

The clinical epidemiology of thyroid disease in Sri Lanka

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Introduction

Diseases of the thyroid gland are common. As many as 2% of all women have thyroid disease and 3-4% have clinically detectable thyroid nodules at some time of their lives¹. It is less common in men. However life threatening complications such as thyroid storm, myxoedema coma and malignancy are uncommon. Hence patients with thyroid disease are not often admitted to hospital. Nevertheless thyroid disease causes considerable morbidity but its impact is unnoticed as no systematic records of thyroid disease are maintained in Sri Lankan hospitals. Data are scarce on the prevalence and natural history of thyroid disease in Sri Lanka. We therefore studied these aspects of thyroid disease from 1990 to date. This paper summarises the studies performed during this period and discusses their significance.

Community based studies

Data on the prevalence of thyroid disease in communities is scarce. The best known community based study of thyroid disease is the Whickham survey in the UK. Over 2500 non hospitalised patients were screened clinically and biochemically for thyroid disease. In this study 2-3% of the population had thyroid disease¹.

In 1991 we conducted a community based study of the prevalence of non communicable diseases in Sri Jayawardenepura^{2,3}. During the course of this study patients underwent a physical examination during which presence or goitre was recorded. The presence of previous medical illness and medication history was also recorded. Of the 630 subjects studied 10 had goitres. A further 14 had a history of thyroid disease. All were women. The prevalence of thyroid disease in suburban Sri Lanka is 3.4%.

Hospital based studies

I have maintained a computerised database (registry) of all endocrine patients referred to me from October 1990 to date. The database commenced as a collection of filed case record forms and evolved into a relational database in EPINFO 5 and now in EPINFO 6. The database contains records of initial assessment and follow-up of 510 patients with thyroid disease. Of these 168 had hyperthyroidism, 234 hypothyroidism, 64 sub clinical hypothyroidism and 54 euthyroid goitres.

Hypothyroidism

The term hypothyroidism is used to denote thyroxine deficiency while disease of a sufficient chronicity severity to give the typical clinical features is referred to as myxoedema. Elevation of TSH alone with normal thyroxine and no clinical symptoms or signs is termed sub clinical hypothyroidism. The commonest cause of hypothyroidism is chronic autoimmune thyroiditis^{4,5}. We assessed the frequency of this entity among hypothyroid patients in our clinic.

176 hypothyroid patients with goitre underwent fine needle aspiration and thyroid antibody (microsomal antibody) tests in addition to tests of thyroid function. 53 (30%) had cytological evidence of chronic autoimmune thyroiditis. The remainder were classified as "colloid goitres". Of these 35 (65%) had microsomal antibodies (titre >1/6400) thus confirming a high prevalence of chronic lymphocytic thyroiditis. This has implications for using the goitre rate as an index of iodine deficiency disease. Many public health related projects are initiated on data based on studies of goitre rate as an index of IDD. Our data suggest that the goitre rate is an inaccurate index of IDD in Sri Lanka. The high prevalence of goitre in the community can be attributed to IDD. Iodide intake which is currently increasing in Sri Lanka can influence the development of thyroid autoimmunity. There is

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evidence from both animal and human studies that the incidence of autoimmune thyroid disease is increased with higher levels of iodide intake⁶. Thus if most goitres are due to autoimmune thyroid disease increased iodine intake may lead to accelerated autoimmune damage to the thyroid⁶.

The goitre is not usually painful in chronic autoimmune thyroiditis (Hashimoto's disease). The presence of pain usually indicates a diagnosis of sub acute (De Quervains) thyroiditis. We encountered two patients with CAT who had a painful goitre. This rare presentation has been reported in 8 cases in the USA⁷.

Subclinical hypothyroidism

The term subclinical hypothyroidism is used to denote a condition where the patient presents with vague symptoms or is asymptomatic and T4 is normal but TSH is elevated⁵. 54 patients with subclinical hypothyroidism were referred to our clinic. 12 had a TSH greater than 10 mu/l. 32 were positive for microsomal antibodies and 16 had chronic autoimmune thyroiditis on fine needle aspiration cytology. Patients were followed up for variable periods. All patients had at least one year follow up during which thyroid function was reassessed. 6 became hypothyroid in this year. All 6 were from those with thyroid antibodies and 5 had TSH levels greater than 10 mu/l. These findings are much higher than in previous published results of progression of subclinical disease to overt hypothyroidism⁸. The influence of recent increase in iodine intake by compulsory iodisation of salt may have contributed to this. However the numbers are too small to extrapolate this data to a national level and a larger study is indicated.

