DISTRIBUTION OF SERUM T3/T4 QUOTIENT IN EUTHYROID GOITROUS SUBJECT IN NIGERIA- A PROBABLE BIOCHEMICAL MARKER OF GOITER ENDEMIA.

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Objective.
To determine the relationship between the serum levels of (T4) thyroxin, (T3) Tri-iodothyronine, and (TSH) Thyrotropin versus the goiter size in an endemic euthyroid goitrous subject.

Materials and Methods.
Serum levels of thyroxin (T4), Tri-iodothyronine(T3), and thyrotrophin (TSH) were determined by "ELISA" technique in 58 adult euthyroid goitrous subjects with various grades of endemic giotre, and in 42 adult normal subjects used as control.

Findings.
The serum thyroxin (T4) levels were depressed to a low normal range in most of the subjects with advanced goitre, while Tri-iodothyronine (T3) levels were in the high normal to supra normal region.
Thyroid size was found to bear a negative correlation with serum Thyroxin (T4) levels levels($r = 0.6$; $p=0.05$) and positive correlation with Tri-iodothyronine(T3) levels ($r = 0.8$; $p=0.001$), as well as with serum thyrotropin (TSH) concentration ($r = 0.9$; p-0.001). The serum T3/T4 ratio showed a strong positive correlation with the size of the enlarged thyroids in this group of patient, ($r = 0.8$; $p=0.001$).

Conclusion.
The findings suggest that the serum T3/T4 ratio in the euthyroid goitrous subjects may probably be used as a valuable biochemical indicator in the epidemiological assessment of endemic goiytre in a population.

INTRODUCTION.

Previous studies carried out in the region showed that about two third of the area of Plateau State lies within an established endemic goiter zone, with Bassa Local Government Council (LGC) as a severely affected area (goiter prevalance (G.P) 25% in school children and 42% in adults; urinary iodide excretion (UIE) in children 9.04± 5.7 ug/dl and urinary thiocyanate 239±182 mg/dl; drinking water iodide (DWI) . 0048 (ppm)] 1-5 .Several thyroid hormone abnormalities are found in the subject with endemic goiter 4-7 . Thus, the level of serum THS and thyroglobin (Tg) have been found to be valuable biochemical markers of goiter size in endemic areas 6-8. In present investigation we determined the changes in thyroid hormones (T4, T3 and TSH) in the serum samples of subjects with various degree and duration of endemic goiter in Plateau State, Nigeria. An effort has also been made to establish the relationship (if any) between an attempt to determine whether the changes in serum level of this ratio can be used as a possible biochemical marker in the general epidemiological assessment of endemic goiter in a population.

MATERIALS AND METHODS.

Fifty eight adult euthyroid goitrous subjects (16 males and 42 females), (age range 17-59 years), and 42 normal adult subjects (11 males and 31 females) (age 16-55 years) who were used as controls were studied. The euthyroid goitrous subjects including some from the Binci-Zagun joint market of Bassa LGC of Plateau State, Nigeria, during our epidemiological survey on endemic goiter (1-5). Each goitrous subject was given a thorough clinical examination and the degree of thyroid enlargements was graded by palpation according to the criteria of assessing 'total goiter grade' (TGR) for a population as recommended by Demaeyer, lowenstein and Thilly 2,9, and shown below. All the goitrous subjects assessed in this study were clinically euthyroid.

Classification of endemic Goitre (Demaeyer et al 2.)

Grade	Description
0	Normal thyroid
La	Thyroid distinct by palpation And definitely larger than Normal for usually not visible With head in a normal or Extended position.
1b	Thyroid easily palpable and visible with the head in an extended position. The small nodule also qualifies the patient for inclusion in this group.
2	Thyroid easily visible with head in a normal Position.
3	Goiter visible at a distance (usually about the size of a fist of the observer).
4	Monstrous goiter.

The subgroups of the subjects with the various grades of endemic goiter assessed in the present investigation is shown below.

