CONTROVERSIES ON THE AETIOLOGY OF ENDEMIC GOITRE IN SRI LANKA

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ABSTRACT

Endemic goitre is widely prevalent in the wet zone of Sri Lanka. The exact aetiology of endemic goitre has not been fully understood though iodine deficiency has been thought to be the commonest cause. This study involved the investigation of hundred and eleven euthyroid goitrous female patients with regard to their thyroid status. The gland was assessed according to the classification endorsed by the WHO and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD), and categorised into 3 grades. The tests included measurement of total serum thyroxine, triiodothyronine and thyroid stimulating hormone levels and 2 and 24 hour iodine uptakes following the administration of a tracer dose of radioactive iodine. Thyroid hormone levels were found to be within the specified 'normal' ranges, but a trend was observed whereby an increase in goitre size was associated with a fall in total serum thyroxine levels, which was not significant, a rise in total triiodothyronine, being significant between grades 2 & 3 ($p < 0.05$), and a significant fall in serum thyroid stimulating hormone levels between grades 1 & 2 ($p < 0.03$), as well as between grades 2 & 3 ($p < 0.05$). The radioactive iodine uptakes at both 2 & 24 hours showed a rise with increase in the size of the gland, the uptakes between grades 2 & 3 were significant in both instances, ($p < 0.01$) and ($p < 0.05$) respectively. The biochemical picture seen in these patients is not in keeping with that seen in patients from areas of confirmed iodine deficiency.

Introduction

Endemic goitre is widely prevalent in the endemic belt which extends throughout the Western, Sabaragamuwa, Southern, Central and part of the Uva provinces; i.e. the whole of the south-western sector of Sri Lanka (Fig. 1).

In a recent survey carried out by Fernando et al (1 989), of school children, an overall goitre prevalence rate of 18.8% was observed. The incidence was highest in the district of Kalutara (30.2%). In comparison to the surveys carried out in 1947 - 49 and 1963, there has been an increase in the prevalence of endemic goitre in Sri Lanka.

The exact aetiology of endemic goitre has not been fully understood. Although Wilson found that the iodine content of water in the affected areas was low, she felt that factors other than environmental iodine deficiency, such as goitrogens in food were also involved (Wilson 1950, 1954).

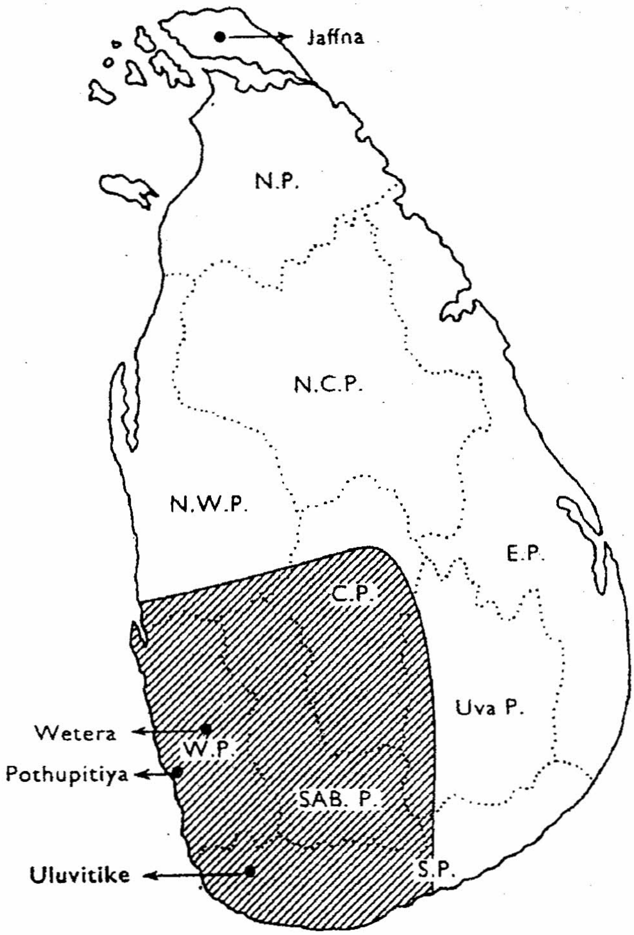

Fig. 1. The areas in Sri Lanka where goitre is endemic (shaded area) and non-endemic (rest of the country). Provinces are marked by abbreviations: N.P., Northern Province; N.C.P., North Central Province; N.W.P., North Western Province; C.P. , Central Province; S.P., Southern Province; E.P., Eastern Province ; S.AB.P., Sabaragamuwa Province; Uva P., Uva Province; and W.P. Western Province.

Factors concerned in the aetiology of goitre are

1) Iodine deficiency

Endemic goitre is thought to be mainly due to iodine deficiency. It is paradoxical that while a deficiency causes endemic goitre, an excess of iodine could also cause enlargement of the thyroid as in iodide goitre. An excess intake of iodine, arbitrarily defined as 2 mg or more per day, inhibits proteolysis and release of thyroidal hormones and produces 'iodide goitre'.

