Thyroid Hormones in Conditions of Chronic Malnutrition

A Study with Special Reference to Cancer Cachexia

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Circulating levels of thyroid hormones (T_4, free T_4, T_3) and reverse tri-iodo thyronine (rT_3) and thyroid-hormone binding globulin were related to the nutritional state of patients with cancer cachexia, patients with malnutrition due to other reasons and to well-nourished patients with acute illness. Hospitalized weight-stable and well-nourished patients served as controls. Malnourished patients with or without cancer and acutely ill patients had a low T_3 syndrome involving both peripheral metabolism of thyroid hormones and the hypothalamus–pituitary–thyroid gland axis. T_3 levels were correlated to altered protein metabolism and protein nutritional state. There were pronounced elevations of circulating rT_3 concentrations in patients with serum albumin concentration less than 35 g/l irrespective of diagnosis. The results indicate that the low T_3 syndrome in our patients is secondary to insufficient caloric intake. It seems to be maintained by the abnormal nutritional state and is related closely to protein metabolism. The authors found no differences between the low T_3 syndrome in cancer patients suffering from cachexia compared with that of patients with malnutrition caused by other factors.

ALTHOUGH PATIENTS with progressive malignancy demonstrate many of the clinical features of hyperthyroidism such as elevated energy expenditure,[1] increased lipid,[2] glucose,[3,4] and protein metabolism,[5] and wasting of peripheral tissues, we recently reported evidence of low T_3 syndrome in such patients.[3] Although the low T_3 syndrome in cancer patients seemed most likely to be secondary to anorexia and altered nutritional state, no studies have reported on thyroid hormone levels in relation to nutritional state of malnourished patients with and without cancer.

The aim of this study was to establish such relationships before and after nutritional support, and to evaluate whether cancer cachexia differed from nonmalignant cachexia with regard to thyroid hormone metabolism.

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Material and Methods

Patients

The clinical details and the nutritional status of the patients are seen in Table 1. Malnourished cancer and noncancer patients, acutely ill patients, and hospitalized well-nourished patients were studied. All patients were selected on clinical grounds by one of us (K.L.), which means that they did not show any other sign of disease such as diabetes, renal impairment, etc. None of the patients was on medical therapy of known importance for the study before the measurements. All patients were hospitalized for at least 3 to 4 days before our measurements and had eaten the same well-balanced hospital diet of their own choice of similar overall fat (34%), protein (18%), and carbohydrate (48%) composition.

This study was approved by the Ethical Committee of the University of Gothenburg and informed consent was obtained from each patient.

Group I

Cancer patients. This group consisted of 22 weight-losing cancer patients (stage III or IV) with local and distant metastases and a history of weight loss exceeding 7% of their normal body weight. None was totally bedridden, but all patients had clinical signs of malnutrition and cachexia. The diagnoses were confirmed by angiography, computerized tomography, and histologic evaluation of tumor biopsies. None of the patients had received any treatment for their disease before the study. The diagnoses were: gastric carcinomas,[2] colonic carcinomas,[2] pancreatic carcinoma,[2] hepatic carcinoma,[2] pulmonary carcinoma,[2] prostatic carcinoma,[2] hypopharyngeal carcinoma,[2] oesophageal carcinoma,[2] malig-

