the

remainder presented with acute alcoholic hepatitis and/or alcoholic cirrhosis. Alcohol intoxication was absent at the time of blood sampling. The results from these two groups are compared in Fig. 1 and the clinical information of the hepatic patients is tabulated in Table I. The data of two hepatic patients were deleted from the calculation of group means. One of these patients, P. W., No. 6, was considered to have primary hypothyroidism besides his liver disorder. The other patient, J. P., No. 4, had a history of Graves' disease for which he had received ^{131}I therapy 6 yr before.

The recovery of unlabeled T_3 added to a pool of serum from patients with liver disease did not differ from the recovery data of a pool of normal serum, in agreement with the observation by Chopra, Solomon, Chopra, Young, and Chua Teco (21). Bilirubin added into the assay tubes up to 100 mg/dl did not shift the curve of TSH standard.

The studies of patients with alcoholic liver disease are shown in Table II. The mean levels of serum total and free T_4 of the normal subjects were 8.6±1.7 μg/dl and 2.1±0.3 ng/dl, respectively. The mean levels of the total and free serum T_4 of the hepatic patients were 8.1±2.7 μg/dl and 3.3±0.9 ng/dl, respectively. There was no difference between the mean total serum T_4 levels, while the mean free serum T_4 level of the hepatic patients was significantly higher than that of the normal subjects ($P < 0.001$).

The mean serum T_3 concentration of the normal controls was 126±23 ng/dl. The mean serum T_3 concentration of the hepatic patients was 85±50 ng/dl. The difference between the T_3 levels of these two groups was statistically significant ($P < 0.001$). 21 of the patients had T_3 levels below the range of normal controls and many had T_3 values low enough to be compatible with advanced hypothyroidism. The serum free T_3 fraction was high, so the serum free T_3 was low in the patients with low serum total T_3 and high in the patients with normal levels of serum total T_3. The mean serum free T_3 level was the same for both groups (0.27 and 0.28 ng/dl). The reduction of serum T_3 in the hepatic patients was proportionately greater than the reduction of their serum T_4 values. The mean total T_4/total T_3 ratio of the normal controls was 62 ±9, whereas that of the liver patients was nearly doubled, 117±52 ($P < 0.05$). A similarly significant difference between the free T_4/free T_3 ratios of the normal controls (7.5) and the hepatic patients (14.4) was observed. The reduction of serum total and free T_3 levels was poorly correlated with the levels of serum transaminase or alkaline phosphatase (Table III). However, it showed a positive correlation with the serum albumin concentration ($r = 0.471$) and a negative correlation with the serum bilirubin concentration ($r = -0.547$). Therefore, the alteration of serum T_3 level more closely reflected the synthetic capacity of the liver than its cellular integrity.

The mean serum TSH level of the normal subjects was 3.1±0.6 μU/ml. The mean serum TSH of the hepatic patients was 7.1±3.8 μU/ml. The difference between the TSH values of these two groups was statistically significant, with a P value of < 0.001. Six of these patients had TSH values above 10 μU/ml, a level commonly used for the diagnosis of primary hypothyroidism. Sera were available for the measurement of serum free T_4 and T_3 in five of these six patients. All of them had high levels of serum free T_4. Only two of these patients showed reduced levels of serum free T_3, while the others had either high or normal levels of serum free T_3. None of these patients were clinically hypothyroid and none had findings of Hashimoto's thyroiditis. The levels of TSH could not be correlated with the levels of serum free T_4 ($r = 0.098$), serum free T_3 ($r = 0.035$), or the ratio of free T_4 to free T_3 ($r = 0.024$). Some of the patients who had marked re-

TABLE III

The Relationship between the Liver Function Tests and the Thyroid Function Tests Expressed by the Pearson's Correlation Coefficients

	Serum bilirubin	Serum transaminase	Serum alkaline phosphatase	Serum albumin
Total T_4	0.425*	0.014	0.044	0.352*
Total T_3	0.547*	0.152	0.200	0.471*
Total T_4/total T_3	0.622*	0.202	0.230	0.348*
Free T_4	0.144	0.166	0.003	0.125
Free T_3	0.531*	0.209	0.252	0.376*
Free T_4/free T_3	0.696*	0.242	0.257	0.384*
TSH	0.226	0.012	0.189	0.182

* $P < 0.05$.

