

# Inhibited $^{131}\text{I}$ Uptake but Normal Release of Thyroid Hormone by Thyroid Gland in Response to TSH Administration in Subclinical Hypothyroidism

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## ABSTRACT

**Background:** Subclinical hypothyroidism is characterized by normal circulating thyroid hormone levels with super-normal TSH concentrations in absence of clinical manifestations. In majority of subjects, an etiologic factor is often identified. Moreover, therapy with levothyroxine normalizes serum TSH concentration while maintaining normal thyroid hormone concentrations. However, the exact pathophysiology of these thyroid hormone alterations is not well defined. **Objective:** Major steps in synthesis *i.e.* iodine uptake and the release of thyroid hormones in response to SC TSH administration were assessed in subjects with subclinical hypothyroidism. **Methods:** 10 men and 5 women with subclinical hypothyroidism, ages 42 - 76 years and 10 euthyroid men (39 - 70 years) participated. 24 hr  $^{131}\text{I}$  iodine thyroid uptake and serum  $\text{T}_3$ ,  $\text{T}_4$  and TSH concentrations were determined prior to and after SC administration of recombinant human TSH, 0.9 mg for two consecutive days. Comparisons were conducted for 24 hour uptake values as well as serum  $\text{T}_3$ ,  $\text{T}_4$  and TSH levels obtained prior to and after TSH administration. **Results:** In subjects with subclinical hypothyroidism 24 hour  $^{131}\text{I}$  thyroidal uptakes were normal (10% - 30%). However, the mean value was significantly lower, ( $p < 0.05$ ) as compared to euthyroid volunteers. 24 hr uptakes rose following TSH administration in both groups. However, the rise was significant ( $p < 0.01$ ) only in normal subjects. Furthermore, both the mean absolute uptake and the mean % rise following TSH administration were markedly significantly lower in subjects with subclinical hypothyroidism in comparison to normal subjects. Serum  $\text{T}_3$  and  $\text{T}_4$  concentrations in subjects with subclinical hypothyroidism were not significantly different in comparison to normal subjects. Serum TSH concentrations were supernormal and therefore were significantly higher in subjects with subclinical hypothyroidism in comparison to normal subjects and rose markedly in both groups following TSH administration with no significant difference among groups. Serum  $\text{T}_4$  and  $\text{T}_3$  rose significantly from PreTSH levels in both groups ( $p < 0.05$ ). However, the rises were not significantly different between groups. **Conclusion:** In subjects with subclinical hypothyroidism secondary to Hashimoto's thyroiditis, 24 hour  $^{131}\text{I}$  Thyroid uptake is inhibited prior to as well as following SC TSH administration in comparison to normal subjects with maintenance of normal hormone release.

**Keywords:** Subclinical Hypothyroidism;  $^{131}\text{I}$  Thyroid Uptake; Thyroid Hormone Release

## 1. Introduction

Subclinical hypothyroidism is a syndrome characterized by normal circulating thyroid hormone levels with simultaneous supra-normal TSH concentrations frequently in absence of clinical manifestations of hypothyroidism [1-18]. In majority of these subjects, a known etiologic factor *i.e.* presence of antithyroid antibodies, previous treatment for hyperthyroidism, external neck radiation or surgery and use of drugs known to induce hypothyroidism, etc. is frequently identified [6-10,13-15]. Moreover, therapy with levothyroxine normalizes serum TSH concentration while continuing to maintain normal thyroid

hormone concentration [6-10,12-19]. However, the exact pathophysiology of these unusual thyroid hormone alterations is not clearly defined.

It is also well established that several physiologic steps have to be intact to induce synthesis and release of thyroid hormones and TSH promotes each of these steps beginning with iodine uptake and ending with release of thyroid hormones by the thyroid gland [20,21]. Moreover it is also well documented that the major aberration of a single step in thyroid hormone synthesis or release results in clinical hypothyroidism, whereas, a minor inhibition of any of these individual steps induces a goiter without a clinical hypothyroidism [20-24]. Therefore we studied the major steps in synthesis *i.e.* iodine uptake and

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the release of thyroid hormone in response to administration of TSH in subjects with subclinical hypothyroidism.