TABLE 1. *Nutritional State in Study and Control Patients (Mean ± SE)*

	Malnourished Cancer Patients (N = 22)	A*	Malnourished Noncancer Patients (N = 14)	Acutely Ill Patients (N = 9)	B†	Well-nourished Controls (N = 11)
Age (years)	63 ± 4		65 ± 3	48 ± 7	‡	68 ± 4
Height (cm)	171 ± 2		172 ± 2	178 ± 3		174 ± 2
Weight (kg)	52.6 ± 2.0		54.0 ± 3.7	77.4 ± 5.5		73.4 ± 3.4
Body weight index (actual/ideal)	0.72 ± 0.03		0.72 ± 0.03	0.96 ± 0.06		0.96 ± 0.04
Weight loss (kg)	10 ± 1	‡	6 ± 1	2 ± 1		—
Total body potassium (mmol)	2332 ± 100		2284 ± 140	3650 ± 247 (N = 3)		3346 ± 231
Total body potassium index (actual/ideal)	0.74 ± 0.04		0.73 ± 0.02	—		1.0 ± 0.05
Albumin (g/l)	28 ± 1	‡	33 ± 1	27 ± 2	§	40 ± 2
Prealbumin (g/l)	0.10 ± 0.01	‡	0.18 ± 0.02	0.14 ± 0.02	§	0.28 ± 0.02
Haemoglobin conc (g/l)	116 ± 3		122 ± 4	113 ± 7		128 ± 6
Erythrocyte sedimentation rate (mm/hr)	50 ± 9		56 ± 11	84 ± 12	‡	31 ± 7
Abnormal liver function tests	7/22		2/12	4/5		4/11
Body temperature (C)	37.1 ± 0.1		37.0 ± 0.1	37.8 ± 0.2	‡	36.9 ± 0.2
Triceps skinfold (cm)	7.4 ± 0.8		7.4 ± 0.9	7.4 ± 2.1		11.4 ± 1.3
Mid-arm circumference (cm)	21.8 ± 0.7	‡	23.8 ± 1.3	—		26.5 ± 0.8

The nonparametric Mann-Whitney U-test was used.
* A: Malnourished cancer *versus* malnourished noncancer patients.
† B: Acutely ill patients *versus* well-nourished controls.
‡ $p < 0.05$.
§ $p < 0.01$.

nant melanoma,[1] urinary bladder carcinoma,[1] retroperitoneal carcinoma,[1] testis carcinoma,[1] and carcinomas of unknown origin.[2] Seven patients had abnormal liver screen tests (alkaline phosphatase, aspartate and alanine amino transferase activities), but none of them had abnormal bilirubin concentrations.

Group II

Malnourished patients without cancer. This group consisted of 14 noncancer patients. All these patients were malnourished but without other sign of disease at the time of study. They had lost around 11% of their normal weight. The time course of weight loss differed among the patients, but all of them had noticeable, continuous weight loss in the weeks before the measurements. Chronic malnutrition was caused by a recent episode of a pancreatic fistula that did not cause any extrarenal loss of nitrogen (N = 1), previous treatment of hepatic and renal trauma leading to endogenous bile-duct fistula (N = 1), senile depression (N = 6), chronic gastric ulcer (N = 4), or several years of malabsorption after gastric resection with dumping-symptoms as the main reason for depressed food intake (N = 1), and anorexia nervosa (N = 1).

Group III

Acutely ill patients. Nine patients with no signs of overt malnutrition were examined in a state of acute illness expected to lead to malnutriton and change in body composition. These patients were under treatment in the Intensive Care Unit. They were studied at this time 3 to 4 days after the onset of their illness. They were selected to approximately age-match the cancer patients in Group I. They had not lost weight significantly at the time of the study, and they had received nutritional support if they were unable to eat. The diagnoses were septicaemia (N = 1), second-degree burn injury (N = 3) (15–20% of body surface area), acute pancreatitis (N = 3), initial hypovolemic shock due to acute gastroenteritis with positive bacterial cultures from enteric contents (N = 1), and perforated ulcer of the oesophagus (N = 1). Two of these patients needed ventilatory support. All patients received saline as sole intravenous infusion solution 8 to 12 hours before blood samples were taken. All patients had been given appropriate medical treatment including antibiotics. None of the patients had received steroids before the study.

Group IV

Well-nourished controls. Nine patients were hospitalized for operation of uncomplicated gallstone disease, varicose veins and inguinal hernia. They were selected from our list of out-patients and were hospitalized 3 to 5 days before the study. Two patients were hospitalized for bleeding due to anticoagulant therapy more than a week before our measurements. All control patients were

weight-stable, without any history of previous weight loss, had no other known disease, and were not under medical therapy.