TABLE IV

The Serum Thyroid Hormones in Patients with Acute Viral Hepatitis

Patients	T_4			T_3			TSH
	Total	Free fraction	Free	Total	Free fraction	Free	
	μg/dl	%	ng/dl	μg/dl	%	ng/dl	μU/ml
1	10.2	0.043	4.4	95	0.310	0.30	5.0
2	12.5	0.029	3.6	130	0.225	0.29	6.8
3	15.4	0.026	4.0	168	0.193	0.32	5.7
4*	16.8			192			4.0
5	7.4	0.021	1.6	202	0.187	0.38	4.6
Patient mean	11.4	0.030	3.6	149	0.229	0.32	5.5
±SD	3.4	0.009	0.8	46	0.057	0.04	1.0
Control mean	8.6	0.024	2.1	126	0.256	0.28	3.1
±SD	1.7	0.001	0.3	23	0.028	0.02	0.6
P	<0.01	<0.050	<0.001	NS	NS	<0.025	<0.001

* Data deleted from calculation.

duction of serum free T_3 had serum TSH level below 10 μU/ml. (Patients 7, 8, 9, 10, 11, 17, 19, 20, 25).

The number of patients with acute viral hepatitis included in this study was small. As compared to the normal controls, they appeared to have higher values of serum total and free T_4 as well as higher values of serum TSH (Table IV). Their ratios of total T_4 to total T_3 (88±21) and free T_4 to free T_3 (12±4) suggest that the patients with acute viral hepatitis also have lowered serum T_3 levels relative to the levels of serum T_4.

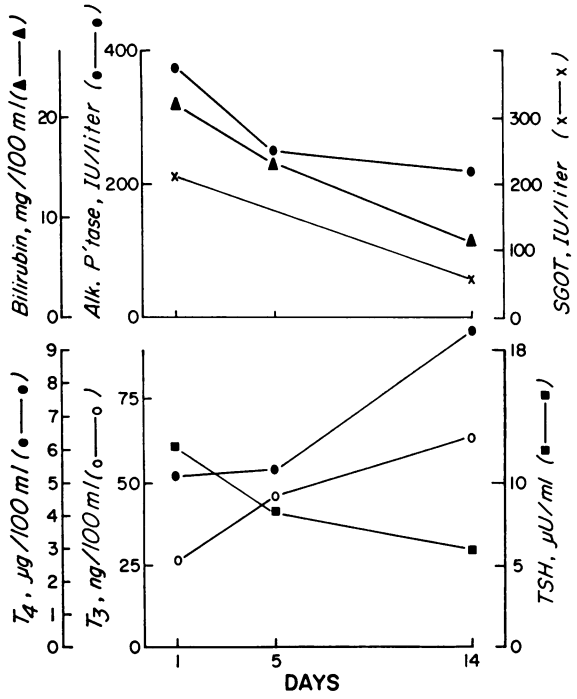

FIGURE 2 A 53-yr-old white man (W. W.), who presented with a history of chronic and acute alcohol abuse and acute alcoholic hepatitis. He had jaundice and hepatomegaly. His hepatic dysfunction improved on diet and bed rest.

A longitudinal study of liver function, serum TSH, T_4, and T_3 was carried out in two hepatic patients with moderately severe alcoholic hepatitis. The results of these patients were similar and one of these studies is depicted in Fig. 2. The results demonstrated that the alterations of serum TSH and T_3 were transient and reversible in acute hepatic disease. Upon improvement of the liver function, serum TSH and T_3 also showed a tendency to normalize in accord with the reversible liver damage.

Another group of seven normal medical personnel and four patients with advanced but stable liver cirrhosis, and without clinical ascites, were included for the study to estimate the extrathyroidal T_4 conversion rate to T_3. Each subject was given T_4, 0.25 mg/day, by mouth starting 2 wk before the kinetic study to suppress the thyroidal secretion of T_4 and T_3. TSH, T_4, and T_3 levels in these subjects were followed during the first 10 days. The mean serum TSH of the normal subjects was 4.8±2.4 μU/ml at the start and 4.5±2.4 μU/ml at the end of study. The serum T_4 level in the normal subjects was 10.2±1.7 μg/dl at the start and 10.8±1.5 μg/dl at the end of study. The mean serum T_3 rose from 122±23 ng/dl to 156±31 ng/dl. Three of the seven normal subjects showed only a transient rise of serum T_3 value, which returned to the original levels before the end of the study. The results obtained from

