REVIEW
OF
LITERATURE
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The thyroid gland as a distinctive histologic entity found only in vertebrates.

The universality and persistence of thyroid gland through all evolutionary changes in the vertebrate series certainly indicates a functionally important role.

Thyroid gland was the first endocrine gland to be recognized as such by those symptoms with excess or deficient function in mid nineteenth century.

With the advent of radioactive iodine, physiological investigations, first by Goshman (1955) and later by Leloup, Barrington and Sage, Roche et al and Clements Merliini, sought to elucidate the interrelation between endostyle and thyroid in terms of control of biochemical functions of the thyroid gland.

Brent and Herrhman studied effects of thyroxin therapy on patients with severe non thyroid illness and low serum thyroxine concentration. Thyroxin administration rapidly normalized serum $T_4$ concentration but $T_3$ concentration did not increase. Thyroxin therapy in the said study did not augment thyroid hormone action nor did it improve survival. Decreased conversion of $T_4$ to $T_3$ in the periphery has been postulated to be the predominant cause of low $T_3$ levels inspite of $T_4$ therapy.

Mc Larty et al (1975) in a study of 30 patients of myocardial infarction showed a sequential and progressional fall in serum $T_3$ and $T_4$ levels from the time of admission reaching abnormally low in all sick patients, who died in their series.
Eisenberg et al (1980) studied a group of seventy-three patients within 48 hours of admission to the intensive care unit. They found that non survivors had a greater prevalence of decreased serum total T₄ and total T₃ than survivors.

Kaptein et al (1981) evaluated the prevalence and prognostic relevance of alterations in thyroidal indices prospectively in 195 patients requiring intensive medical therapy and in 75 critically ill patients with serum total T₄ levels below 3 µg/dl. In 195 patients, serum total T₃ and total T₄ levels were reduced in 69% and 43% respectively. Decreased total T₄ levels had the highest correlation with mortality (P<0.001) and correctly predicted outcome in 70% of patients. Other thyroidal indices, which were significantly different between survivors and non-survivors, correlated with total T₄ and did not contribute independently to prediction accuracy when assessed by discriminant function analysis.

Becker et al (1982) randomized burn patients with the sick euthyroid syndrome to receive either T₃ or placebo therapy. T₃ treatment did not alter mortality. The sick euthyroid syndrome accompanying starvation has a protein sparing effect. Administration of exogenous T₃ to prevent the fall in serum T₃ with fasting results in increased muscle protein breakdown, increased gluconeogenesis, and increased fat catabolism. There are no data to support routine thyroid hormone treatment of patients with the sick euthyroid syndrome.

Slag M F, Morley JE, Elson MK et al (1981) measured thyroid function in 86 patients hospitalized in an intensive care unit. They
found hypothyroxinemia with normal thyroid stimulating hormone in 22% of the patients, and was associated with high mortality.

<table>
<thead>
<tr>
<th>T₄ levels</th>
<th>mortality</th>
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<tbody>
<tr>
<td>&lt;3.0μg/dl</td>
<td>84%</td>
</tr>
<tr>
<td>3.0-5.9μg/dl</td>
<td>50%</td>
</tr>
<tr>
<td>&gt;5.0 μg/dl</td>
<td>15%</td>
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There was a high correlation between low T₄ levels and mortality.

J.N. Carter, JM Corcoran et al (1974) detected striking abnormality in 75 sick euthyroid patients. There was a highly significant reduction in the mean free serum triiodothyronine levels with most patients having total T₃ levels in the hypothyroid range. The severity of the illness correlated well with the reduction in total serum T₃ levels. The mean free serum T₃ concentration was significantly lower than in the control patients. The mean total serum thyroxin (T₄) levels were also significantly reduced, although unlike the total serum T₃ levels they remained within the normal range. The total serum T₄ /T₃ ratios were generally higher in the sick euthyroid patients compared with the controls. Serum TSH was not increased in any patients.