Investigative Protocol

Patients who entered the study were investigated as follows: total body potassium was measured and nutritional assessment was made. After an overnight fast, blood samples were taken for measurements of thyroid hormones and albumin. Afterwards, eight cancer patients and five malnourished patients without cancer who were in the need of nutritional support, received a nasogastric tube, and a liquid-formula diet was administered continuously 24 hours/day with a pump for 2 weeks. Nutritional assessment was performed in those patients before nutrition and after the 14-day-period on nutrition. Thirteen other patients (five cancer and five malnourished patients without cancer, three well-nourished controls) were subjected to TRH-infusion after an overnight fast as described below. Body temperature was measured sublingually with a digital probe.

Nutritional Status

Nutritional assessment included physical examination and measurements of body weight, height, triceps skinfold, mid-arm circumference, total body potassium, serum albumin and prealbumin concentration. Total body potassium was measured in a whole-body counter. Patients were considered to be malnourished according to the criteria described elsewhere.[6]

Biochemical Analyses

Venous samples were drawn from the cubital vein. After centrifugation, serum was stored at −20 C until analyzed. Albumin was measured colorimetrically (bromocresol-green) and prealbumin by rocket immunoelectrophorsis. Serum thyroid hormones and TSH were measured by radioimmunoassay kits from Diagnostic Products Corporation (Los Angeles, CA): blood haemoglobin concentration, erythrocyte sedimentation rate and liver tests; and alanine amino transferase, aspartate aminotransferase, and alkaline phosphatase activites were determined according to routine procedures at the Department of Clinical Chemistry.

Enteral Nutrition

Food intake was measured in patients receiving nasogastric tube-feeding. Eight of the cancer and five of the malnourished patients without cancer were re-examined after 2 weeks of enteral nutrition. These patients did not differ in any respect from the other patients in the groups they belonged to. They received a formula diet (Clinifeed 400®, Roussel Company, Paris, France), which was given at a rate of 30–40 kcal/kg × 24 hours (1900 kcal and 70 g protein per day) for 2 weeks. These patients were on clinical grounds allowed to eat what they wanted in excess of the infused formula diet. Their spontaneous oral intake was before nutrition: 26 ± 2 kcal/kg/day (mean ± SE) in cancer patients and 31 ± 9 kcal/kg/day in malnourished patients without cancer; during enteral nutrition day 12–14: 13 ± 5 kcal/kg/day in cancer patients and 26 ± 7 kcal/kg/day in malnourished patients without cancer.

TRH Infusion

Five malnourished cancer patients, five malnourished patients without cancer and three well-nourished control patients were examined by prolonged TRH infusion as described by others.[7] These patients did not differ in any respect from the other patients of the groups they belonged to. After an overnight fast, TRH was infused over 4 hours with the patient at rest in bed. TRH, in 500 ml of saline, was given intravenously by means of an infusion pump. One microgram of TRH was infused per minute and after 4 hours a bolus dose of 500 μg TRH was given during 1 minute. Blood samples for measurements of TSH and thyroid hormones were drawn from the contralateral cubital vein as follows: two 30 minutes before infusion; 3 immediately before infusion; during infusion after 30, 90, 150, 210, 240, 245, 255, 270 and 300 minutes. A bolus of TRH (500 μg) was given (Figs. 1A–C) 240 minutes after start of infusion.

Statistics

Nonparametric statistics (Mann-Whitney U-test) were used in group comparisons.[8] Linear regressions were computed by the least-square method. With respect to nutritional state and physiologic variables, malnourished cancer patients were compared with malnourished patients without cancer, and patients with acute illness were compared with well-nourished controls (Table 1). Patients suffering from malnutrition and acute illness were compared to well-nourished controls with respect to thyroid hormones (Table 2). The effect of enteral nutrition in malnourished cancer and noncancer patients was evaluated by comparing nutritional state and biochemical variables before and after nutritional by means of Wilcoxon's test for paired observations (Tables 3 and 4). P-values less than 0.05 were considered statistically significant.