the four hepatic patients are shown in Fig. 3. During T_4 replacement, the mean serum TSH level fell slightly in the four hepatic patients from 12.4±6.8 to 9.4±5.1 μU/ml ($P < 0.01$). The serum T_4 level was unchanged, 7.0±1.6 μg/dl at the beginning and 8.5±1.7 μg/dl at the end of the study. The serum T_3 level was below normal in all of the hepatic patients at the start of the study. It failed to show any rise in three of the four patients during the study, although the average serum T_3 level rose from 48±2 to 62±32 ng/dl. These findings showed that in the hepatic patients, supplement of T_4 substrate did not always normalize the serum T_3 level. Therefore, failure of hypothalamus, pituitary, or thyroid cannot account for the reduced serum T_3 level in most of the hepatic patients.

Kinetic analysis of T_4 and T_3 in these seven normal subjects and four hepatic patients are tabulated in Table V. These normal subjects and hepatic patients did not show a significant difference in their disappearance rates, turnover rates, and volumes of distribution of either T_4 or T_3. The two groups also showed similar metabolic clearance rates. In the normal subjects, the MCR of T_4 was 1.1±0.1 liter/day (mean±SD) and the MCR of T_3 was 22.6±4.1 liter/day. In the hepatic patients, the MCR of T_4 was 1.0±0.2 liter/day and the MCR of T_3 was 19.2±4.0 liter/day. However, the hepatic patients showed a definite failure to convert T_4 to T_3 as compared to the normal subjects. The seven normal subjects had a range of T_4 to T_3 conversion rates 31.4–40.2%, with a mean of 35.7±6.4%. The four hepatic patients had a range of T_4 to T_3 conversion

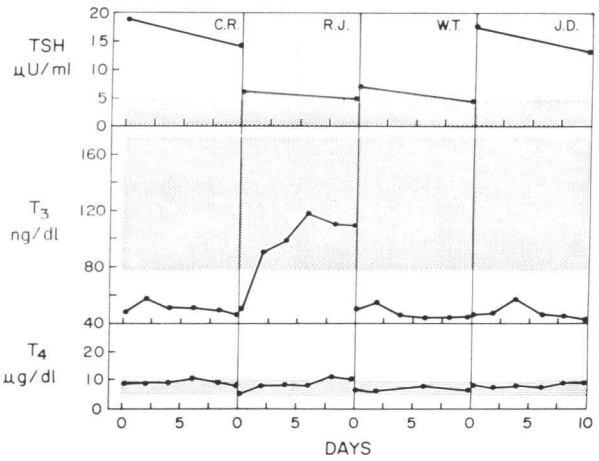

FIGURE 3 Four patients with advanced, but stable hepatic cirrhosis were given oral T_4, 0.25 mg/day. Serial serum samples were assayed for TSH, T_4, and T_3 during the initial 10 days.

TABLE V

The Thyroxine Conversion Rate to Triiodothyronine in Normal Subjects and Hepatic Patients

	Serum level		Metabolic clearance rate		Disposal rate		T_4 to T_3 conversion rate
	T_4	T_3	T_4	T_3	T_4	T_3	
	μg/liter		*liter/day*		*μg/day*		%
Normal subjects							
R. C.	111	1.45	1.05	25.77	116	37	38.9
R. M.	120	1.58	0.88	18.03	105	28	32.2
R. St.	116	1.36	1.14	27.72	132	38	34.1
F. A.	76	1.27	1.03	16.32	79	21	31.4
H. W.	101	1.62	1.17	24.71	119	40	40.2
H. A.	117	1.80	1.19	23.35	139	42	36.3
R. Sa.	103	1.43	1.01	22.16	104	32	36.5
Mean	106	1.50	1.07	22.58	114	34	35.7
±SD	15	0.18	0.11	4.12	20	7	3.3
Liver patients							
C. R.	95	0.51	0.99	19.83	94	10	12.8
R. J.	90	0.99	0.79	14.94	71	15	25.1
W. T.	62	0.41	0.97	17.60	60	7	14.5
J. D.	76	0.36	1.36	24.30	104	9	10.0
Mean	81	0.57	1.03	19.17	82	10	15.6
±SD	15	0.29	0.24	3.96	20	3	6.6
P	0.025	0.001	NS	NS	0.050	<0.001	<0.001

All values were normalized to 70 kg body wt.

