ORIGINAL RESEARCH

Pattern of sub-clinical dysthyroidism in a post-thyroidectomy cohort: Implications for supplementary treatment

Ronald Kintu-Luwaga[1], Timothy Makumbi[2], Cathy Kilyewala[2], Jane O. Fualal[1]

1. Mulago National Referral Hospital, Kampala, Uganda
2. College of Health Sciences, Makerere University, Kampala, Uganda

Correspondence: Dr Ronald Kintu-Luwaga (kintu2r@gmail.com)

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Abstract

Background
Defective thyroid functioning is referred to as dysthyroidism. Despite incomplete thyroidectomy or thyroxine supplementation, post-thyroidectomy patients may still experience dysthyroidism. Many times, this may be sub - clinical. This study aimed to assess the prevalence and pattern of sub-clinical dysthyroidism following thyroid surgery.

Methods
In this prospective cohort study, 40 patients were consecutively recruited following conventional thyroidectomy and followed up to 12months. All patients were euthyroid at surgery. At 12 months serum TSH, T4 and T3 levels were measured and the patients clinically assessed. The prevalence and pattern of dysthyroidism was analysed statistically against the patient demographics, clinical and peri-operative variables for significance, using stata version 13. The confidence interval was at 95% and the statistical significance at a p-value of <0.05.

Results
The mean age was 44.3 years (M:F= 1: 12.3). 20% of the patients had medical comorbidities. The types of surgery performed were sub-total thyroidectomy (55%), near total thyroidectomy (25%) and total thyroidectomy (20%). The prevalence of postoperative dysthyroidism was 52.5%. 22.7% of patients who underwent sub-total thyroidectomy had dysthyroidism. Most patients (90%) who were on thyroxine supplement (following total or near total thyroidectomy) still developed dysthyroidism (P= 0.017). The type of resection done had the greatest significance (P= 0.000). Other factors associated with dysthyroidism albeit non-significantly were history of pre-operative hyperthyroidism, middle age (40 - 60 years), and female gender.

Conclusions
The prevalence of dysthyroidism in this cohort was high which may reflect the broader picture among post - thyroidectomy patients in this setting. Regular biochemical testing in post-thyroidectomy patients is important to identify and correct dysthyroidism early. This requires frequent follow-up and accurate dose adjustment, based on objective assessments like weight or body mass index.

Keywords: post-thyroidectomy, dysthyroidism, hypothyroidism, hyperthyroidism, sub-clinical dysthyroidism, prospective, cohort

Introduction

Thyroid surgery results in altered function of the thyroid gland, corresponding to the extent of resection. The change in functionality will manifest biochemically, clinically or both ways. This disorder in thyroid function is called Dysthyroidism. Biochemical changes can be detected earlier than clinical manifestations and are based on the key hormonal assays of Thyroid Stimulating Hormone (TSH), Thyroxine (T4) and Triiodothyronine (T3).[1,2] The sub-clinical or pre-clinical patient has a high risk of progressing to clinical disease and should be identified and treated early.[3] These assays are considered the gold standard in assessing and predicting functionality of thyroid gland tissue. TSH measurement is the most sensitive,[2,4,5] since in the presence of an intact hypothalamus-pituitary-thyroid axis, its level will change before the free -T4 and free -T3 levels,[2,4-7] so it should

be used as the first line test. Conversely, a normal TSH level virtually excludes significant thyroid dysfunction. Current standards necessitate that laboratories use at least third generation TSH assays with a functional sensitivity of <0.01mIU/L.[4,5] Sensitivities of 0.004 mIU/L or <0.002 μIU/ml can be achieved with 4th and 5th generation assays respectively,[1] for detecting much lower levels of TSH, especially for patients on suppressive therapy for thyroid cancer.[8,9]

In addition to surgery, other factors may alter thyroid function,[1,2,9,10] such as autoimmune antibodies and infections causing thyroiditis with attendant hypothyroidism, Graves' disease associated with hyperthyroidism, or genetic anomalies leading to thyroxine resistance and TSH-receptor dysfunction.[2,6]

Presence of interfering antibodies may lead to spurious results.[2,6] Some drugs do interfere with thyroid function and readings.[1,2,9,11] Generally, all these factors should be considered while assessing thyroid dysfunction. Chronic alcohol use also reduces thyroid function,[12] and obesity is generally associated with higher serum TSH and thyroid hormones.[13]

Timing of the test is equally important; pre-prandial testing (on starved patients) should be avoided as it is associated with increased incidence of sub-clinical hypothyroidism.[1,2,9,14] The biochemical tests should be correlated with the clinical picture before drawing a supplementation plan, this improves accuracy of diagnosis so that over-treatment or under-treatment is avoided.