Results

Nutritional Status (Tables 1 and 3)

Malnourished patients with and without cancer were comparable, but malnourished cancer patients may

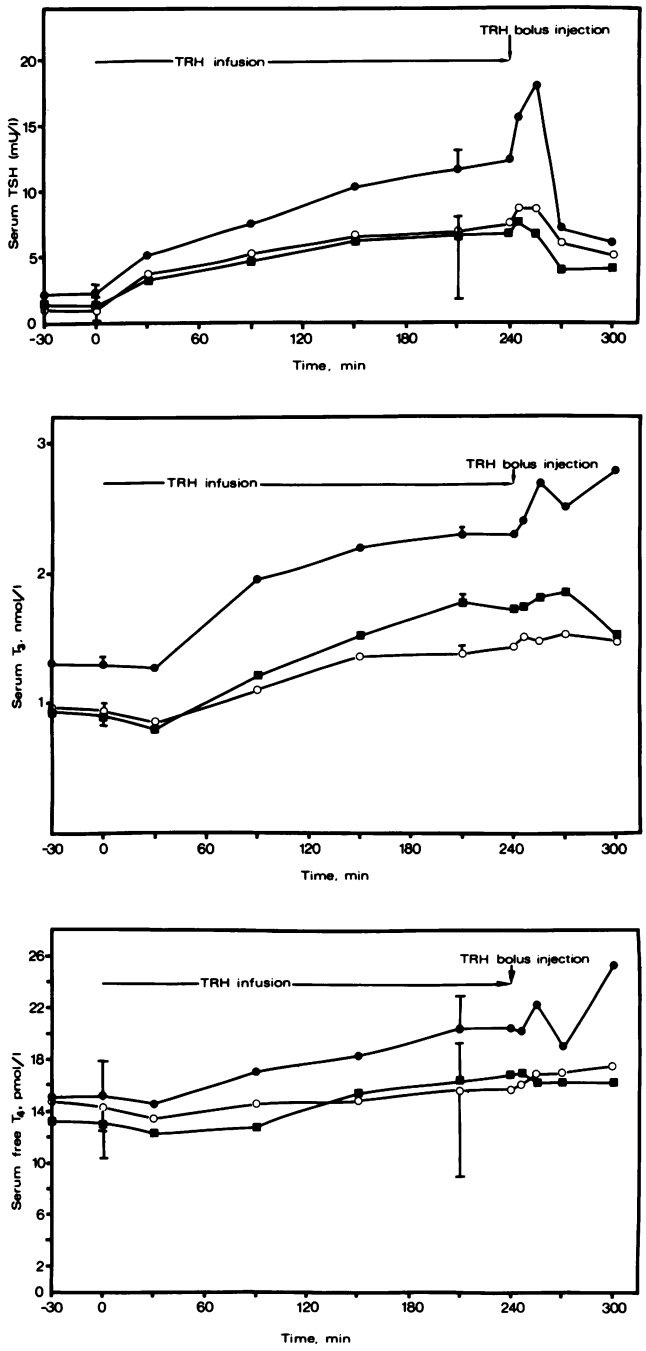

FIG. 1. *A, top; B, middle; C, bottom.* Serum free T_4, T_3, and TSH before and during infusion of TRH in five malnourished cancer patients, five malnourished patients without cancer, and three well-nourished controls. Bars indicate SE. ■ = Malnourished cancer patients; ○ = malnourished noncancer patients; and ● = well-nourished controls.

have been slightly more protein malnourished than noncancer patients as evaluated from lower plasma proteins. Acutely ill patients were comparable in most respects to well-nourished patients but had significantly higher body temperature. The low concentrations of albumin and prealbumin in acutely ill patients probably were due to haemodilution during treatment. Malnourished cancer patients differed from well-nourished patients in all nutritional variables. Two weeks of enteral nutrition improved the nutritional state of malnourished patients with and without cancer with regard to body weight, body potassium and mid-arm circumference. The lack of increased plasma protein during feeding may have to some extent been due to an expanded plasma volume supported by a tendency to a lower haemoglobin concentration in malnourished noncancer patients.