2) Geological factors

New soils formed after the last ice period, i.e. those subjected to glaciation, contain less iodine and are said the be associated with endemic goitre. However, Mahadeva & Shanmuganathan (1967) stated that the geology of the land seems to have no bearing on the endemicity of goitre, and that soils of endemic areas are mainly the red - yellow podzolic soils and to some extent the reddish lateritic soil overlying the precambrian or archean rocks. Sedlak et al, (1964) found that the nature of the soil influences the content of goitrogens in plants. Stanbury and Hetzel (1985) stated that geologic factors are important secondarily by affecting the iodine or goitrogen concentration in the water, food or both.

3) Goitrogens

Goitrogens are substances that affect the utilisation of iodine by the thyroid gland. Chesney et al, (1928) demonstrated the development of goitre rabbits fed on cabbage. Since then vegetables of the genus Brassica have been found to contain goitrogens such as thiocyanates and isothiocyanates. Cyanogenic glucosides have been found in cassava, maize, bamboo shoots, sweet potato and lima beans. The glucoside are converted to thiocyanates by tissue enzymes. Goitrogens may also contaminate sources of drinking water.

4) Trace minerals

Beckett et al, (1987) demonstrated a decrease in conversion of thyroxine to tri-iodothyronine in selenium-deficient rats. Deficiencies of copper and iron in rats have been shown to decrease circulating thyroxine concentrations and selenium deficiency in chicks to decrease circulating thyroxine and tri-iodothyronine concentrations. These results suggest an important relationship between thyroid activity and trace mineral concentrations in the body.

5) Pollution

McCarrison (1906) observed that in drinking waters, faecal contamination could decrease the amount of available iodine. He confirmed it by feeding this water to volunteers, some of whom developed goitre in about 2 weeks. Hettche (1956) concluded that it was due to an injurious substance of the urochrome group occurring in contaminated water supplies. Vought et al, (1974) have shown that cultures of *E. coli* contain an antithyroid compound which diminishes the ^{131}I uptake in rats. It is also possible that non-bacterial constituents of polluted water may act on iodine to make it non-available to man.

6) Genetic factors

The problem that needs explanation is, among those living in the same environment, and eating the same type of food, why only some develop goitre while others do not. Is there a genetic predisposition? We are aware that goitre tends to occur in the same family, and this may be due to sharing the same micro-environment or to hereditary factors. Heredity does not appear to be the main factor, but it could be a secondary or contributory cause. A multifactorial mode of genetic transmission involving several inherited characteristics such as iodine trapping and binding and other aspects of thyroid hormonogenesis, which affect the capacity of the thyroid gland to adapt to iodine deficiency, is possible.

Materials and Methods

All female goitrous subjects referred to the thyroid clinic at the Nuclear Medicine Unit, University of Peradeniya, between 8.30 am and 9.00 am were included in this study. Tests of thyroid function including radioiodine uptakes are only carried out at this unit. Thus all state hospital referrals and the majority of private consultation referrals for thyroid function tests are made here. The patients seen are therefore a good representation of the population suffering from thyroid disorders. The reason why only female goitrous patients were included in this study was because this sample was collected over a limited period of time, and since male patients were relatively few in number they were not taken into consideration.

These female patients ages ranged from 35 to 37 years. All 111 euthyroid goitre patients having normal total thyroxine ('IT4), total triiodothyronine ('IT3) and Thyroid Stimulating Hormone (TSH) concentrations were included in this study. The majority of patients were free of clinical manifestations of thyroid disease. A brief clinical history and examination was then carried out by one examiner. Details of thyroid dysfunction, size and duration of goitre were noted.

We used the following baselines (NETRIA, 1986) for our study.

Thyroid hormones	**Normal values**
Triiodothyronine (T3)	60 - 200 ng/dl
Thyroxine (T4)	4 - 12 μgrams/dl
Thyroid stimulating hormone (TSH)	0.45 - 5.0 mU/1

The gland was assessed according to the classification endorsed by the WHO and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD 1990, 1994), and categorised into 3 grades, as follows:-

Grade 1	An enlarged thyroid that is palpable but not visible when the neck is in a normal position (this includes former grades la & lb).
Grade 2	Thyroid enlarged, visible with the neck in the normal position.
Grade 3	Thyroid greatly enlarged, visible from far.

The tests included measurements of

1) Total serum thyroxine (TT_4) and total serum triiodothyronine (TT_3) concentrations by the standard RIA (radioimmunoassay) techniques.

2) Thyroid stimulating hormone concentrations by the IRMA (immunoradiometric assay) technique.

3) 2 hour and 24 hour radioiodine uptakes, following the administration of a tracer dose of ^{131}I.

Analysis

The results were statistically analysed according to the 'Independent t test', which was carried out by comparing results of grade 1 & 2 patients, as well as grade 2 & 3 patients.

Results

Table 1 represents the mean values for age and duration of goitre between the 3 grades of the euthyroid group (Table I, Fig 2).

Table I. Comparison of mean values for age (years) and duration of goitre (years) between grades In the euthyroid group. Mean ± SE.

	GRADE 1 (n=21)		GRADE 2 (n=62)		GRADE 3 (n=28)
AGE (years)	35.85 ± 2.75		36.88 ± 1.44		36.62 ± 2.33
significance of		t = 0.35		t = 0.10	
the difference		n.s.		n.s	
DURATION OF GOITRE (years)	1.85 ± 0.27		3.34 ± 0.43		5.85 ± 0.70
significance of		t = 1.97		t = 3.16	
the difference		$p < 0.05$		$p < 0.002$	

n.s. = not significant

The mean ages of patients in grade 1, 2, 3 & a control group were 35.85, 36.88, 36.62 and 32.77 years respectively. These differences in age were not statistically significant.