This study aimed to assess the prevalence and pattern of sub-clinical dysthyroidism following thyroid surgery in our setting and thereby establish adequacy of monitoring and treatment or supplementation of these patients.

Methods

This was a prospective non-interventional cohort study carried out at Mulago National Referral Hospital, in Uganda. At the endocrine surgery unit, among other operations, about 4 thyroidectomies are carried out per week or ~200 per year.[15] The thyroid conditions operated include multi-nodular goitres, Grave's disease, thyroid nodules and malignancy.[15] All patients are euthyroid or corrected to euthyroid state before surgery.

In 2014, 40 patients underwent conventional thyroidectomy, with the extent of surgery/type of thyroidectomy determined independently by individual patient factors and the handling surgeon. After surgery those who consented to participate in the study were consecutively recruited. All the patients were followed up to the end-point of the study – at 12months. During this time, those with intervening problems were investigated and managed accordingly. At 12months, the patients were assessed for features of hyperthyroidism and hypothyroidism and the clinical findings and the thyroid hormone profile (TSH, T4 and T3 levels) were documented.

The hormonal assays were done using an ISO certified Cobas 6000 analyser in the accredited clinical chemistry laboratory of the hospital. Samples were drawn into red-top blood collection tubes and delivered to the laboratory within 2hrs. Turnaround time was between 5-12hrs dependent on load.

Results analysis: The participants' demographic data was grouped into continuous and categorical variables, and analysed as means and proportions respectively. The patient independent variables and the corresponding TFT measurements were tallied and tabulated into contingency tables. The prevalence and pattern of dysthyroidism was analysed statistically against the patient demographic, clinical and peri-operative variables for significance - using Fischer's Exact Test or Pearson's chi-square test for the categorical variables, and independent T-test for the numerical variables, at a confidence interval of 95%. The statistical significance was at a p-value of <0.05. Statistical analysis package stata version 13 was used.

Consent to participate in the study was obtained from all participants, and ethical approval was granted by the Mulago Hospital Ethics Committee.

Results

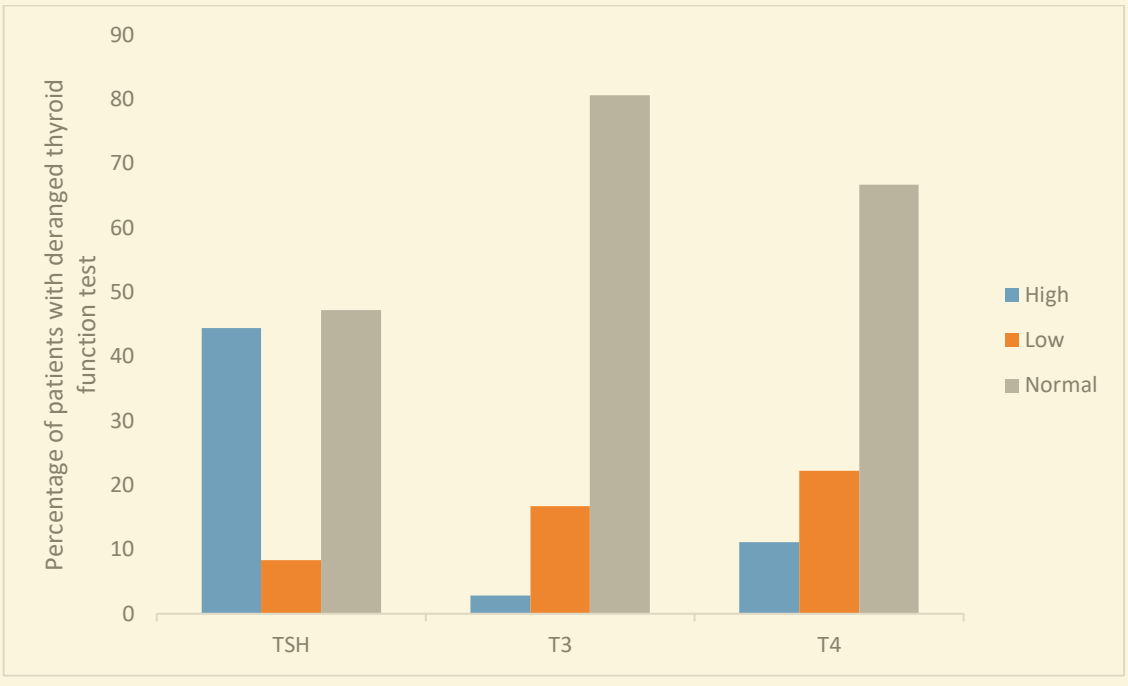
The study cohort comprised of 40 participants (n=40), with a mean age of 44.3years, ranging from 19 – 70years. 92.5% were female. The most frequently offered surgery was sub-total thyroidectomy (55%), followed by near total-(25%) and total thyroidectomy (20%). 20% of the patients had medical co-morbidities.