J.N. Carter, C.J. Eastman et al (1976) studied to elucidate the Mechanism of low circulating T₃ Concentrations. The disappearance rate of I¹²⁵-T₃ from the circulation of five representative sick euthyroid patients were studied and found to be slower, but not significantly so, compared with three control subjects, thus excluding an increased destruction rate as the cause of low T₃ levels.
Decreased monodeiodination of \( T_4 \) to \( T_3 \) in sick euthyroid patients was confirmed by paper chromatography of extracted serum obtained 48 hours after an i.v. injection of \(^{125}\)I-T\(_4\) into two severely ill patients from the intensive therapy unit and a control subject. Peaks of radioactivity corresponding to \(^{125}\)I-T\(_4\) and \(^{125}\)I-T\(_3\) were detected in the control subject, but only a single peak corresponding to \(^{125}\)I-T\(_4\) was detected in the ill patients.

Aaron R. Zucker et al (1985) studied 9 children admitted to the ICU. Approximately 24 hours after admission to the ICU, patients had a mean serum \( T_4 \) concentration of 6.4 \( \pm \) 1.1 \( \mu \)g/dl (normal 4.2 to 11.8 \( \mu \)g/dl in the age range of patients studied) and mean serum \( T_3 \) of 74.4 \( \pm \) 22.7 ng/dl (normal 80 to 210 ng/dl in the age range of patients studied). Six of nine patients had both serum \( T_4 \) and \( T_3 \) levels below normal for age despite basal serum TSH levels of <2.5 \( \mu \)IU/ml (normal < 6\( \mu \)IU/ml in the age range of patients studied).

N. Uzel and O. Neyzi (1986) investigated thyroid functions in critical illness in infancy. Serum thyroxine (\( T_4 \)), triiodothyronine (\( T_3 \)) and thyroid stimulating hormone (TSH) concentrations were measured in 13 such patients. Significantly lower initial and subsequent \( T_4 \) values were found in the fatal group as compared with the control group. Initial \( T_3 \) concentrations both in fatal cases and in patients who recovered were significantly lower than those in the controls. Subsequent \( T_3 \) values in the group who recovered showed a relative increase, but in the fatal cases a further decrease in \( T_3 \) levels accompanied by a decrease in \( rT_3 \) levels to values comparable to those of the controls, was observed in the terminal stage.
N.K. Anand, RSK Sinha, Harish Chellani (1994) studied 30 infants with severe acute systemic illness and 30 healthy controls age and sex matched. Their T₃, T₄ and TSH levels were measured at admission and recovery or before death. They found that serum T₃ levels in infants were significantly lower than the controls with normal T₄ and TSH levels at admission. Both serum T₃ and T₄ levels increased with recovery. It was also noticed that T₃ and T₄ values were significantly reduced at or near death when compared with the admission levels.

Stirling (1962) worked on the thyroid in malnutrition. He observed that the average weight of the thyroid is lower in the Jamaican than in the British and American infants.

Francisco Beas, F Monckeberg et al (1966) worked on the thyroid response to TSH in a group of 16 patients with severe marasmus and 9 normal controls of the same age. The radioiodine uptake and the oxygen consumption were determined in both groups before and after administration of a single dose of TSH. The results suggested that the low function of thyroid gland found in marasmic infants were not only due to a decrease of TSH but also a deficit of thyroid function per se.

Graham et al (1973) had studied the thyroid hormone levels in nutritionally normal infants and in infants with marasmus on marsmic kwashiorkor. In their study, in the normal subjects, serum thyroxine was higher during the first year of life than at birth or after one year. Free thyroxine was higher at 2to3 months of age than later. TBG decreased slightly but not significantly with age. Elevated TSH of cord serum decreased to normal adult levels by 2 to3 months. Despite
normal TBG, serum thyroxine may be decreased in marasmus and during recovery. Free thyroxine may be high to low initially and normal or low during recovery, serum TSH was low or normal at both times. In Kwashiorkor, low TBG accounts for low thyroxine but free thyroxine was normal or elevated, TSH was normal. During recovery, TBG returned to normal but thyroxine only partially elevated and free thyroxine decreased as did TSH.

