Thyroid Uptake Versus Thyroid Salivary Ratios: Which is More Reliable for Post-Operative Thyroid Functional Assessment in Patients with Recurrent Hyperthyroidism?

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Abstract

Introduction: Tc-99m pertechnetate thyroid uptake has been introduced as a useful adjunct to measurement of hormonal levels in patients with recurrent hyperthyroidism after surgery for toxic goiter. A crude but relatively accurate estimate of thyroid function can be obtained by comparing thyroid to salivary gland activity at 20 minutes.

Purpose: We aimed in the current study to assess the value of Tc-99m pertechnetate thyroid uptake (TU) and thyroid-salivary ratios (both thyroid/salivary ratio: TSR and salivary/thyroid ratio; STR) in diagnosis of post-operative recurrent hyper-functioning thyroid tissue.

Patients and Methods: The current study included 114 patients presented for thyroid scintigraphy 3-9 months post subtotal thyroidectomy for toxic goiter (73 Grave's disease & 41 toxic nodular goiter). Ten patients proved to have hypothyroidism were excluded from the study. All patients were subjected to clinical history and examination, thyroid hormonal profile, Tc-99m pertechnetate thyroid scan with calculation of TU, TSR and STR 20min after injection of the radiotracer. Thyroid uptake per unit weight of residual thyroid tissue was also calculated. TU value was considered normal if it is in the range of 0.3 to 3.75%.

Results: According to thyroid hormonal profile, patients were divided into two main groups, Group 1: Included 25 patients with hyperthyroid state. The mean value of TU was 10.2%. The mean value of TSR and STR were 11.75 and 11.1%. Twenty-three patients had both indices pointing to hyperthyroidism. The sensitivity of the thyroid uptake value for diagnosis of hyperthyroidism in this group of patients was 68%, while the sensitivity for both TSR and STR was 92%, with a statistically significant difference between both figures (p<0.001). Group 2: Included the remaining 79 patients with normal thyroid hormonal profile. Their mean uptake value was 1.58%, while the mean value of TSR and STR were 2.5% and 57%. All patients in this group had normal thyroid uptake level. The specificity of TU for diagnosis of recurrent hyperthyroidism was 100% versus 97.5% for both TSR and STR. The mean thyroid uptake per unit weight of residual thyroid tissue in group 2 was 6.4, which is significantly less than that reported for group 1 (19.5%) (p<0.001).

Conclusion: Thyroid uptake value has lower sensitivity (68%) than thyroid salivary ratios (TSR & STR) (92%) in diagnosis of post-operative recurrent hyperthyroidism with comparable specificity. So, TSR and STR are more reliable than Tc-99m pertechnetate TU in diagnosis of recurrent hyperthyroidism post operatively and may be applied in this group of patients for assessment of the functional status of residual thyroid tissue. Thyroid uptake per unit weight of remaining thyroid tissue is significantly higher for recurrent toxic state compared to euthyroid state; this may represent a new useful functional index, warranting further randomized study on much larger number of patients to verify its exact value.

Key Words: Tc-99m thyroid scan – Recurrent hyperthyroidism – Thyroid uptake – Thyroid/salivary ratio.

Introduction

RECURRENT hyperthyroidism after surgery for toxic goiter was reported to occur in 0.6 to 17.9% of patients. Factors affecting post operative thyroid function include severity of the disease prior to surgery, patient age, presence of high levels of thyroid autoantibodies before surgery, size of the gland, evidence of lymphoid infiltration and how much of the gland was removed [1].

Radioactive iodine (I-131) was the first radiopharmaceutical used in the evaluation of thyroid function, yet, because of its obvious disadvantages Tc-99m pertechnetate was introduced for estimation of thyroid uptake in 1975 by Sokole et al. [2]. Now it has been established as a useful adjunct to measurement of hormonal levels in patients with suspected thyroid disease. A crude but relatively accurate estimate of thyroid function can be obtained by comparing thyroid to salivary gland activity at 20 minutes. Normally the thyroid gland has slightly higher activity compared to salivary glands. Much higher thyroid activity is diagnostic
of hyperfunctioning gland. The overall accuracy of this method compared to radioactive iodine (I-131) uptake is 94% [3,4].