Groups	No of subjects	Sex distribution M/F	Age (years) (mean = SD)
Goiter grade 1 (la + 1b)	12	2/10	(18.6 = 1.2)
Goiter grade 2	14	4/10	(29.6 = 4.9)
Goiter 3	14	5/9	(38.2 = 11.2)
Goiter grade 4 (monstrous goiter)	18	5/13	(41 = 9.2)
Total	58	16/42	(39. 2 = 9.3)

The normal subjects of the control group were selected from the medical students, and teachnical and clerical staff of the Jos University Teaching Hospital in Jos metropolis (a non-endemic region goiter rate 0.4%) (1-5). Blood samples were collected in the morning hours and the clear sera (devoid of haemolysis, lipaemia or icterus) obtained by centrifigution, were subjected to the determination of total thyroxine (T4), total triioddothyronnine (T3) and thyrotrophin (TSH) levels using enzyme linked immunosorbent assay (ELISA) teachnique (1-3).

The commercial test kits used in the above analysis were obtained from the manufaccturer " Boehringer Mannheim Immuno Diagnostica" Mannheim, West Germany. The samples were analysed in batches and the accuracy of the results checked by the inclusion of international quality control serum sample 'precinorm U' (also supplied by the above manufacturer). The intra and inter batch variation (imprecision) was less than 8% C.V in each batch of the investigation. The results obtained were subsequently matched with the corresponding normal reference values for the local population which was earlier established in the Department 10. The descriptive statistical analysis and correlation studies were done with the help of 'Apple Lle' microcomputer using ANOVA Diskette. None of the subjects assessed in this study showed any features of nephritic syndrome, hepatic dysfunction, or severe manultrition, nor was there any history of taking oral contraceptives or pregnancy among the females, all of which may alter a normal serum T4 level significantly by causing changes in TBG .levels. The cases of clear hyperthyroidism (T4- 124 NMOL/1 and TSH 5mu/1) and hyperthyroidism (T4-58nmol/1 and TSH-5mu/1) were functionally euthyroid. Thus 18 cases of hyperthyroidism (17 with T4 elevation and 1with T3 toxicosis) and 31 cases of clear primary hypothyroidism detected during this investigation were eliminated from the study.

RESULTS.

Table 1 shows the distribution of the mean serum values of T4, T3, TSH and T3/T4 ratio in the goitrous subjects in the present investigation, with respect to their thyroid size. The result shows a weak negative linear correlation (r = -65, p=0.05) levels showed significant positive correlatons with the degree of thyroid enlargements (r =.865, p=0.001; r = . 916, p=0.001 respectively) (Table 3 and fig.1). The serum level of T4 was generally in the low-normal region in most of the patients, while that of T3 was on the opposite direction (high normal to supra normal regions) and this was particularly marked in the subjects who had large goiters (see fig.1). The serum T4 levels in all the goitrous subjects were however within the normal reference range values (58-125 nmol/1), whereas a number of subjects (34 cases) with grade2, grade3 and grade 4 thyroid enlargements showed serum T3 values in hyperthyroid range (-2.38nmol/1), (with normal TSH levels consequently exhibiting a marked elevation in the T3/T4 ratio.

Figure 1 confirms our earlier observation on the relationships between the goiter size and the serum level of T4 and T3 in the goitrous subjects. It shows that the level of serum T3 was elevated to the hyperthyroid range(-2.38 nmol/1) in 16 subjects (27%) with grade 4; 12 subjects (19%) with grade3; 5 subjects(9%) with grade2 and subject (2%) with grade1 goitre. The serum TSH was, however, within normal reference range values (.5-5mu/1) in these subjects, eliminating the possibility of T3 toxicosis.

Figure 2 shows the relationships between the thyroid size and the serum level of T3/T4 quotients in the euthyroid goitrous subjects(r = .834; p=0.001). It further reveals that the values observed in the group with grade 1 goitre were significantly not different from those in control group; while serum values in the subsequent groups (of grades2,3 and 4 goitres) carried a more consistent correlation with the rising goiter size.

Table 1: Relationship between the mean serum level of T4,T3, TSH and T3/T4 quotients and the degree of thyroid enlargements in subjects with endemic goiter.

		Serum hormones(means = SD.)			
Goiter	(N)	T4(nmol/1	T3(nmol/1	T3/T4	TSH(mul/1)
Control	(42)	96.8 = 10.6	1.74 =.32	0.018=004	2.18=1.8
1.	(12)	113.3=5.4	2.07=.37	0.018=005	2.91=2.1
2.	(14)	99.9=7.2	2.41=29	0.024=.005	3.31=1.7
3	(14)	85.2=5.3	2.78=41	0.029=.006	4.2=1.1
4.	(18)	81.6=9.6	3.06=.48	0.043=.006	4.9=1.6
r (Between goiter grades & serum Hormones)		-0.65 (p-.05)	+0.834 (p.-.001)	+0.834 (p-.001)	+0.916 (p-.001)