Ischaemic heart disease in hypothyroidism

Hypothyroidism is associated with ischaemic heart disease and dyslipidaemia. We assessed the frequency of dyslipidaemia and macrovascular disease in 100 patients with hypothyroidism attending an endocrine clinic in a Sri Lankan teaching hospital and 100 controls matched for age and gender from a previous community survey⁹. Macrovascular disease was assessed using a modified WHO questionnaire and modified Minnesota coding of ECG recordings. 16 percent of hypothyroid patients and 14.3% of controls had

Hypercholesterolaemia ($P < 0.05$). Macrovascular disease was present in 10.4 percent of hypothyroid patients and 8.2 percent controls. Significant differences were seen in the prevalence of electrocardiographic abnormalities (10% vs 6% ($p < 0.05$)) in hypothyroid patients when compared to controls. We concluded that hyperlipidaemia and macrovascular disease is common in hypothyroid patients in Sri Lanka and accounts for significant morbidity.

Euthyroid goitre

The asymptomatic goitre is a common finding in women. We performed fine needle aspiration in all 54 patients with euthyroid goitre referred to us as FNA is regarded as a first line investigation in the management of thyroid enlargement. 24 had lymphocytic infiltration suggesting that they were due to chronic autoimmune thyroiditis. In areas presumed to be iodine deficient (such as Sri Lanka) the goitre rate is used as an index of iodine deficiency. In countries which are iodine deficient such as Japan 50% of all goitre are due to autoimmune thyroiditis¹⁰. Our findings suggest that in some areas of Sri Lanka such as the Colombo district the rate may not be an accurate index of iodine deficiency disease.

The management of euthyroid goitre in Sri Lanka is still controversial. Many patients with euthyroid goitre who presented to us had been prescribed thyroxine to encourage shrinking of the goitre.

Hyperthyroidism

Diagnosis

It is routine practice in Sri Lanka to order T3 T4 and TSH when investigating thyroid disease. Hormonal assays are costly investigations. With the development of specific assays for TSH many endocrinologists recommend that the TSH assays be used as a single first line test to assess thyroid function^{11,12}. In some countries such as Australia, insurance companies impose practice guidelines by financial fiat and refuse to reimburse the cost of multiple thyroid function tests in the absence of an abnormal TSH report¹³. The older generation of TSH assays (used in the National Hospital Sri Lanka, NHSL) lacked the sensitivity to distinguish between

low-normal TSH and the suppressed TSH of hyperthyroidism. Thus while it is appropriate to request both thyroxine (T4) and thyrotrophin (TSH) when using the older assays it would be inappropriate to do this to diagnose or monitor thyroid disease using the third generation TSH (TSHs) assays. Due to long delay in obtaining results from the NHSL lab many patients are investigated in the private sector which uses TSHs assays. In some instances the Ministry of Health authorises performance of tests in private laboratories. Unfortunately most doctors request T4, T3 and TSHs in these patients. We applied the Australian Health Insurance Commission (AHIC) algorithm¹⁴ to thyroid function tests in patients with hyperthyroidism referred to our endocrine clinic.

178 patients with hyperthyroidism were referred to our endocrine clinic between September 1995 and March 1996. Of these 73 had been investigated at a private laboratory using TSHs. The referring doctors had requested T4, T3 and TSH(s) in all patients. We audited the use of diagnostic tests using the Australian Health Insurance Commission (AHIC) algorithm to determine whether TSHs reliably predicted T4 levels

72 patients had elevated T4 levels while only 1 patient had isolated elevation of T3. The cost of each hormonal assay is Rs 250 at commercial rates. All 73 patients had a suppressed TSH(s).

In order to confirm a diagnosis of hyperthyroidism 72 unnecessary T4 assays costing Rs 17,750 were performed. In order to confirm a diagnosis of T3 toxicosis in one patient 71 T3 assays were performed at a cost of Rs 17,500. In all Rs 35,000 was spent unnecessarily.

The use of this algorithm in all patients with thyroid disease resulted in saving \$ 23,000 in one large Australian Hospital. No data are available for using this algorithm in Sri Lanka. We conclude that in our clinic population a TSHs based algorithm is reliable in diagnosing hyperthyroidism. The universal implementation of this algorithm in Sri Lanka will result in considerable savings to patient, employers and insurance companies. We recommend that practice guidelines based on this algorithm be formulated and circulated among medical practitioners.

Table 1. Thyroid status 6 months after treatment with 6 mCi of radioiodine

	Hyperthyroid	Euthyroid	Hypothyroid
Graves disease	14	5	8
Toxic nodular goitre	6	24	3

Treatment

Radio active iodine is used as a first line agent in the treatment of hyperthyroidism¹⁵. The accepted dose of radio active iodine needed to cure hyperthyroidism is not known. It has been demonstrated that thyroid size or measures of isotope uptake do not provide useful information for calculating the optimal dose of I¹³¹¹⁶. Many centres use a single fixed dose of radio iodine. It is believed that the dose may vary between those with Graves disease and multinodular goitre^{17,18,19,20}. We studied two groups of patients, one with Graves disease and the other with toxic nodular goitre.