The rationale beyond this study is the observation from our own experience in clinical practice that it is not unusual for patients with clinical and laboratory evidence of post operative recurrent hyperthyroidism to have thyroid uptake level within normal range (0.3-3.75%) [3]. This was emphasized by the finding of El-Refaie and Kamal [5] that normal thyroid uptake level was encountered in the only 3 patients in their study who underwent thyroidectomy for Grave's disease, with established recurrent hyperthyroidism on both clinical and laboratory basis.

The aim of the current study is to assess the value of Tc-99m pertechnetate thyroid uptake and thyroid-salivary ratios (both thyroid/salivary ratio: TSR and salivary/thyroid ratio: STR) in diagnosis of post operative recurrent hyper-functioning thyroid tissue and to detect which is more reliable for diagnosis of recurrent hyperthyroidism in this group of patients.

Patients and Methods

The current study included 114 patients presented for thyroid scintigraphy 3-9 months post subtotal thyroidectomy for toxic goiter (73 Grave's disease & 41 toxic nodular goiter).

All patients were subjected to:

- Full clinical history and examination.
- Estimation of serum level of free T3 (FT3), free T4 (FT4) and TSH. Patients with established hypothyroidism were excluded from the study.
- Tc-99m pertechnetate thyroid scan with calculation of:
  A- Thyroid uptake (TU).
  B- Thyroid uptake per unit weight of residual functioning thyroid tissue.
  C- Thyroid/salivary ratio (TSR).
  D- Salivary/thyroid ratio (STR).

Thyroid uptake estimation was performed after intravenous injection of 5mCi Tc-99m pertechnetate using the installed software of ADAC vertex plus dual head gamma camera. In brief, pre and post injection syringe images were acquired and anterior view of the neck was acquired 20 minutes post injection. Regions of interest (ROT’s) were drawn around the thyroid gland and background. Uptake value was considered normal if it is in the range of 0.3 to 3.75% [3]. If more than this, the residual thyroid tissue was considered to be over functioning (hyperthyroid state). As the software gives automatically the weight of residual thyroid tissue, uptake per unit weight of residual thyroid tissue was calculated by dividing the uptake value by the weight of residual thyroid tissue multiplied by 100.

Calculation of thyroid/salivary ratios was performed in the same study with thyroid uptake. After acquiring the anterior view of the neck, ROI’s were drawn on the submandibular glands and the thyroid gland residue. Counts per pixel were determined for each ROI and thyroid/salivary ratios were calculated as follows:

- **TSR**: Counts per pixel thyroid ROI divided by counts per pixel salivary glands ROI x 100. (normal value <6%, if more than 6 the result points to hyperthyroid state) [5].
- **STR**: Counts per pixel salivary glands divided by counts per pixel thyroid gland x 100. (normal value >16.5%, if less than this figure the result points to hyperthyroid state) [5].

Results

Ten patients proved to have hypothyroidism; they were excluded from the study. The remaining 104 patients have an age range of 21-67 years (mean age 33±19), out of these patients, 91 (84%) were females.

Forty-nine patients (47%) have one or more symptoms suggestive of hyperthyroidism, the commonest was palpitation followed by nervousness. Twenty-one patients had more than one symptom (Table 1).