The mean duration of goitre in patients grade 1 was 1.85 years, while a significantly longer ($p < 0.05$) duration of 3.34 years was observed in patients of grade 2. Likewise, a highly significantly longer ($p < 0.002$), duration of 5.85 years was observed in patients of grade 3.

Table II illustrates the mean values for total thyroid hormones TT_3 , TT_4 and TSH for each grade (Table II, Fig 3, 4, 5).

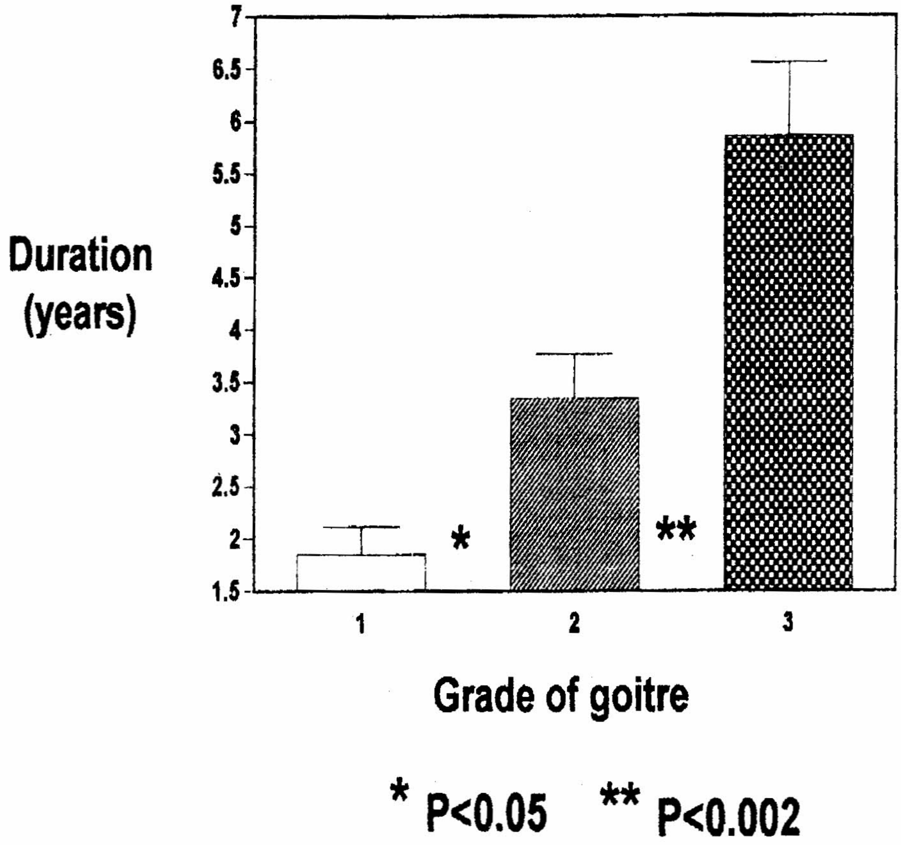

Fig. 2. Relationship between duration and grade of goitre.

Table II. Comparison of mean concentrations of thyroid hormones between grades in the EUTHYROLD group. Mean $\pm$ SE.

	GRADE 1 (n = 21)		GRADE 2 (n = 62)		GRADE 3 (n = 28)
TT_3 ng/dl	116.85 $\pm$ 7.08		118.85 $\pm$ 3.66		131.20 $\pm$ 4.87
significance of the difference		t = 1.27 n.s.		t = 1.95 $p < 0.05$	
TT_4 μg/dl	8.90 $\pm$ 0.25		8.30 $\pm$ 0.20		8.11 $\pm$ 0.31
significance of the difference		t = 1.63 n.s.		t = 0.53 n.s.	
TSH mU/1	2.71$\pm$0.20		2.15$\pm$0.13		1.70$\pm$0.15
significance of the difference		t = 2.16 $p < 0.03$		t = 1.98 $p < 0.05$	

n.s. = not significant

The mean serum TT_3 , concentration in grade 1 was 116.8 5 ng/ dl while in grade 2 was 118.85 ng/dl. No significant difference was observed between these two groups. On the other hand, a significantly higher ($p < 0.05$) TT_3 concentration was observed in patients of grade 3 when compared with grade 2, recording a mean value of 131.08 ng/dl.

Serum TT_4 concentrations observed were 8.90 μg/dl, 8.30 μg/dl and 8.11 μg/dl in grade 1, 2 and 3 respectively. No significant differences were observed between these three groups.

Serum TSH concentrations in grade 1 was 2.71 mu/1, while a significantly lower ($p < 0.03$) concentration of 2.15 mu/ 1 was observed in patients of grade 2. Likewise, a significantly lower($p < 0.05$) concentration of 1. 71 mu/1 was observed in patients of grade 3, when compared with grade 2.

Table III. shows the RAIU levels 2 hours and 24 hours after swallowing a tracer dose of radioiodine ^{131}I (Table III, Fig. 6, 7).