Local Reference Values 10. Serum T4=58-125nmol/1
" T3=1.03-2.38 nmol/1

DISCUSSION

Goiter is a unique example of iodine deficiency disorders (IDD), and is manifested by a variety of physiologic and anatomical compensatory changes in the thyroid gland primarily to overcome the effect of iodine deficiency present in the environment. One of such compensatory mechanisms evident in the present investigation is the gradual enlargement of the thyroid gland with consequent diminished synthesis of iodine rich thyroxine (T3) molecule in association with a concurrent preferential increased synthesis of iodine deficient but more potent triiodothyronine (T3) molecule, coupled with a gradual increase in serum TSH level in the goitrous subjects from endemic zone (see Table1). This is probably an attempt by the enlarging gland, in the form of a metabolic adaptation to iodine deficiency, to maintain the euthyroid status of the subject with the minimum iodine-supply available to it. The peripheral conversion of T4 to T3 is also reportedly increased in such subjects with endemic goiter (11,12). A low-normal serum T4 and high normal to supra-normal serum T3 with mildly elevated serum TSH levels (which presumably maintain the euthyroid status of the gland) are, therefore, frequent findings in subjects with endemic goiter living in iodine deficient areas (7,8,11,12) and this has consistently been observed in the goitrous subjects of the present investigation (fig.1 and Table3).

Furthermore, in the present study the level of serum T3 in many of the subjects assessed (34 in total) (58%) with differnet grades of thyroid enlargement was found in the hyperthyroid range (T3 2.38 nmol/1) compared to the corresponding

normal reference range values (1.03-2.38 nmol/ seen in the local population (see fig.1).

However, all the subjects found in these groups were clinically euthyroid, with no suppression of serum TSH in the group, probably suggesting that such abnormal rise in serun T3 levels in these goitrous subjects, in part, may have been due to the preferential increased synthesis of T3(preferential peripheral conversion of T4 to T3 coupled with increased intraglandular MIT/DIT ratio), and partly due to a concomitant rise in serum thyroxine binding globulin (TBG) levels which also can bind T3 significantly. Nevertheless, a significant rise in endemic zone is known to occur (13,14).

The progressive serial rise in the level of serum T3/T4 ratio with the increasing goiter size in the euthyroid goitrous subjects of the present investigation was found to be statistically highly significant (r =.834,p.-.001)(see fig.2) whether this can be used as an additional biochemical indicator(apart from the TSH which is known to be a better marker of goiter endemia) in determining the severity of goiter endemicity in a population (especially in terms of the distribution of relative thyroid sizes among the goitrous subjects) cannnot be categorically stated from the evidence fathered in the present work but is highly suggestive. It is pertinent to note in this regard that similar relationship between the size of thyroid gland and level of serum TSH and thyroglobulin relationship between the size of thyroid gland and level of serum TSH and thyroglobin (Tg) has been reported in subjects from edemic zones.(14,15,16).

It is further emphasized that by measuring the ratio of serum T3/T4 values, the interfering effects of the carrier proteins such as TBG, pre-albumin and albumin which might significantly influence the level of serum thyroid hormones in endemic zones, can be minimized (if not nullified) and thus the ratio would provide a better index as marker of goiter endemia than the estimation of the level of serum T3 alone, which however, also showed a significant correlation with the goiter size in the present investigation (see fig.1). In the analysis of serum T3/T4 quotients we further observed that there is virtually no difference in its values between the subjects with grade 1 goiter (mean.018=.005) and those of control (mean.018=.004). However, the serum values in the subsequent groups (subjects with grades 2, 3, and 4 goiters) showed a consistent serial rise with the increasing thyroid size(see fig.2). This might imply that the serum value of this ratio can be a useful biochemical guide (in addition to having other established biochemical markers such as urinary D serum TSH 12, Tg (15) and, to some extent serum TBG concentrations (14) to the epidemiological assessment of "Visible Goitre Rate" (VGR) (17) seems to carry a better correlation (see fig.2).

Our study also shows a direct correlation between serum TSH level and the size of endemic goiter, confirming the similar relationship reported in earlier studies.

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Legends for the figures:

Fig1. Distribution of serum T4 and T3 values in subjects with various Grades of endemic goiter and in those in the control group.

Fig2. Correlation between serum T3/T4 quotients and the grades of the endemic goiter.