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number of patients</th>
<th>% symptomatic patients (49)</th>
<th>% out of total (104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpitation</td>
<td>31</td>
<td>63.3</td>
<td>29.8</td>
</tr>
<tr>
<td>Nervousness &amp; irritability</td>
<td>26</td>
<td>53</td>
<td>25</td>
</tr>
<tr>
<td>Menstrual disorders</td>
<td>17</td>
<td>34.7</td>
<td>16.3</td>
</tr>
<tr>
<td>Heat intolerance</td>
<td>9</td>
<td>18.4</td>
<td>8.7</td>
</tr>
<tr>
<td>Weight loss</td>
<td>7</td>
<td>14.2</td>
<td>6.7</td>
</tr>
<tr>
<td>More than one symptom</td>
<td>21</td>
<td>42.8</td>
<td>20.2</td>
</tr>
</tbody>
</table>

According to thyroid hormonal profile, patients were divided into two main groups:

**Group 1**: Included 25 patients with hyperthyroid state as proved by thyroid hormonal profile (22 with overt hyperthyroidism and 3 with subclinical hyperthyroidism).
The mean value of thyroid uptake in this group was 10.2%, with a range of 2.4% to 35.3%. Seventeen patients (68%) had elevated thyroid uptake level (>3.75). The remaining 8 patients had thyroid uptake value within normal range.

The mean value of TSR and STR were 11.75 and 11.1% ranging from 4.7 to 30.1% and 3.5 to 21.4% in the whole group respectively. Twenty-three patients had both indices pointing to hyperthyroidism. Only 2 patients had normal TSR and STR (<6% and >16.5% respectively) (Table 2).

The sensitivity of the thyroid uptake value for diagnosis of hyperthyroidism in this group of patients was 68%, while the sensitivity for both TSR and STR was 92%, with a statistically significant difference between both figures (p<0.001).

The mean thyroid uptake value per unit weight of residual thyroid tissue in this group was 19.5%.

### Table (2): TU, TSR and STR in group 1 (25 patients) with hyperthyroid state.

<table>
<thead>
<tr>
<th>Value</th>
<th>Hyperthyroid state</th>
<th>Normal</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>TU</td>
<td>17</td>
<td>8</td>
<td>10.2%</td>
<td>2.4-35.3%</td>
</tr>
<tr>
<td>(N=0.3-3.75%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSR (N&lt;6)</td>
<td>23</td>
<td>2</td>
<td>11.75%</td>
<td>4.3-30.1%</td>
</tr>
<tr>
<td>STR (N&gt;16.5)</td>
<td>23</td>
<td>2</td>
<td>11.1%</td>
<td>3.5-21.4%</td>
</tr>
</tbody>
</table>

TU: Thyroid uptake.  
TSR: Thyroid/salivary ratio.  
STR: Salivary/thyroid ratio.

**Group 2:** Included the remaining 79 patients with normal thyroid hormonal profile. Their mean uptake value was 1.58% (range 0.7-2.9%), while the mean value of TSR and STR were 2.5% and 57% with a range from 1.3-7.2% and 14.5-96% respectively. All patients in this group had normal thyroid uptake level. On the other hand, only 2 patients had TSR and STR point to hyperthyroid state, with normal values in the remaining 77 patients (Table 3).

### Table (3): TU, TSR and STR in group 2 (79 patients) with normal thyroid hormonal profile.

<table>
<thead>
<tr>
<th>Value</th>
<th>Hyperthyroid state</th>
<th>Normal</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>TU</td>
<td>79</td>
<td></td>
<td>1.58%</td>
<td>0.7-2.9%</td>
</tr>
<tr>
<td>TSR</td>
<td>2</td>
<td>77</td>
<td>2.5%</td>
<td>1.3-7.2%</td>
</tr>
<tr>
<td>STR</td>
<td>2</td>
<td>77</td>
<td>57%</td>
<td>14.5-96%</td>
</tr>
</tbody>
</table>

The specificity of TU for diagnosis of recurrent hyperthyroidism in the current study was 100 versus 97.5% for both TSR and STR, with no statistically significant difference between both figures.

The mean thyroid uptake per unit weight of residual thyroid tissue in the current study was 6.4%, which is significantly less than that reported for group 1 (19.5%) (p<0.001).