## 2. Subjects and Methods

10 men and 5 women with ages 42 - 76 years with established diagnosis of subclinical hypothyroidism, manifested by normal T<sub>4</sub> and T<sub>3</sub> and supra normal TSH levels, participated in the study after obtaining informed consent. 10 euthyroid men with ages 39 - 70 years participated as controls, also after providing informed consent. Normal serum T<sub>4</sub>, T<sub>3</sub> and TSH levels were documented prior to participation. The study protocol was approved by the research and development committee as well as the human studies subcommittee. The study was conducted at Veteran's Affairs Medical Center in Des Moines, Iowa. The subjects were diagnosed to manifest Hashimoto's thyroiditis as documented by elevated titers of antithyroperoxidase antibody.

24 hr <sup>131</sup>I thyroid uptake and serum TSH, T<sub>4</sub> and T<sub>3</sub> concentrations were determined on two occasions at interval of 2 - 3 weeks prior to and after SC administration of recombinant human TSH (Thyrogen, Genzyme Laboratories), 0.9 mg for two consecutive days. <sup>131</sup>I uptakes were conducted in the local nuclear medicine department. Serum T<sub>4</sub>, T<sub>3</sub>, and TSH concentrations were determined by local clinical laboratory using well established commercial assays. During the procedure of TSH stimulation, <sup>131</sup>I was administered on the day prior to 2<sup>nd</sup> TSH injection; 24 hr thyroidal uptake and serum TSH, T<sub>3</sub> and T<sub>4</sub> levels were determined on the next day. Comparisons were conducted between subjects with subclinical hypothyroidism and euthyroid volunteers for 24 hour uptake values as well as serum T<sub>3</sub>, T<sub>4</sub> and TSH levels obtained prior to and after TSH administration. The comparisons were performed by statistical analyses using paired student's t-test and analysis of variance. All values are provided as mean ± standard error of mean (SEM).

## 3. Results

In all subjects with subclinical hypothyroidism 24 hour <sup>131</sup>I thyroidal uptakes were within the normal range [10% - 30%] as defined previously by the local nuclear medicine department. However, the mean value was significantly lower, (p < 0.05) as compared to euthyroid volunteers (Table 1). These 24 hr uptake values rose following TSH administration in both groups of participants. However, the rise was significant (p < 0.01) only in normal subjects. Furthermore, both the mean absolute uptake value and the mean % rise following TSH administration from preTSH uptake values were markedly significantly lower in subjects with subclinical hypothyroidism in comparison to normal subjects (Table 1).

Serum T<sub>3</sub> and T<sub>4</sub> concentrations in subjects with sub-

clinical hypothyroidism were within normal range as established by the clinical laboratory. Moreover, the mean levels were also not significantly different in comparison to normal subjects. (Table 2) Serum TSH concentrations were supernormal and therefore were significantly higher (p < 0.01) in subjects with subclinical hypothyroidism (8.6 ± 1.5 uU/ml) in comparison to normal subjects (2.3 ± 0.8 uU/ml) and rose markedly in both groups following TSH administration with no significant difference among the elevations between both groups (78 ± 7 uU/ml Vs 70 ± 9 uU/ml). Serum T<sub>4</sub> and T<sub>3</sub> rose significantly from PreTSH levels in both groups (p < 0.05). However, the rises were not significantly different between both groups of subjects (Table 2).

## 4. Discussion

The presence of iodine organification defect in subjects with Hashimoto's thyroiditis has been well documented [22,25]. Moreover, this defect is attributed to destruction of the enzyme thyroperoxidase induced by the antibody.