Thyroid Hormones (Tables 2 and 4)

Thyroid hormones in study groups (Group I–III) were compared with well-nourished controls (Group IV). Thyroxine (T_4) was only significantly decreased in acutely ill patients, while T_3 were depressed in malnourished patients with and without cancer, and acutely ill patients. All study groups showed a tendency to elevated rT_3 levels, but this was increased significantly only in cancer patients. Acutely ill patients had lower TBG levels, probably due to haemodilution (Table 2).

Two weeks of enteral nutrition did not cause any significant changes in thyroid hormones evaluated in subgroups of malnourished patients. However, when malnourished cancer and noncancer patients were pooled, there was a significantly increased T_3 level (Table 4).

Figures 2A–C show the relationship between plasma thyroid hormones and plasma albumin in all patients. There was a positive correlation between T_3 or fT_4 versus albumin, while rT_3 levels were increased irrespective of diagnosis when plasma albumin was lower than 35 g/l.

TRH Infusions

Figures 1A–C show TSH and thyroid hormone levels in response to TRH infusion in comparable groups of malnourished patients with and without cancer as related to well-nourished controls. Due to large variation and small number of patients, it is difficult statistically to ascertain possible differences, but visual inspection of the curves indicated that TSH levels seemed to increase more in well-nourished controls compared with malnourished patients. The relative response was less different among the groups (results not shown). Similar changes were also found with respect to T_3 and fT_4. In general, it seemed that a bolus injection of TRH caused a more pronounced release of TSH and appearance of T_3 and fT_4 in well-nourished patients after 4 hours of constant infusion of TRH. Thyroxine and rT_3 levels did not change in response to TRH in any of the groups. These results agree with those reported from the same kind of

TABLE 2. *Plasma Levels of Thyroid Hormones, Thyroid Stimulating Hormone (TSH) and Thyroid Binding Globulin (TBG) (Mean ± SE)*

	Cancer Patients (N = 22)	Malnourished Noncancer Patients (N = 14)	Acutely Ill Patients (N = 9)	Well-nourished Controls (N = 11)
Free T_4 (pmol)	10.4 ± 0.6†	13.0 ± 0.9†	8.7 ± 0.8*	15.1 ± 0.5
T_3 (nmol/l)	0.88 ± 0.08†	1.13 ± 0.10†	0.68 ± 0.10*	1.59 ± 0.10
T_4 (nmol/l)	100 ± 3	107 ± 8	69 ± 6*	107 ± 6
rT_3 (nmol/l)	0.63 ± 0.07†	0.40 ± 0.08	0.47 ± 0.08	0.29 ± 0.01
TSH (mU/l)	1.4 ± 0.1	1.3 ± 0.1	1.2 ± 0.1*	1.6 ± 0.2
TBG (mg/l)	23.0 ± 0.9	23.7 ± 1.0	17.0 ± 0.9†	22.8 ± 0.72

The Mann-Whitney U-test was used.
* $p < 0.05$ *vs.* well-nourished controls.
† $p < 0.01$ *vs.* well-nourished controls.

investigation in healthy well-nourished individuals subjected to short-time experiments of fasting and refeeding.[7]

Discussion

This study has evaluated levels of thyroid hormones in different groups of patients with and without overt malnutrition. Three study groups have been examined, namely malnourished cancer patients, malnourished patients without cancer, and acutely ill patients without overt malnutrition as compared with a group of patients without any sign of malnutrition or disease of known importance for thyroid hormone metabolism. The two groups with overt malnutrition were comparable with respect to age[9,10] and nutritional state, although the noncancer patients may have been slightly more protein malnourished judging from plasma protein levels. The acutely ill patients were not overtly malnourished and had normal body composition. It is therefore obvious that depressed thyroid hormones are not secondary to changes in nutritional state only. They thus seem to be a means of adapting to altered energy homeostasis as soon as energy balance starts to be negative,[1] irrespective of whether this is mainly due to depressed food intake, as in progressive cancer disease, or to an increased energy expenditure as, in trauma and sepsis.[11-14] Our acutely ill patients received nitrogen and calories in amounts that should cover their essential nutritional needs. Hence, it is likely that thyroid hormone levels in acute disease are

TABLE 3. *Nutritional Status of Malnourished Patients before and after Two Weeks of Nasogastric Tube-Feeding*