**Discussion**

Hyperthyroidism is a clinical syndrome that results from the presence of supraphysiologic circulating levels of thyroid hormone and can occur as a consequence of numerous disease processes [6]. Hyperthyroidism occurs more commonly in young age females. The reported annual incidence is 36 female and 8 males per 100000 [7]. In the current study females represent 84% of the whole study population. This goes with previous reports confirming female predominance.

Surgery is one of the three therapeutic modalities available for hyperthyroidism. For the toxic multinodular goiter the specific surgical procedure is a near total thyroidectomy with removal of at least 85% of the gland, notably those parts shown to be active on scintiscans. While for primary diffuse toxic goiter, subtotal thyroidectomy is the surgical procedure of choice which aims to leave one eighth of thyroid tissue on each side [1,7]. All our patients underwent subtotal thyroidectomy, yet, they were performed by different surgeons in several hospitals using different techniques. This points to some variation in size of thyroid tissue left in place after surgery which was confirmed by the thyroid scan, with no solid data about the exact volume planned to be left in each patient.

Avoiding hypothyroidism is one of the main challenges when operating for thyrotoxicosis, as subtotal thyroidectomy is one important cause of decreased thyroid reserve. Permanent hypothyroidism is the major post operative complication after surgery in those patients. It ranged from 4% and 29.7% [1]. The incidence of patients who developed post operative hypothyroidism in the current study is 8.8% which is within the previously reported range. Although it has been assumed that hypothyroidism will usually develop within 1 year after operation, if it is to occur at all, long term studies showed a progressive increase in the cumulative incidence with time similar to that produced by radioiodine but of a lesser magnitude. The overall frequency of some impairment of thyroid function is even higher than frank hypothyroidism. Eventual thyroid failure is a frequent consequence of the overfunctioning thyroid process itself, so, the large increase in cumulative frequency of hypothyroidism with time that follows surgery or I-131 therapy is both expected and unavoidable. Treatment that
destroys thyroid tissue would accelerate the emergence of hypothyroidism resulting from the disease process itself [6].

The ability of the thyroid to produce sufficient thyroxin after thyroidectomy reflects not only the size of the remnant but also the pre-existing pathological processes within the gland. An inverse relationship exists between the frequency of recurrence and that of hypothyroidism. The incidence of recurrent hypothyroidism varies from 0.6 to 17.9% [1].

In the current study, recurrent hyperthyroidism was encountered in 21.9% of patients, a bit higher than reported incidence. This could be related to different surgical techniques employed in the current study, with more residual thyroid tissue left in place in some patients, which have an influence on determining post thyroidectomy functional state.

Actually, the relative frequency of permanent hypothyroidism and recurrent hyperthyroidism partly depends on the quantity of thyroid tissue left in place. What is more remarkable that among patients whose thyroid glands vary greatly in size and degree of hyperthyroidism and who are operated upon by different surgeons using different techniques, a normal metabolic state is restored, at least for long periods, in majority of patients. This favorable outcome may result because the amount of tissue remaining after operation is alone insufficient to sustain a normal metabolic state and hence becomes stimulated by the necessary quantity of endogenous TSH. In this way, the patient’s haemostatic mechanism provides the adjustment in thyroid function that surgery, quite naturally, could not [6]. This was confirmed in the current study where post operative euthyroid state was found in 79 patients, representing 69.3% of the whole patient population.

Thyroid scintigraphy with estimation of thyroid uptake level represents an indispensable step in establishing the diagnosis of hypothyroidism and clarifying its underlying etiology. To circumvent the problem of high radiation burden from I-131, several other methods have been used to measure thyroid uptake [8]. As Tc-99m is trapped but not organized by the thyroid, it can be used for estimation of thyroid uptake level. Tc-99m pertechnetate has become the tracer of choice for estimation of thyroid uptake. Normal thyroid uptake of Tc-99m pertechnetate is only 0.3-3.75% of the injected dose [3]. The use of Tc-99m pertechnetate has several advantages over the use of I-131 [9].