**Table 1. Mean 24 hour <sup>131</sup>I Thyroid uptake values prior to (PreTSH) and following SC administration of recombinant human TSH 0.9 mg daily for 2 days (postTSH) in 15 subjects with Subclinical Hypothyroidism (SC HypoT) and 10 Euthyroid Volunteers (Normal).**

Subjects	24 hour <sup>131</sup> I uptake Basal	24 hour <sup>131</sup> I uptake post TSH absolute value	24 hour <sup>131</sup> I uptake post TSH absolute rise	24 hour <sup>131</sup> I uptake post TSH % rise
SC hypo T	13 ± 2* (11 - 17)	16 ± 3* (14 - 20)	4 ± 1* (2 - 5)	22 ± 3* (12 - 25)
Normal	25 ± 4 (18 - 28)	51 ± 9† (37 - 66)	24 ± 5 (17 - 36)	80 ± 10 (54 - 106)

\*—Significantly lower than Normal, p < 0.01; †—Significantly higher than Basal, p < 0.01.

**Table 2. Mean Serum T<sub>4</sub> (ug/dl), T<sub>3</sub> (ng/dl) and T<sub>3</sub> Resin Uptake (%) Levels prior to (Pre TSH) and following SC administration of recombinant human TSH 0.9 mg daily for 2 days (postTSH) in 15 subjects with Subclinical Hypothyroidism (SC HypoT) and 10 Euthyroid Volunteers (Normal).**

Subjects	SC Hypo T	Normal
Pre TSH T <sub>4</sub>	8.3 ± 0.7	8.4 ± 0.6
Post TSH T <sub>4</sub>	10.2 ± 1.1*	10.4 ± 1.2*
Pre TSH T <sub>3</sub>	136 ± 11	141 ± 12
Post TSH T <sub>3</sub>	166 ± 17*	170 ± 16*
Pre TSH T <sub>3</sub> RU	40 ± 2	41 ± 3
Post TSH T <sub>3</sub> RU	41 ± 2	41 ± 2

\*—Significantly higher than Pre TSH, p < 0.05.

However, all subjects with Hashimoto's thyroiditis do not manifest clinical hypothyroidism with low T<sub>4</sub> and high TSH levels. Some present with goiters without thyroid hormonal changes while others manifest subclinical hypothyroidism whereas still others manifest no abnormalities in terms of thyroid hormone concentrations or goiters. The variability in presentations may be attributed to either the magnitude of a sole defect of organification, or may be due to the presence of multiple defects of minor degrees [20-22,25]. A similar pathophysiologic milieu may explain the variability of manifestation of hypothyroidism in subjects treated with certain drugs *i.e.* Lithium, Amiodarone etc. [26,27]. It is likely that these drugs inhibit release of thyroid hormones by the thyroid, thus adding injury to the insult in subjects susceptible by the presence of a minor inhibition of on step in thyroid hormone synthesis and release *i.e.* subjects with Hashimoto's thyroiditis with organification defect or subjects with minor iodine deficiency, and therefore manifest hypothyroidism [25]. Alternatively, subjects who do not manifest hypothyroidism may lack any other abnormality in synthesis of thyroid hormone *i.e.* absence of Hashimoto's thyroiditis or iodine deficiency [25-29].

This study demonstrates that in subjects with Hashimoto's thyroiditis manifesting subclinical hypothyroidism, iodine uptake by the thyroid gland is inhibited but release of the thyroid hormones is still intact. Thus, it is plausible that blocking another step *i.e.* release of the thyroid hormones by the thyroid gland would induce multiple step abnormality in these subjects and promote progression to clinical hypothyroidism as noted with administration of drugs [25-27]. Therefore we believe that manifestation of clinical hypothyroidism may be attributed to a major abnormality in a single step in synthesis and release of thyroid hormone by the thyroid gland *i.e.* long term Hashimoto's thyroiditis, major iodine deficiency or other major individual step, *e.g.* congenital hormonogenetic defect. Alternatively, clinical hypothyroidism may manifest with presence of minor defects in multiple steps in thyroid hormone synthesis and release. Finally, a single step minor abnormality may be responsible for goiter without clinical hypothyroidism or with subclinical hypothyroidism.

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