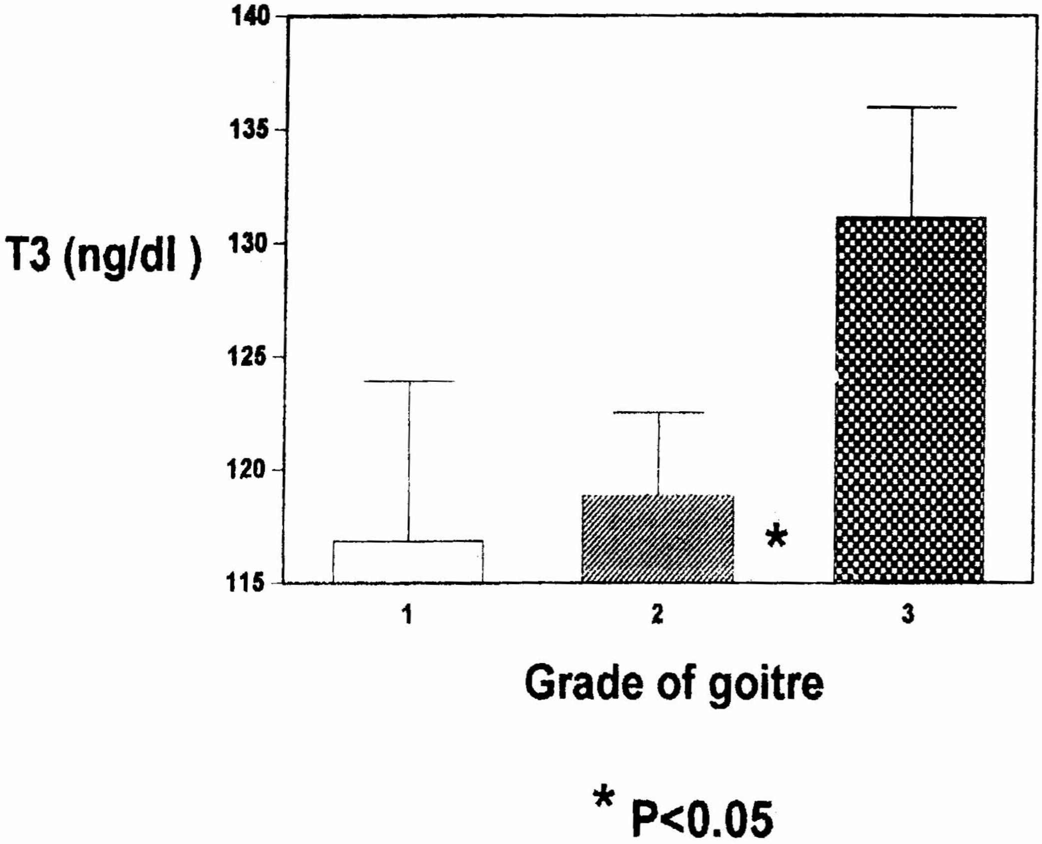

Fig. 3. Relationship between total T3 and grade of goitre.

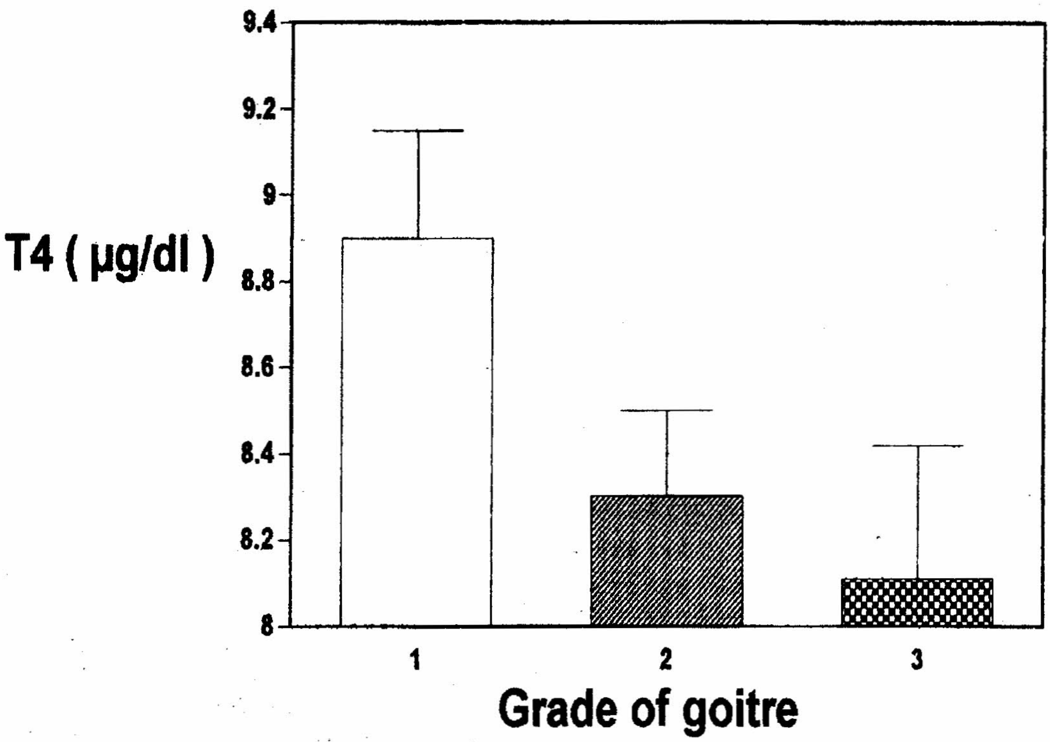

Fig. 4. Relationship between T4 and grade of goitre.