	Albumin (g/l)	Pre-albumin (g/l)	Body Weight (kg)	Weight Index (Actual/Ideal)	TBK* (mmol)	TBK Index (Actual/Ideal)	Triceps Skinfold (mm)	Midarm Circumference (cm)	Haemoglobin Conc. (g/l)
Before nutrition cancer patients (N = 8)	29 ± 1	0.13 ± 0.02	53.5 ± 4	0.70 ± 0.05	2201 ± 132	0.64 ± 0.04	6.7 ± 1.7	21.6 ± 1.3	106 ± 4
After nutrition cancer patients (N = 8)	28 ± 2	0.13 ± 0.03	57.8 ± 4.6‡	0.76 ± 0.06‡	2677 ± 251‡	0.79 ± 0.08‡	7.8 ± 0.9	23.9 ± 1.2†	105 ± 6
Before nutrition malnourished patients (N = 5)	33 ± 4	0.23 ± 0.07	58.4 ± 8.0	0.76 ± 0.07	2474 ± 359	0.76 ± 0.07	7.1 ± 1.3	23.7 ± 2.7	132 ± 6
After nutrition malnourished patients (N = 5)	32 ± 3	0.22 ± 0.05	61.7 ± 8.4‡	0.81 ± 0.07†	2632 ± 322†	0.82 ± 0.07‡	7.9 ± 1.2	23.0 ± 2.6	117 ± 7
All patients (N = 13)	31 ± 2	0.17 ± 0.03	55.4 ± 3.6	0.74 ± 0.04	2306 ± 156	0.69 ± 0.04	6.9 ± 1.0	22.3 ± 1.2	116 ± 5
All patients (N = 13)	30 ± 2	0.16 ± 0.03	59.4 ± 4.2‡	0.78 ± 0.04‡	2658 ± 189‡	0.80 ± 0.05‡	7.8 ± 0.9	23.6 ± 1.1†	110 ± 4

Wilcoxon's test for paired observations was used.
* TBK = total body potassium.
† $p < 0.05$ *vs.* before nutrition.
‡ $p < 0.01$ *vs.* before nutrition.

TABLE 4. *Plasma Levels of Thyroid Hormones, Thyroid-Stimulating Hormone (TSH) and Thyroid-Binding Globulin (TBG) in Malnourished Patients before and after Two Weeks of Nasogastric Tube-Feeding (Mean ± SE)*

	Free T_4 (pmol)	TSH (mU/l)	T_3 (nmol/l)	T_4 (nmol/l)	rT_3 (nmol/l)	TBG (mg/l)
Before nutrition cancer patients (N = 8)	9.8 ± 0.7	1.12 ± 0.15	0.90 ± 0.13	106 ± 5	0.49 ± 0.08	25.2 ± 1.3
After nutrition cancer patients (N = 8)	9.6 ± 1.2	1.46 ± 0.30	1.20 ± 0.28	95 ± 7	0.53 ± 0.13	24.3 ± 1.6
Before nutrition malnourished patients (N = 5)	12.2 ± 1.7	1.31 ± 0.11	1.25 ± 0.29	105 ± 18	0.36 ± 0.09	22.4 ± 1.4
After nutrition malnourished patients (N = 5)	12.2 ± 1.4	1.50 ± 0.30	1.55 ± 0.15	98 ± 7	0.21 ± 0.05	21.4 ± 1.7
Before nutrition all patients (N = 13)	10.8 ± 0.8	1.19 ± 0.10	1.03 ± 0.14	106 ± 7	0.44 ± 0.06	24.1 ± 1.09
After nutrition all patients (N = 13)	10.6 ± 1.0	1.47 ± 0.19	1.34 ± 0.18*	96 ± 5	0.41 ± 0.09	23.2 ± 0.82

Wilcoxon's test for paired observations was used.