rates 10.0–25.1%, with a mean 15.6±6.6% ($P < 0.005$). In the normal subjects the estimated disposal rates of T_4 and T_3 were 114±20 μg/day and 34±7 μg/day, respectively, with a T_4 disposal to T_3 disposal ratio of 3.5. In the hepatic patients the disposal rate of T_4 was found to be low, 82±25 μg/day, which suggests impairment of T_4 absorption in some of the patients. The T_4 tablets were given by the nursing staff to both groups, and the patients did not have other symptoms of malabsorption. The mean T_3 disposal rate in the cirrhotic patients was reduced to 10±3 μg/day with a T_4 disposal/T_3 disposal of 8.2, suggestive of a 70% decrease of T_3 production by T_4 deiodination. These findings suggest a significant impairment of peripheral T_4 conversion to T_3 in patients with advanced liver cirrhosis that leads to reduced serum T_3 level.

DISCUSSION

The production of T_3 is now believed to come from both thyroidal secretion and peripheral thyroxine conversion (1–4). The maintenance of serum T_3 within its normal range is, therefore, a function of the concentration of serum T_3 binding proteins, the T_3 disposal rate, the thyroidal T_3 secretion rate, and the T_4 to T_3 conversion rate. Recently, several laboratories reported a significant reduction in the serum total T_3 (21, 22) and free T_3 levels (21) in the hepatic patients. The cause of these changes was believed to be failure of T_4 to convert to T_3. In the present study, four patients with advanced but stable liver cirrhosis were given T_4 by mouth, 0.25 mg/day, for 10 days. Three of the four patients without other signs of malabsorption failed to elevate their serum T_3 value. Chopra and colleagues (21) also observed a normal T_3 rise in response to administration of thyrotropin-releasing hormone in patients with liver cirrhosis. Therefore, pituitary or thyroidal failure is not a likely etiology for the reduced serum T_3 level. This conclusion is supported by the measurement of the MCRs and the disposal rates of T_4 and T_3 and the T_4 to T_3 conversion rates with noncompartmental analysis in normal subjects and cirrhotic patients. The normal subjects had a T_4 disposal/T_3 disposal ratio of 3.5, while the cirrhotic patients had a significant increase of T_4 disposal/T_3 disposal ratio to 8.2. The mean T_4 to T_3 conversion rate was 34% for the normal subjects and 16% for the cirrhotic patients.

The kinetic data of normal subjects obtained from the present study showed a much larger fraction of the extrathyroidal T_3 pool (46±9%) derived from T_4 conversion than that reported in our earlier study (31%) (3). Due to methodologic difficulty in the competitive protein-binding assay of T_3, the serum T_3 level reported in our earlier study (3) was approximately twice our current serum T_3 level for normal subjects, determined by radioimmunoassay. Radioimmunoassay of the same serum samples used in our earlier study (3) would modify our original conclusion and allow that approximately 62% of the total extrathyroidal pool of T_3 or 82% of the daily T_3 production was derived from T_4 conversion in subjects with normal thyroid function. Similar estimates were reported by other investigators using radioimmunoassay for T_3 measurements (4, 5). Our present study employed a different experimental design and a different method of calculation from our earlier study (3). Yet the T_4 to T_3 conversion rate estimated by the present study was 36%, similar to the estimate of 33% reported in our earlier study (3) and close to the estimate of 42% reported by Surks, Schadlow, Stock, and Oppenheimer (28). Such agreement between different methods and different laboratories lends support to the validity of our present method of calculation and to the conclusion of our present study, that the T_4 to T_3 conversion rate in the hepatic patients is reduced despite the fact that only a small number of liver patients were studied in the present report.

As compared to the average values of normal subjects, these cirrhotic patients had a 50% reduction in their mean T_4 to T_3 conversion rate and 70% reduction in their mean T_3 disposal rate. The kinetic study of hepatic patients reported by Inada and Sterling (18) did not include the kinetics of T_3. The present study agrees with their conclusion that the hepatic patients have essentially normal T_4 disappearance rates, but our estimation of the T_4 disposal rate was slightly lower than that of normal controls. In another kinetic study of the hepatic patients, McConnon, Row, and Volpe reported reduced T_4 production, normal serum total T_3 level, and elevated serum free T_3 level and T_3 production (29). These results are difficult to reconcile with the findings of other investigators (18, 21), as well as with our own observation (22), and underline the importance of proper staging and grouping of hepatic patients. McConnon and colleagues also used a competitive protein-binding technique now believed to overestimate serum T_3 levels.