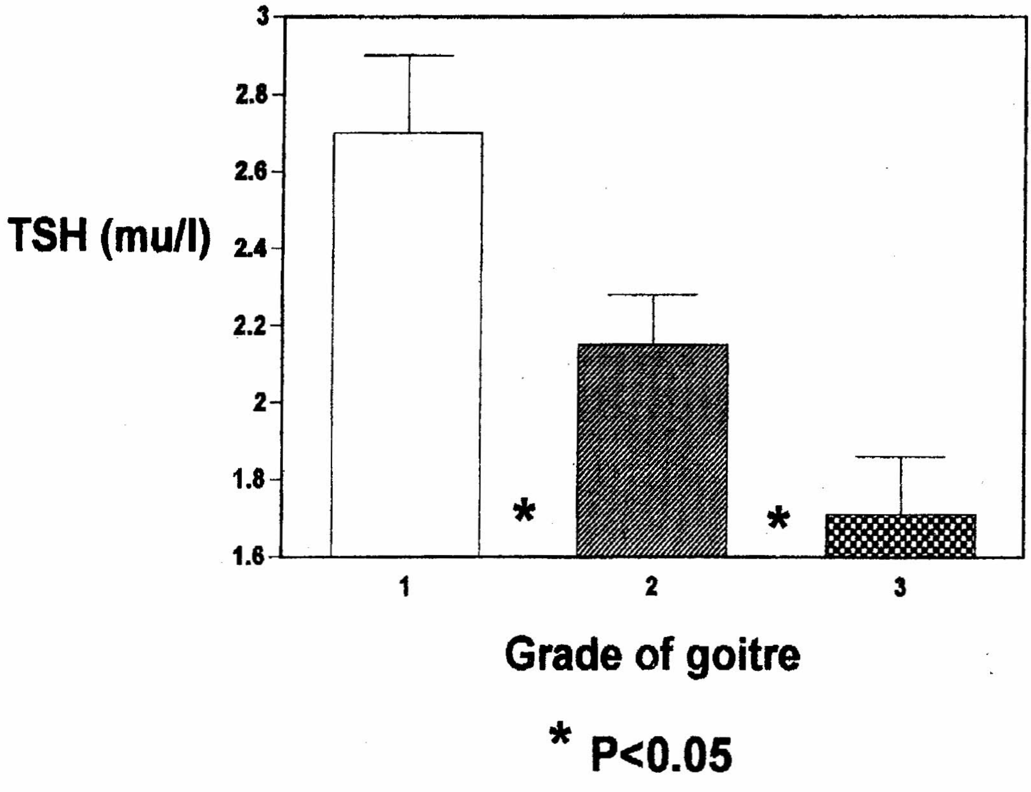

Fig. 5. Relationship between TSH and grade of goitre.

Table III. Comparison of mean percentage radioactive uptake at 2 hours and 24 hours, between grades in the euthyrold group. Mean $\pm$ SE.

	GRADE 1		GRADE 2		GRADE 3
RAIU - 2H	16.46±2.23		22.13±1.67		30.94±3.65
significance of		t = 1.79		t = 2.51	
the difference		n.s		$p < 0.01$	
RAIU - 24H	45.44±4.32		53.35±2.09		63.19 ± 5.79
significance of		t = 1.78		t = 1.98	
the difference		n.s		$p < 0.05$	

n.s. = not significant

RAIU at 2 hours showed a trend, with grade 1 exhibiting a mean uptake of 16.46% and grade 2 exhibiting an uptake of 22.13%. No significant difference was seen between these two groups.

A significant increase (p < 0. 0 1) of 30.94% was observed in grade 3 when compared with grade 2.

Similarly RAIU at 24 hours showed a similar pattern, with grade 1 exhibiting a mean uptake of 45.44%, while grade 2 exhibited a mean uptake of 53.35%. No significant difference was observed between these two groups. Grade 3 showed a significantly higher (p < 0. 05) mean uptake of 63.19%, when compared with grade 2