Malhotra et al. [10] compared radioactive iodine and Tc-99m pertechnetate thyroid to parotid ratio in primary hyperthyroidism. They showed its significance in diagnosis of grave’s disease with significantly higher figure compared to euthyroid patients. Also, El-Refaie and Kamal [8] reported that thyroid submandibular ratio is a simple, fast and accurate method for evaluation of thyroid functional status. It is very practical in busy departments. It also carries the potential advantage of being not affected by the volume of the remaining thyroid tissue after thyroidectomy. The latter is thought to have an impact on thyroid uptake level.

The finding that it is not unusual for patients with established recurrent hyperthyroidism after surgery to exhibit normal thyroid uptake level was observed in clinical practice and was reported by El-Refaie and Kamal [5]. This encouraged us to apply other quantitative indices for assessment of function of residual thyroid tissue in this group of patients. Thyroid salivary ratios (TSR and STR) were used to assess thyroid function in this group of patients in the current study. The overall sensitivity of thyroid uptake in diagnosis of recurrent hyperthyroidism was found to be 76%. This figure was 92% for both TSR and STR, with a statistically significant difference between both figures, with comparable specificity, favoring the use of TSR or STR for diagnosis of this particular disease entity. Actually, the normal thyroid uptake level encountered postoperatively in patients with recurrent hyperthyroidism may be related to post operative change in thyroid depth, size and shape. Also, perhaps the normal range for post operative state should be different from that for non thyroidectomized patients, particularly its upper limit. The latter appears to be not fitting for this group of patients of recurrent hyperthyroidism after surgery and may be responsible for such false negative results in those patients.

The mean value of thyroid uptake in the current study for the euthyroid group is 1.58%, no single patient in this group has thyroid uptake level more than 3.0. Only 17 had thyroid uptake more than 2, the rest of the patients (62 patients) representing 78.5% had uptake value less than 2 i.e. less than 50% of the expected applied normal range. The latter may be in need to be revised for this particular group of patients to allow for elimination of the uptake of the already removed portion of the thyroid gland and represent the real normal uptake value in thyroidectomized patients. A multicentric randomized study is needed to be done on a large number of patients who underwent thyroidectomy
to establish the exact normal range fitting those patients to be applied as the post thyroidectomy expected normal range of thyroid uptake.

The mean uptake value per unit weight of residual thyroid tissue in the neck was significantly higher in the toxic group compared to the euthyroid group (19.5% versus 6.4%), with a statistically significant difference between both figures. This may represent a new functional index that can be employed for assessment of thyroid function, warranting evaluation in randomized trial on much more number of patients.

In conclusion, hypothyroidism and recurrent hyperthyroidism are post operative complications after subtotal thyroidectomy for toxic goiter, occurring in around 9% and 20% respectively. The majority of patients (around 70%) maintain euthyroid state. Thyroid uptake value has low sensitivity in diagnosis of recurrent hyperthyroidism (68% sensitive). On the other hand, thyroid salivary ratios (TSR & STR) are more sensitive (92% sensitivity) than thyroid uptake in diagnosis of this group of patients, with comparable specificity. So, TSR and STR are more reliable than Tc-99m pertechnetate TU in diagnosis of recurrent hyperthyroidism post operatively and may be applied in this group of patients for assessment of function of residual thyroid tissue.

The currently applied normal range of TU that is applicable for intact thyroid gland appears to be not fitting and not applicable postoperatively for patients who underwent subtotal thyroidectomy. This points to the need of revising this normal range and creating a more fitting normal range to be applied for thyroidectomized patients that would be more useful in estimation of the exact functional status of residual thyroid tissue.

Thyroid uptake per unit weight of remaining thyroid tissue is significantly higher for recurrent toxic state compared to euthyroid state, this may represent a new useful functional index, warranting further randomized study on much larger number of patients to verify its exact value.

References