A total of 10 (27.8%) patients received thyroxine supplementation soon after surgery or during routine follow-up. Of these, only one did not have dysthyroidism at the time of study follow-up. In other words, most of the patients (90%) who were on thyroxine supplement still developed dysthyroidism, and this was significant statistically (P-value= 0.017). The type of surgery had the greatest significance (P-value= 0.000) where by the majority of those who underwent total or near total thyroidectomy ended up with dysthyroidism, despite the fact that most of them had been started on thyroxine supplementation soon after surgery. 22.7% of those who underwent sub-total thyroidectomy developed dysthyroidism, indicating failure of their remnant thyroid tissue to regain normal function, which corresponds to some reports highlighting the onset of hypothyroidism after sub-total thyroidectomy.[16]

The overall prevalence of dysthyroidism in this cohort was high at 52.5% (more than half the participants). Dysthyroidism was commonest among the 40-60yr age group (Figure 1) probably because they were the biggest age group. Notably, a bigger proportion (72.7%) of the younger age group (< 40years) had dysthyroidism, while among the elderly (> 60years) only 1 out of 5 had dysthyroidism. According to gender, dysthyroidism occurred more among the females who represented the great majority of the study group. About half of the females, and all males had dysthyroidism but this was not statistically significant. Despite being corrected to euthyroid state before surgery, patients with prior hyperthyroidism were more likely to have post-opera-

Table 1: Characteristics of the study population with regard to dysthyroidism						
	Dysthyroidism					
	No	Yes	Total	No	Yes	Total
	N	N	N	%	%	%
Patient age group						
<40	3	8	11	27.3	72.7	100
40-<60	11	12	23	47.8	52.2	100
>=60	4	1	5	80	20	100
Total	*18*	*21*	*39*	*46.2*	*53.8*	*100*
Pearson X^2= 3.909						
P-value= 0.142						
Gender of the patient						
Female	19	18	37	51.4	48.6	100
Male	0	3	3	0	100	100
Total	*19*	*21*	*40*	*47.5*	*52.5*	*100*
Pearson X^2= 2.934						
P-value= 0.087						
Medical comorbidities						
Yes	6	2	8	75	25	100
No	13	19	32	40.6	59.4	100
Total	*19*	*21*	*40*	*47.5*	*52.5*	*100*
Pearson X^2= 3.033						
P-value= 0.082						
Resection done						
Sub-total	17	5	22	77.3	22.7	100
Near-total	1	9	10	10	90	100
Total	1	7	8	12.5	87.5	100
Total	*19*	*21*	*40*	*47.5*	*52.5*	*100*
Pearson X^2= 17.389						
P-value= 0.000						
Taking thyroxine supplement						
Yes	1	9	10	10	90	100
No	14	12	26	53.8	46.2	100
Total	*15*	*21*	*36*	*41.7*	*58.3*	*100*
Pearson X^2= 5.713						
P-value= 0.017						

Figure 1. Pattern of dysthyroidism among post-thyroidectomy patients.



tive dysthyroidism (71.4%), but this was also not statistically significant.

Only two patients (25%) with medical co-morbidities had dysthyroidism but this was statistically insignificant. The type of resection done had great statistical significance, with a large percentage of those who had total and near total thyroidectomy (90% and 87.5%) respectively, having dysthyroidism.

According to Figure 1, the commonest form of dysthyroidism was hypothyroidism as depicted by the high TSH (blue bar) in the TSH column, this also corresponds to the proportionately high number of patients with low T4.

Discussion

This study revealed that the prevalence of sub-clinical dysthyroidism in our setting is high (52.5%), indicating that despite the lack of overt signs and symptoms, a significant number of our post thyroidectomy patients will quietly transit and slip into clinical dysthyroidism. Notably, a big proportion (72.7%) of the younger age group (< 40years) had dysthyroidism, compared to only 20% among the elderly (> 60years), which is ironic because young people would be expected to have more intact physiology to ensure robust thyroid function regeneration. Despite being corrected to euthyroid state before surgery, patients with prior hyperthyroidism were more likely to have post-operative dysthyroidism (71.4%), but this was not statistically significant. Many of these had sub-total thyroidectomy for Grave's disease where the remnant thyroid tissue probably continued to hyper function. Though not supported by most international guidelines, sub-total instead of total thyroidectomy is still offered in such settings where there is concern over the patients' ability to afford lifelong thyroxine replacement therapy.