Sixty four consecutive patients with thyrotoxicosis in whom it was decided to administer radio iodine therapy were studied. In Sri Lanka there are periodic shortages of I¹³¹. Hence many patients who should receive radio iodine as the first line treatment are often treated with carbimazole. When such patients were administered radio iodine treatment antithyroid drugs were stopped for seven days before radio iodine treatment and were not given to the patient for a further one week after radio iodine treatment.

Patients were classified as having Graves disease if they had exophthalmos or pretibial myxoedema. They were classified as having toxic nodular goitre if the goitre was nodular on palpation or if they were shown to have nodular goitre on a technetium scan performed at least seventy two hours before radio iodine treatment. This served to exclude patients with autonomous solitary nodules. Patients with diffuse uptake into a goitre on isotope scanning were classified as having Graves disease. T3, T4, and ultrasensitive TSH tests were performed before radio iodine administration. All patients were given a single six milliCurie dose of radio iodine. Thyroid function tests were performed at three month intervals. Patients who were thyrotoxic at six months were given a second dose of radio iodine.

Of the sixty four patients studied four could not be classified as they did not have any signs of Graves disease and did not have a clinically palpable nodular goitre. Due to interruptions to the supply of isotope technetium scans were not performed in these patients. They were excluded from the analysis. Graves disease was diagnosed in 27 patients and toxic nodular goitre in thirty three. Patients with toxic nodular goitre were older (mean age 51.2 SD 7.6 years) than those with Graves disease (43.3 SD 8.1 years, $p < 0.05$). The prevalence of antithyroid antibodies was lower in patients with toxic multinodular goitre (11 patients, 33%) when compared to those with Graves disease (15 patients, 53%, $p < 0.05$). Twenty two patients (58%) with Graves disease had clinical evidence of ophthalmopathy. Six patients had pretibial myxoedema.

Six months after a single five milliCurie dose of radio iodine patients with Graves disease were more likely to have persistent hyperthyroidism when compared to those having toxic nodular goitre (odds ratio 4.85 95% CI 1.33-18.47, $p = 0.005$) (Table 1). The frequency of hypothyroidism was higher in those with Graves disease (odds ratio 4.21 95% CI 0.85-23.25, $p = 0.04$)

Of the 20 patients with persistent hyperthyroidism 12 had T4 levels greater than 15 nmol/l while 6 of those who responded to radioiodine also had high T4 levels. The relative risk for persistent hyperthyroidism was 4.10 95% CI 1.76-9.08, $p = 0.0003$. Levels of T3, or TSH, were not predictive of the outcome of radioiodine therapy.

Twenty patients with hyperthyroidism at six months received a repeat course of radioiodine. Despite a cumulative dose of 15 mCu 3 patients with graves disease and 1 with toxic nodular goitre remained hyperthyroid at 12 months.

The treatment protocol used in this study is used routinely in clinical practice. Six months after a single six milliCurie dose radio iodine, fewer patients with toxic nodular disease had persistent hyperthyroidism when compared to those with Graves disease. This is at variance with the opinion that larger doses of radio iodine should be given to those with toxic nodular goitre. Persistent hypothyroidism is a well known sequel to iodine

therapy. However, a relapse of hyperthyroidism in such patients is uncommon. Therefore, patients who were euthyroid or hypothyroid at six months can be considered to be cured. The results of our study suggest that large fixed doses of radio iodine are not required in toxic nodular goitres.

Previous studies have shown an association with the severity of hyperthyroidism and outcome of radio iodine therapy^{18,21,22}. There were some patients who did not have high titres of T4 had persistent hyperthyroidism at twelve months despite receiving a cumulative radio iodine dose of 15 milliCurie. This suggests that some patients do require higher doses. Our data do not indicate any method for identifying such patients. It is believed that the use of antithyroid drug causes some degree of resistance to radio iodine therapy^{15,16,17}. It has been reported that in patients not given antithyroid drugs a mean dose of 4.9 mCi rendered euthyroid or hypothyroid (cured) as many as 66.3% of patients¹⁷. The results for our series show a lower cure rate for Graves. This may reflect the practice of giving these patients anti thyroid drugs while waiting for iodine therapy to be available at Cancer Institute Maharagama. The lower rate for hypothyroidism in toxic nodular goiter may be explained on the grounds of suppressed uptake of isotope by normal thyroid tissue and enhanced uptake by toxic tissues. In Graves diseases there may be uniform uptake to all thyroid tissues. The 'suppressed' normal thyroid tissue in toxic nodular goitre may have a lower uptake of radioiodine and be protected from the deleterious effects of radio iodine.

We conclude that the standard six milliCurie dose of radio iodine should be used in all patients irrespective of whether they have toxic nodular goitre or Graves disease. Those who have been previously treated with carbimazole may require higher doses²³.

Conclusions

The results of our studies have shown that thyroid disease is a significant cause of morbidity and that screening diagnosis and management of these diseases in Sri Lanka does not seem to follow recommended practice guidelines. There is a need for developing locally applicable guidelines for epidemiological studies and clinical management and implement these at a national levels.

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