Alteration in serum proteins is one of the criteria commonly used in assessing the synthetic capacity in cirrhotic patients. In the serum of hepatic patients, the level of thyroxine-binding prealbumin was reported to be reduced (18, 20). The mean level of thyroxine-binding globulin was found to be normal, but there was wide variability of individual values. In the present study, the mean serum total T_4 was unchanged, but the mean values of both the serum free T_4 fraction and the actual serum free T_4 were elevated in the hepatic patients. At the same time, the mean serum

total T_3 was reduced in the same group. The mean serum free T_3 fraction was elevated so that the actual serum free T_3 was low only in the patients with reduced serum total T_3, and it was elevated or normal in the patients who have normal values of serum total T_3. The resultant mean serum free T_3 of the hepatic patients was in the same range as that of the normal controls. The changes in the serum total and free T_3 were correlated with the severity of liver cirrhosis as reflected by the elevation of serum bilirubin and the reduction of serum albumin. Other investigators also reported elevated concentrations of serum free T_4 (18, 21, 29) associated with reduced concentrations of serum free T_3 (21) in hepatic patients. These findings cannot be explained by alteration of binding proteins alone. Rather, they suggest augmented thyroidal secretion in response to reduced circulating T_3. The synthesis of T_4 is more active than the synthesis of T_3 in the thyroid (30). Therefore, the hepatic patients whose T_3 production is reduced due to impaired peripheral T_4 conversion to T_3, can compensate and maintain a normal serum concentration of T_4 more efficiently than a normal serum T_3 concentration.

Clinical signs of hypothyroidism develop after a prolonged period of thyroid hormone depletion. Our patients probably did not have T_3 depletion long enough to become myxedematous although many of them had biochemical hypothyroidism. In the two patients with acute alcoholic hepatitis, the serum T_3 and TSH levels appeared to parallel and normalize as the liver function improved. Also as a group, the hepatic patients showed a higher mean serum TSH level as compared to the normal controls. However, some of the hepatic patients did not show a significant rise of their serum TSH despite reduced serum total T_3 and free T_3. The level of serum TSH in these patients was not correlated with either serum free T_4, serum free T_3, or the ratio of the two. Nor was it correlated with the results of liver function tests. This puzzling finding is similar to the experience of Chopra and colleagues (21). Recently, reduced serum T_3 level was observed in patients with a wide variety of other illnesses (31–34) and caloric deprivation (35) in whom the serum T_3 level was low and the serum TSH level was in the normal range. The elevation of serum TSH value was reported only in patients with advanced liver disease (21, 22) or renal disease (34). Some of the patients with these disorders were found to have elevated serum free T_4 (18, 21, 31, 33) and tissue T_4 concentration (31). It is possible that T_3 is not the sole biologically active thyroid hormone. The presence of elevated serum and tissue T_4 concentrations is sufficient to keep the patients in an euthyroid state and the basal serum TSH level in the normal range. Most of these patients reported are said to be clinically euthyroid (21). Another postulate for the absence of any compensatory increase of serum TSH could be that a chronic state of T_3 deficiency may alter the T_3 receptor in the pituitary. More work in this area is necessary to understand the TSH response in the hepatic patients as well as in the other low T_3 states.

Among the variety of illnesses associated with reduced serum T_3 level are disorders of the cardiovascular and pulmonary systems, of liver and kidney, neoplasm, and caloric deprivation (21, 22, 31, 35). The relationship between T_3 metabolism and most of these disorders is not explained by our present knowledge. Not uncommonly, the liver patients also may have malnutrition and weight loss. However, a cause and effect relationship may be postulated between liver injury and abnormal T_4 and T_3 metabolism. In in vitro experimentation, perfused liver and liver tissue culture were shown to convert T_4 to T_3 (7, 13). Reduced serum T_3 values (21, 22) were associated with liver cirrhosis and alcoholic hepatitis. The cellular damage of alcoholic hepatitis and cirrhosis was shown to be uniform and diffuse (36). In patients with advanced alcoholic cirrhosis, both the T_4 to T_3 conversion rate and the T_4 disposal/T_3 disposal ratio were significantly reduced. Supplementary T_4 fed to these patients failed to normalize the serum T_3 level. To the extent as the acute liver injury from alcoholic hepatitis was reversible, the alterations in the serum level of T_3 was also reversible. Therefore, our findings are compatible with the postulate that liver may be a major site of the peripheral T_4 conversion to T_3 and extensive liver injury may significantly reduce T_4 conversion to T_3 and circulating T_3 level.

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