Rapid Reversal of Subclinical Hyperthyroidism in Patients with Large Multinodular Goitres after Thyroidectomy

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SUMMARY

A patient is said to have subclinical hyperthyroidism if he has a depressed thyroid stimulating hormone (TSH) level but is clinically euthyroid and has a normal thyroxine (T4) and triiodothyronine (T3) level. The aetiology of this condition is unknown, its progression is uncertain and the value of treatment is doubtful. These 2 cases show a rapid reversal of TSH suppression within a week after thyroidectomy. This suggest an unidentified potent but innocuous suppressor of TSH is produced by some large nodular goitres. Patients with multinodular goitres with subclinical hyperthyroidism can have their anxiety allayed with assurance that their condition is benign and that their TSH suppression is due to the presence of an innocuous substance which is protective in nature. This substance, when isolated, will find a useful place in the prevention and treatment of papillary carcinoma of the thyroid because of its potent effect on the pituitary-thyroid axis without causing any peripheral effects.

KEY WORDS:
Reversal of TSH suppression, Subclinical hyperthyroidism, Multinodular goitre, Thyroidectomy,

INTRODUCTION

Subclinical hyperthyroidism is said to be present if a patient has a depressed thyroid stimulating hormone (TSH) level but is clinically euthyroid and has normal thyroxine (T4) and triiodothyronine (T3) levels. To my knowledge, the rapid reversal of TSH suppression within a week after thyroidectomy in large multinodular goitres has not been documented in the literature. The significance of this observation is discussed.

CASE REPORT

Patient A was a 45 year old female with a large nodule in the right lobe of the thyroid for 3 years. Her pulse was 70/min and she had no symptoms and signs of hyperthyroidism. Ultrasound of the thyroid showed a 4.4 X 2.7X 4.1 cm multi-septate nodule in the right lobe, a 0.5 cm cystic nodule above this large nodule and a 0.4 cm cystic nodule in the left lobe. Right thyroid lobectomy was performed. The specimen comprising the right lobe and isthmus weighed 45 g . Histopathology showed a large benign nodular goitre with areas of haemorrhage, cystic degeneration and fibrosis in the right thyroid lobe. The adjacent thyroid tissue showed areas of nodularity. Serial thyroid function tests (Table I) showed normalisation of TSH levels on the 2nd post-operative day.

Patient B was a 55 year female with a 30 year history of a massive bilateral multinodular goitre. Her pulse was 72/min and she had no symptoms and signs of hyperthyroidism. Ultrasound showed multiple nodules in the left lobe, right lobe and the isthmus. The largest nodule in the left lobe measured 4.6 X 2.2 X 3.2 cm , the largest in the right lobe measured 2.4 X 1.2 X 1.3 cm and the largest in the isthmus measured 1.9 X 1 X 1.7 cm. Total thyroidectomy was performed and recovery was uneventful. The specimen weighed 105 gm and the histopathology was multinodular colloid goitre with areas of haemorrhage, cystic degeneration and fibrosis. Serial thyroid function tests (Table II) showed normalisation of TSH levels on the 6th post-operative day.

DISCUSSION

Subclinical hyperthyroidism is a curious and baffling clinical condition. The patient has a low TSH, normal T3 and T4 levels and has no clinical symptoms and signs of thyrotoxicosis [1]. Since hyperthyroidism is defined by the presence of a low TSH, it is reasoned that the patient is in a "subclinical hyperthyroid" state. Before TSH was widely used as a diagnostic test for hyperthyroidism some 25 years ago, subclinical hyperthyroidism did not exist because a euthyroid patient with normal T3 and T4 levels would have been considered normal. Labelling a patient as having subclinical hyperthyroidism causes patient anxiety as have been shown by the numerous patient enquiries on the internet. Doctors are equally baffled [2] because the pathophysiology of the disease is unknown, the progression of the condition is uncertain, the need for investigation and follow up is unclear and the need for beta blockers before thyroid surgery is unknown. Generally, treatment is felt to be unnecessary except, perhaps, in cases with atrial fibrillation and osteoporosis. If treatment is considered, the duration of treatment is uncertain.

The sparse literature on subclinical hyperthyroidism suggest that the condition can occur in 3 distinct groups - treated Graves disease patients, patients with large multinodular goitres [1-5] and a group with non thyroid disease. Unfortunately, the small case series in the literature did not analysed these groups separately. The aetiology of subclinical hyperthyroidism in multinodular goitres is clearly distinct from the other two conditions. In 7 cases of

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Table I: Serial thyroid function tests of Patient A and B

TEST	PATIENT A			PATIENT B		
	PreOp	D2	D14	PreOp	D1	D6
TSH (N= 0.4 -4.9 mIU/L)	0.25 (low)	0.99 (normal)	2.43 (normal)	0.1 (low)	0.1 (low)	2.1 (normal)
Free T4 (N= 9.0 –19.0 pmol/L)	9.2	13.3	12.6	12.7	15.9	12.4
Free T3 (N= 2.6 – 5.7 pmol/L)	3.8	2.6	4.3	4.5	4.4	4.5

D1= Post op day 1, D2= Post op day 2, D6= Post op day 6 D14= Post op day 14

subclinical hyperthyroidism caused by Graves disease, Woeber KA[3] observed that it can resolve spontaneously (5/7), persist (1/7) or evolve to overt thyrotoxicosis (1/7) after several months. In contrast, all cases of subclinical hyperthyroidism caused by multinodular goitre (9/9) persisted unchanged over time. Smeulers *et al*[4] noted that multinodular glands of more than 35 grams have a greater tendency to secrete low levels of TSH and there was an inverse relationship between TRH-induced TSH release with the size of the thyroid gland. These observations clearly suggest that the aetiology of subclinical thyrotoxicosis in thyroid nodular disease is distinct and unique.

The post operative levels of T3 or T4 levels in these two patients were within the normal range and hardly changed from the preoperative levels yet the TSH suppression rapidly reversed. Hence, this reversal cannot be attributed to changes in T3 or T4. It is postulated that an unidentified TSH suppressor with no peripheral activity is secreted by some clones of cells in large thyroid nodules. This "innocuous TSH suppressor" has a short half life and its biological activity is lost rapidly once the thyroid nodule is removed. The fact that the patients were clinically euthyroid preoperatively and did not have a thyroid storm post operatively without the need for beta blockers re-enforce the idea that this substance has no peripheral activity and is neither T3 or T4.

This potent "innocuous TSH suppressor" of thyroid nodular disease is unlikely to be involved in the pathogenesis of thyroid nodule as TSH suppression is not seen in all cases of thyroid nodular disease, particularly when the nodules are small. Its production is likely to be an adaptive response to retard the growth of progressively enlarging nodule(s) to reduce the risk of carcinogenesis in large thyroid nodular disease. This is consistent with the observation of Fiore E *et al*[5] on 10178 patients that a low TSH level was protective and lowered the risk of papillary carcinoma of the thyroid.

The importance of this case report is in two areas. Firstly, patients with multinodular goitres with subclinical hyperthyroidism can be reassured with the explanation that their TSH suppression is due to the presence of an innocuous substance which is protective in nature. Secondly, translational research by basic scientists following on this observation is likely to result in the isolation of a substance with an important therapeutic role because a drug with potent TSH suppressor activity on the pituitary-thyroid axis without any peripheral effects will be of great value in the prevention and treatment of papillary carcinoma of the thyroid.

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