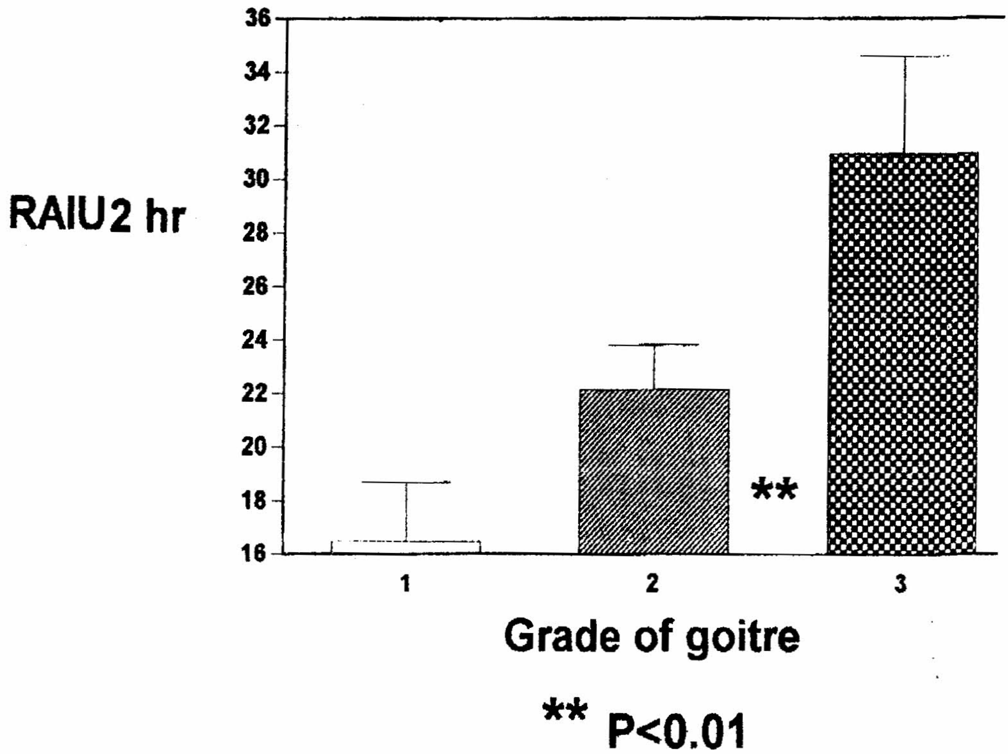

Fig. 6. Relationship between RAIU 2hr and grade of goitre.

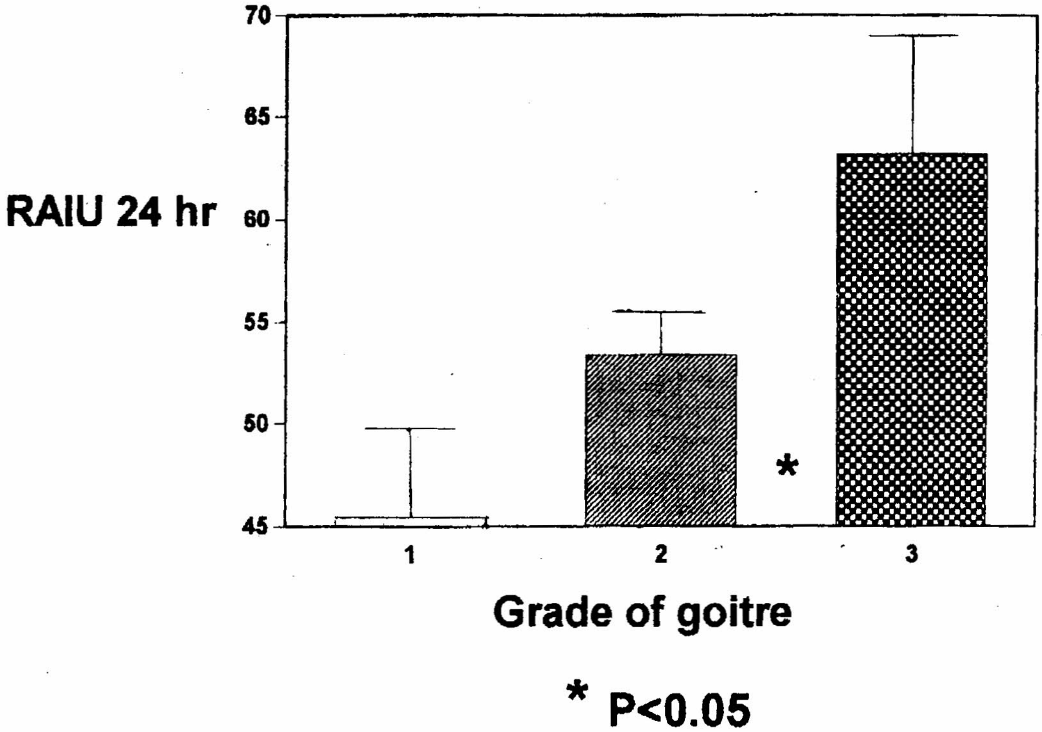

Fig. 7. Relationship between RAIU 24 hr and grade of goitre.

Discussion

The thyroid hormone levels were found to be within the specified 'normal' ranges in this euthyroid group.

TT_4 concentrations when compared with the size of goitre showed a downward trend as the size of the gland increased.

Comparison of TT_3 concentrations with the size of goitre showed a rise in TT_3 concentrations, from grade 1 to 3, the rise being significant between grade 2 and 3 ($p < 0.05$).

Thus, an increase in the size of the gland was associated with a significant increase in TT_3, secretion, reflecting hyperactivity of the gland.

Comparison of serum TSH concentrations with size of the goitre showed a significant fall in TSH concentrations from grade 1 to 2($p < 0. 03$), as well as from grade 2 to 3($p< 0.05$).

TSH is normally responsible for hyperplasia of the cells of the thyroid follicles thereby promoting goitre formation in iodine deficient states. In addition, TSH activates all stages of iodine metabolism in the thyroid, from trapping to the secretion of thyroid hormones.

1) A significant fall in serum TSH concentrations associated with an increase in the size of the gland indicates that thyroid enlargement is independent of the TSH.

2) With an increase in the size of the thyroid gland, a significant increase in TT_3 concentrations was observed, together with a significant fall in TSH concentrations. Here again thyroid hyperactivity is independent of TSH.

The radioactive iodine uptakes at both 2 & 24 hours showed a rise with an increase in the size of the gland, the uptakes between grades 2 & 3 were significant in both instances, ($p < 0.01$) and ($p < 0.05$) respectively.