* $p < 0.05$ *vs.* before nutrition.

not simply correlated to food intake as seems to be the case in acute pure starvation.[15-17] The results in this study are not in entire agreement with those in a previous study that reported elevated T_4 level in patients with advanced breast carcinoma.[18]

It is well known that thyroid hormones are the main regulatory factors of energy homeostasis over a long time-period,[19,20] while the catecholamines are acute regulators,[21] and alterations in catecholamine activity secondarily can alter the sensitivity to thyroid hormones in different tissues.[22] In addition, nutritional aberrations may alter tissue sensitivity to thyroid hormones.[19] The design of the present study does not allow any evaluation in this respect. In spite of this, it is worth noting that patients with overt malnutrition for a preceding period of several months had high rT_3 levels, which suggests that some regulating step might not have been sufficiently sensitive to alterations in nutritional state and whole-body substrate fluxes, these being lower in malnourished patients with and without cancer compared with well-

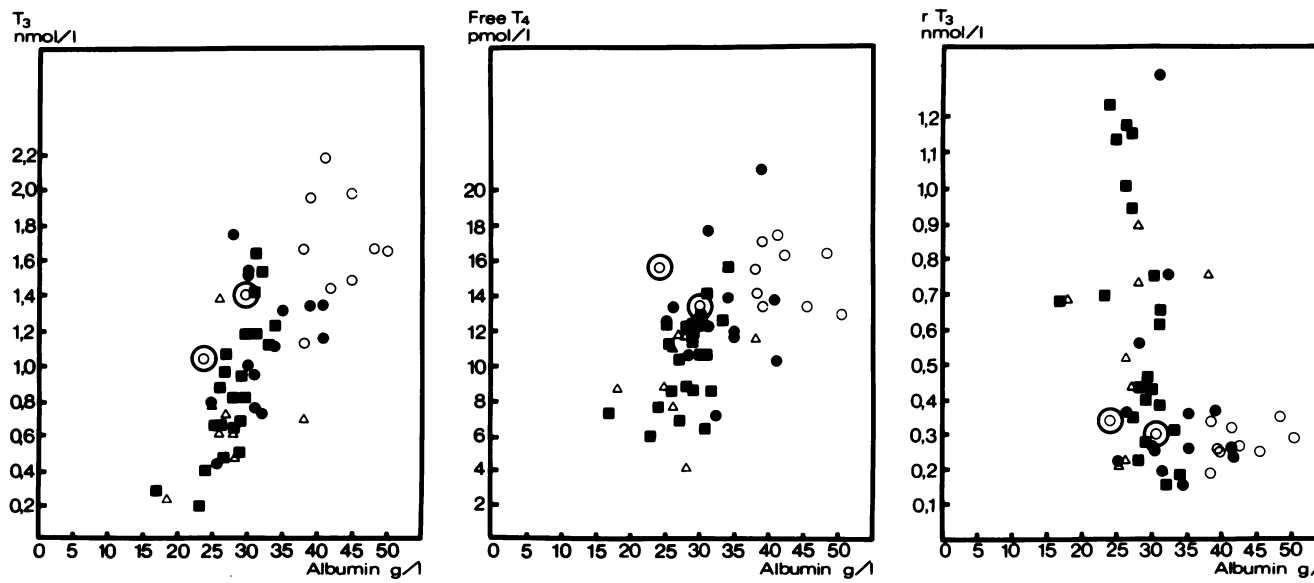

FIG. 2. *A, left; B, middle; C, right.* The relationship between serum albumin and serum T_3, free T_4, and rT_3 in patients suffering from malnutrition, acute illness and in controls. Two well-nourished control patients with low albumin had suffered from blood loss a week before measurements. ■ = Malnourished cancer patients; ○ = malnourished patients without cancer; △ = acutely ill patients; and ● = well-nourished controls. $Y = 0.0475X - 0.4310$, $r = 0.69$, and $p < 0.01$. $Y = 0.2719X - 3.2525$, $r = 0.55$, and $p < 0.01$.