The commonest form of dysthyroidism was hypothyroidism, indicating that our patients either delay to start, miss out, or are being under-dosed on thyroxine replacements. Another reason may be poor adherence to thyroxine therapy prescriptions. Patients should swallow the tablets in fasting state,[17] and in our setting they are instructed to take it early morning before breakfast. The issue of compliance here is very pertinent considering that the proportion of dysthyroidism among those already on thyroxine supplementation was way high, and this was statistically significant (p=0.017). Regarding type of surgery, the sub-groups affected most were total and near-total thyroidectomy (p=0.000) which automatically precipitate hypothyroidism, but both forms of dysthyroidism are witnessed here, further revealing that while many were being under-supplemented, others were actually being over supplemented or taking excess thyroxine. (see graph 1; T4 column – blue & brown bars). Patients after incomplete or sub-total thyroidectomy are considered to have enough remnant tissue to regain full thyroid function after restoration of the hypothalamus-pituitary-thyroid axis which should occur in 4 to 8 weeks, so onset of hypo-thyroidism indicates significant delay or failure to recover this function.[16,18,19] The rate, sufficiency or failure of recovery will depend on patient specific factors,[1,9] like co-morbidities, age and sex,[16,20] as well as the pre-operative hormonal levels of thyrotropin (TSH), thyroglobulin (TG), anti-thyroglobulin (ATA), and anti-microsomal antibody (AMA)[21] - which are all recognised predictors of post-operative hypothyroidism.[19,21] This also underscores the fact that sub-total thyroidectomy done with the intention of preserving normal function is not always rewarding.[16] It is important to remember that this hypothyroidism can also be caused by a pre- or post-operative thyroiditis, among other causes.[16,19,21] Conversely, a state of hyperthyroidism can also recur or occur due to Grave's disease involving the thyroid remnant.[16]

Following lobectomy, some studies have reported a 14.3% incidence of hypothyroidism, requiring thyroxine supplementation.[19] In other reports the risk of these patients developing thyroid insufficiency in their lifetime is higher, at 21%[21] or up to 28%.[19] The onset of overt hypothyroidism following surgery is gradual and may be preceded by subclinical hypothyroidism for many years.[21] Assessment of thyroid function in these patients is recommended four to eight weeks after surgery, followed by quarter yearly for the subsequent year or 2 years,[19] and then annually indefinitely.[16,22,23] However, more frequent monitoring is relevant because patients regain full thyroid function at different rates, while the metabolic demands of others may change from time to time; influenced by factors including advancing age, changing nature of work/occupation/lifestyle and concurrent illnesses or physiological stress. Those with sub-clinical hypothyroidism (elevated TSH) are more likely to progress to clinical hypothyroidism,[1,3] so adequate and timely thyroxine replacement should be administered accordingly.[19,23] The transitory sub-clinical period provides a window of opportunity to do the TFTs and identify the dysthyroidism early to prevent overt disease.[16] Thyroid function tests at the extremes of the normal range may indicate early thyroid dysfunction and repeat tests are indicated in such situations.[1,6,8]

In our setting many patients come from distant rural communities where qualified medical personnel and competent laboratories are scarce, making frequent monitoring very difficult to ensure. Indeed patients cited high transport costs and hardships of travelling long distances as limitations to medical reviews. There's also reluctance to request for or do laboratory tests more frequently due to financial constraints. TFTs cost ~ $25-45, which is a limitation for most patients.[15]

Despite such socio-economic challenges, ensuring adequate and effective thyroxine supplementation among post-thyroidectomy patients requires more frequent follow up and assessment, accurate hormonal assays, appropriate dosing or dose adjustment[1,2,16] based on objective need assessments like body weight (mg/kg) and body mass index (BMI),[24] intense counselling on compliance and closer supervision of those on supplements. Endocrine Unit-based dispensing of thyroxine supplements would ensure that thorough instructions are passed on.

This study is limited by the small population, so a repeat with a bigger sample size would give more valid findings.

Possible assay interference was pre-emptied by ensuring thorough quality assurance as indicated in the methods, and other possible factors interfering with the thyroid function like drugs,[1,11] alcohol use,[9] and obesity[13] have been ruled out among participants in this study. A study to specifically assess factors influencing compliance to treatment with thyroxine among post-thyroidectomy patients in this setting is called for.

Conclusions

There is high prevalence of undetected dysthyroidism in post-thyroidectomy patients in our centre, and probably our broader setting, mainly manifesting as hypothyroidism. A significant number of patients seem to be receiving inadequate thyroxine treatment. There is need to identify, prevent or correct all possible factors affecting adequate supplementation of post-thyroidectomy patients. These patients should be monitored regularly/frequently and offered effective thyroxine supplementation doses calculated from objective assessments like weight or BMI.

Competing interests

All authors declare that they have no competing interests related to this work.

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