Ingenbleek, M.D, Ph.D. and Paul Malvaux, M.D. Ph. D. (1980) studied the peripheral turnover of thyroxine and related parameters in infants of protein caloric malnutrition. The biological half life of thyroxine (T₄) in a group of seven protein calorie malnourished children maintained under steady state conditions was significantly increased as compared with that of seven healthy counter parts (T½ = 2.15± 0.19 verses 3.19± 0.33 days, P <0.001). As a result, the daily fractional turnover rate of T₄ was significantly increased at the acute stage of the disease (K=32.4± 2.9% verses 17.8±16% /day, P<0.001). The related parameters, namely T₄ distribution space ( TDS=1.21±0.16 verses 1.75±0.21 liters) extrathyroidal T₄ pool ( ETP = 52.5± 1.3 verses 1.81± 15.7 μg T₄) and T₄ degradation rate ( TDR = 16.8±2.5 verses 32.0±1.8μg T₄ /day ) were significantly depressed in protein calorie malnourished children compared with healthy children ( P<0.001).

W. John Kalk, Karen J Hofman et al. (1986) studied 15 infants with severe protein energy malnutrition as a model of nutritional nonthyroidal illness. Changes in circulatory thyroid hormones, binding proteins and their interrelationship were assessed before and during recovery. Serum concentrations of total thyroxine and
taiiodothyronine and of thyroxine – binding proteins were extremely reduced. It was concluded that there was reduced binding of T₄ and T₃ to TBG in untreated PEM, which takes 2-3 week to recover. Increased TSH secretion appears to be an integral part of recovery from PEM.

Turkay’s et al (1995) observed the effect of protein energy malnutrition in children on serum levels of total thyroxine (T₄), total triiodothyronine (T₃) and thyrotropin (TSH). There were 107 children of 2 to 60 months in the malnutrition group and 54 healthy age and sex matched control. Serum TT₄ and TT₃ were all reduced in the malnutrition group. This decrease in TT₃ was more significant (P<0.01) in severe malnutrition than in mild PEM. Serum TSH levels in the malnutrition and control groups were similar. These results suggest that the children remained euthyroid and represent an adaptive response to protein energy malnutrition.

Orbak et al (1998) investigated the effect of malnutrition on thyroid gland weight and thyroid hormone levels. 22 children suffering from malnutrition (14 children suffering from marasmus and 8 children suffering from kwashiorkor) and 7 healthy control were studied. Malnutrition was confirmed clinically and according to the welcome trust classification. Serum thyroid hormone concentrations were measured by radioimmunoassay and weight of thyroid gland were evaluated scintigraphically. In the group with marasmus and kwashiorkor, the mean TT₄, TT₃ and FT₄ levels were significantly lower and TSH levels were significantly higher, compared to control. FT₄ was not influenced by PEM. The mean thyroid gland weights of
the group with marasmus and kwashiorkor were higher than that of the control groups.

Das MD et al (1999) worked on thyroid hormone in protein energy malnutrition. The mean serum triiodothyronine and free T₃ (FT₃) levels were significantly lower in malnourished children, whereas the total thyroxine (TT₄) free T₄ (FT₄) and thyroid stimulating hormone (TSH) levels were in the normal range.

Verma et al (2000) studied the effect of protein energy Malnutrition on serum levels of T₃, T₄ and TSH. A total of 100 children of 1-4 year’s of age group were included in the study, of which 20 healthy children with age and sex matched acted as control, 80 children were graded into four groups as per Indian academy of pediatrics (IAP) classification of PEM. Patients with infections were excluded from the study.

Serum T₃ and T₄ levels were reduced in all grades of Malnutrition group. This decrease in T₃ level was significantly low in grade II-IV (grade II P< 0.05 III & IV P<0.001). In grade I PEM, decrease in serum T₃ was not significant. Serum T₄ levels were decreased significantly in all grades of PEM (in grade I and II P< 0.05, grade III P< 0.01 grade IV P<0.001). Serum TSH levels in Malnutrition and control group was similar.

These results suggests that the children in Malnutrition group remained euthyroid and decrease in thyroid hormone levels, probably an adaptive change to PEM, which enable the sick patient to conserve protein.