An early peak as shown by the significant increase in radioiodine uptake at 2 hours following the administration of the tracer dose shows thyroid hyperfunction.

The 24 hour uptake also showed a significant increase between grades 2 & 3, indicating an increase in thyroid activity as the gland gets larger.

Non-toxic diffuse goitre in iodine sufficient parts of the world is called simple goitre. In some young adults, simple diffuse goitre is likely to progress with time, to a euthyroid multinodular goitre with areas of autonomous function. As the amount of autonomous tissue increases, hyperthyroidism develops in middle and old age. The stimulus to this slow progression is not TSH, but may be thyroid growth immunoglobins which stimulate the growth of the thyroid gland (Toft 1989).

A comparable study giving results similar to those in the present study was conducted by Roti et al, (1986), on goitre size and thyroid function in an endemic goitre area in Northern Italy. They found no significant changes in serum T_4 concentrations in subjects with different grades of goitre. Serum T_3 concentrations were higher in subjects with the larger goitres. Serum TSH progressively decreased while serum thyroglobulin concentrations progressively increased with increasing goitre size. TSH response to TRH was diminished in subject with larger goitres. Thus the findings of decreasing TSH concentrations and blunted TSH response to TRH as goitre size increased suggests the possibility of autonomous thyroid function in subjects with larger goitres in subjects residing in areas they claim to be moderately deficient in iodine.

A study conducted by Herath et al, (1 99 1), on radioiodine uptakes and serum T_3, T_4 and TSH concentrations among giotrous and non-goitrous school children in an endemic and non-endemic area in Sri Lanka showed that the T_3, T_4 and TSH concentrations of the goitrous subjects in the endemic areas did not differ significantly from that of the goitrous subjects in the non-endemic areas or from hormone concentrations obtained from the non-goitrous subjects in either area. In the nonendemic area the goitrous subjects had slightly lower concentrations of T_4 and TSH than the controls. On the other hand, they found that the mean iodine uptake at 2 hour and 24 hours were both significantly higher ($p < 0.01$) in the goitrous group than in the control group in both the endemic and non-endemic areas. The uptakes were also higher in the controls in the endemic area than in the goitrous subjects in the nonendemic area. They concluded that the hormone concentrations were of little use in diagnosing iodine deficiency. Iodine uptake on the other hand appeared to be a more sensitive test even in endemic areas. They stated that the higher iodine uptake seen in goitrous subjects in endemic and non-endemic areas suggested that iodine deficiency is an important etiological factor for goitre in Sri Lanka. The 24 hour uptake of the control group in the endemic area was higher than that of the goitrous subjects in the non-endemic areas suggesting that the clinically normal subjects of the endemic area showed evidence of iodine deficiency. In this study a raised iodine uptake has been assumed to be due to iodine deficiency, whereas a raised uptake could also be observed in hyperactivity of the thyroid gland as in autonomous functioning of the thyroid. The absence of significant differences in hormone concentrations between goitrous patients and controls also throws some doubt on the aetiology as been iodine deficiency.

A study conducted by Balasuriya et al, (1992) on the role of iodine content of drinking water in the aetiology of goitre in Sri Lanka, analysed 609 samples of drinking water collected from scattered sources from the eight districts of Kandy, Matale, Kalutara, Anuradhapura, Polonnaruwa, Colombo, Puttalam and Gampaha for iodide content. The median iodide content of all districts except Gampaha were above 10μg/l, with Anuradhapura showing the highest content. Geographic variation was observed in the iodide content of drinking water. The iodide content was related to the depth of the water source, tube wells were found to have a high iodide content while the surface sources had a relatively low iodide content. A good negative correlation of goitre prevalence to iodide content of drinking water was observed, with the median iodide content of districts of low goitre prevalence being nearly four times higher than the medians of districts of high and intermediate prevalence. In general, iodide levels observed in this study were higher than the levels reported from other endemic areas. The difference in iodide content of drinking water of cases of goitre and controls was minimal, and only 20% of the sample had values below 10μg/l. The occurrence of goitre in regions where there is no shortage of iodine in the water has been reported from many countries and also from Sri Lanka as far back as 1968 (Mahadeva et al, 1968). It seems reasonable to postulate that factors other than low iodine intake from drinking water may play a part in the aetiology of goitre in Sri Lanka.

Piyasena et al, (1979), who compared radioiodine uptake in goitrous and non~goitrous subjects in endemic areas and non-goitrous subjects in non-endemic areas in Sri Lanka, stated that non- goitrous subjects in endemic areas showed significantly elevated thyroidal radioiodine uptakes over control subjects in non-endemic areas. There were no differences between serum T_4 T_3 and TSH concentrations in non -goitrous subjects from either area. In comparison to non-goitrous controls in the same area, goitrous subjects showed a significant elevation of radioiodine uptake, depression of serum T_4 and elevation of serum T_3 concentrations. About 2/3 of the goitrous cases were found to have significantly elevated serum TSH concentrations over non-goitrous controls in the same area. No correlation was found between elevated serum TSH and age and sex of the subjects or size and duration of goitre. They concluded that in Sri Lanka, the first adaptation to iodine deficiency seemed to be an increase in iodine uptake by the thyroid as shown by the non-goitrous subjects from endemic areas having significantly elevated uptakes over those in non-endemic areas. No increase in serum TSH or T_3 could be demonstrated in this group, but where goitre was present an increased TSH was observed in the majority of cases together with a rise in T_3.