nourished and healthy subjects.[23] According to this view, one would expect a substantial decrease of rT_3 after a period of chronic malnutrition.[24] In this context, it should be emphasized that physical exercise can prevent the increase in rT_3 levels associated with semi-starvation.[25] The fact that the response to TRH infusion seemed to be less than normal in malnourished patients with and without cancer supports the conclusion that low T_3 syndrome in cancer-induced chronic malnutrition involves both the pituitary–thyroid level and peripheral tissues in a similar way as in acute pure caloric deprivation.[7,26] The lower increase in TSH and T_3 levels during constant infusion of TRH and after the bolus injection after 4 hours of constant infusion suggests that both pituitary pool, the synthesis of TSH and the conversion of T_4 to T_3 were diminished in malnourished patients. It is not possible to decide where the trigger for the development of a low T_3 syndrome is located in the kind of patients examined in this study, but the end-stage adaptation engaged both central and peripheral mechanisms. The correlations between thyroid hormones and plasma albumin support the close association between such regulatory enzymes and the actual protein nutritional state. Albumin is, as a single factor, one of the most sensitive and predictive factors in indicating malnutrition in a general sense.[6,27] Moreover, in several studies, the level of albumin indicating malnutrition is actually around 35 g/l, the level where rT_3 started to rise, irrespective of the cause (diagnosis) of hypoalbuminemia in our patients. Thus, rT_3 levels might be an additional variable to include in studies aimed at predicting morbidity and incidence of malnutrition. Our results agree with experimental results indicating that synthesis and processing of albumin were more sensitive to hypothyroidism than nonsecretory hepatic proteins.[28]

Two weeks of enteral nutrition for our malnourished patients improved their nutritional state in relation to increase in body weight, whole-body potassium and mid-arm circumference. The abnormalities in thyroid hormones were not normalized, but T_3 levels increased significantly, supporting a partial normalization. The lack of normalization may be due to the fact that nutritional state was not sufficiently improved, that dietary composition was less than optimal,[17,29] or that albumin concentrations were not changed at all. Unchanged albumin levels during a short period of nutritional support is a well-recognized phenomenon,[27] probably due to dilution of the intravascular pool. The incomplete normalization of thyroid hormones in our malnourished patients on a complete diet contrast to the complete normalization after 2 days of refeeding with glucose only in obese patients who had starved for 4 days.[15] This again supports the contention that food intake is not the only factor determining the low T_3 syndrome.

It has become evident that thyroid hormones are potent regulators of protein homeostasis in skeletal muscles[30,31] and also regulate protein metabolism in liver cells.[32] This means that hypothyroidism leads to depressed protein synthesis. Hypothetically, a low T_3 syndrome therefore may maintain a block in protein synthesis of skeletal muscles even when parenteral and enteral nutrition is given in sufficient amount to patients, and hence a less than optimal response to nutritional support. A similar question has been addressed experimentally in our laboratory.[33] Malnourished tumor-bearing mice received exogenous supplementation of thyroxine to achieve normal levels of circulating thyroid hormones during progressive growth of the tumor. This lead to a protection of RNA content and RNA activity in skeletal muscles in spite of the fact that muscle nitrogen did not increase. This suggests an increased turnover of proteins in malnourished animals as well. Prevention of the development of a low T_3 syndrome by thyroxine supplementation made the situation worse for the tumor-bearing hosts, since they did not increase their spontaneous food intake to keep up with their whole-body demand. In order to reverse the block in protein synthesis in skeletal muscles more rapidly, it might be fruitful to supplement patients with low doses of thyroxine in conditions of low T_3 syndrome when nutritional demands can be covered artificially by parenteral and nasogastric tube-feeding. Such supplementation should perhaps not be given to cancer patients, since tumor growth seems to be stimulated by normal levels of thyroxine.[34–36] These questions only can be answered in future studies.

In conclusion, the low T_3 syndrome in chronic malnutrition and acute illness is not simply secondary to nutritional state or food intake. The degree of adaptation to low T_3 levels is associated with the protein metabolism and the protein nutritional state, in agreement with previous results indicating that protein-sparing diets can prevent the development of a low T_3 syndrome in spite of hypocaloric intake.[37] The end-stage adaptation in cancer-induced malnutrition is similar to that found in malnourished patients without cancer with regard to thyroid metabolism.[38]

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