According to numerous studies conducted in areas where iodine deficiency has been confirmed as being the cause of goitre, the affected population was borderline euthyiiod with a trend towards hypothyroidism in protracted disease e.g., Guinea in West Africa(Konde et al, (1994). The biochemical picture in the Guinea study showed that Total T_4 (TT_4) and Free T_4 (FT_4) were significantly decreased in stage 0 compared with those in controls. Even in the absence of goitre, most FT_4 values were at the lower limit of normal. Serum TSH concentrations were at the upper limit of normal in subjects without goitre and showed in stages 1, 11 and 111 a progressive rise proportionate to the thyroid swelling. FT_4 and TSH were negatively correlated. Conversely, the enhanced production of TT_3 and FT_3 appeared as the direct consequence of TSH hypersecretion, aiming at sparing iodine and maintaining euthyroidism. This picture differs from that seen in our study.

Deo & Subramaniam (1971) observed in their studies that although urinary iodide excretion in patients with endemic goitre was lower than in normalise, it was generally higher than that observed in several other endemic areas, indicating that environmental iodine deficiency is mild in the endemic area in Ceylon.

Controversies regarding the aetiology as being due to iodine deficiency

The controversies include

1)goitre in animals is rarely seen in Sri Lanka. No case of goitre has been observed amongst cattle, buffalo, goats, pigs or dogs, in Sri Lanka (Wilson, 1954; Mahadeva and Shanmuganathan, 1967).

2) recent studies conducted by Fernando et al (1989), have shown that goitre is highly prevalent even in coastal towns like Kalutara, in spite of the diet, being generally rich in iodine, even of the poor, who consume rice, pulses, coconut, dry fish and fresh fish(Mahadeva et al, 1968).

3) the high prevalence of goitre in the Wet Zone of Sri Lanka is thought to be due to the leaching of iodine from the soil. This phenomenon occurs near large mountain ranges like the Himalayas, Andes and Alps in Switzerland. However, Sri Lanka has no such mountain ranges.

4) the consumption of 100 - 150 µg of iodine per day was recommended by the WHO, after investigating iodine metabolism in endemic goitre in Sri Lanka (Subramaniam and Deo, 1966). The mean consumption of iodine in the goitre endemic zone of Sri Lanka (taking into account cooking losses) is 240 µg/l, well in excess of the recommended value. This prompted a recommendation that at least 400 µg of iodine should be available in the daily food sources, though the use of this large intake has not been substantiated (Mahadeva et al, 1968).

Previous studies conducted by Wilson (1954) on the incidence of goitre in school children found a high percentage of thyroid enlargement in girls in the wet areas, whereas in boys the incidence was only moderate. In the dry areas, the incidence amongst both girls and boys in the school population was low. In this study the iodine content of drinking water was analysed in only 6 samples, 4 which were from the wet area, and 2 from the dry area. Three samples from the wet area had iodine concentrations ranging from 1.4 - 2.7 μg/l, while 1 sample from the dry area had a very high iodine concentration of 61.0 μg/l. Wilson concluded that the high incidence of thyroid enlargement in Southwest Ceylon may be due to the scarcity of iodine in the drinking water, the recent deterioration in the diet (high carbohydrate and low protein), the known faecal contamination of water supplies perhaps limiting the availability of the iodine, and the possibility of goitrogenic agents in the diet.

Another survey on the incidence of goitre in school children conducted by Deo and Subramaniam (1971) reported a goitre prevalence of 12 - 54% in the endemic areas, with the greatest incidence in Horana. Females were more affected than males. No goitre was seen in school children in Jaffna, and these children were used as controls. Here again only 6 samples of urine were analysed for iodine from Horana; a mean concentration of 20.15 μg/l of creatinine was obtained. Unfortunately, urine from the controls was not analysed. 4 samples of drinking water were also analysed for iodine (2 samples each from Horana and Galle), and mean concentration of 1.34 μg/l and 1. 16 μg/l were obtained respectively. The controls from Jaffna gave a mean concentration of 9.2 μg/l of iodine. Deo and Subramaniam stated that although urinary iodide excretion in patients with endemic goitre was lower than normal, it was generally higher than that observed in several other endemic areas, indicating that the environmental iodine deficiency is mild in the endemic area in Ceylon. They concluded that endemic goitre in Ceylon is characterised by high 24 hour thyroid uptake of ^{131}I, raised thyroidal iodide clearance and 48 hour PB ^{131}I, lowered excretion of urinary iodide, low plasma inorganic iodide and low content of iodine in water, confirming endemic goitre in Ceylon is due to iodine deficiency.

Summary

Thyroid function was studied in III euthyroid goitrous females. Serum TT_4 and TT_3, concentrations were measured by standard RIA techniques, and serum TSH concentrations were measured by the IRA technique.

1) No significant change in serum T_4 concentrations was found in subjects with different grades of goitre.

2) Serum T_3 concentrations were significantly higher in subjects with the larger goitres.

3) Serum TSH concentrations showed a progressive significant decrease with increasing goitre size.

4) RAIU after 2 hours and 24 hours following the administration of a tracer dose of radio iodine showed a significant increase in uptakes by the gland with increasing goitre size.

These results suggest the possibility of autonomous thyroid function in the subject with larger goitres.

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