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CLINICAL RESEARCH

Thyroid Insufficiency. Is TSH Measurement the Only Diagnostic Tool?

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Abstract

Purpose: *To evaluate and compare laboratory indices of thyroid function.*

Design: *Practice-based retrospective study of patients' records.*

Materials and Methods: *The records of all hypothyroid patients seen in a private practice in Antwerp, Belgium, between May 1984 and July 1997 were reviewed. Only records with insufficient data were excluded; 832 patients were included in the study. Of these, 287 could also be followed during replacement therapy.*

Results: *A score of 8 main symptoms of hypothyroidism, serum thyroxine radioimmunoassay (T4-RIA), serum T4-RIA/thyroid binding globulin (TBG), 24 h urine free triiodothyronine (T3) were considered before and after treatment. The score of these 8 main symptoms is a reliable expression of their illness in 97% of hypothyroid patients. 24 h urine free T3 correlates better with the clinical status of hypothyroid patients ($R^2 = 0.30$) than serum T4-RIA ($R^2 = 0.12$), and even better than T4-RIA/TBG ($R^2 = 0.19$). Other investigators were unable to find any correlation between serum thyroid stimulating hormone (TSH) or serum free T4 and thyroid symptoms. The dosage of natural desiccated thyroid (NDT) has a correlation with 24 h urine T3 of $R^2 = 0.50$.*

Conclusions: *In this study symptoms of hypothyroidism correlate best with 24 h urine free T3.*

Keywords: hypothyroidism, serum thyroxine radioimmunoassay, serum thyroxine/thyroid binding globulin, natural desiccated thyroid, Armour thyroid, 24 h urine free triiodothyronine.

INTRODUCTION

From clinical experience we know that the highly celebrated serum thyroid stimulating hormone (TSH) test, even the third generation procedure, as well as the serum free thyroxine (T4) test, correlate poorly with the clinical status of the thyroid diseased patient. Therefore, we are interested in showing that another test, the 24 h urine free triiodothyronine (T3) test, correlates well with the symptoms of thyroid disease. We started by composing a list of generally accepted symptoms upon which to rely as an objective base reflecting the clinical status of the patient. We soon noticed that, from this extended list, a small series of the most frequently seen symptoms could be isolated. As a test for the reliability of our views, we compared this restricted list of main symptoms before and after

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TABLE 1. Age and sex distribution in 832 hypothyroid patients

Age (years)	11–20	21–30	31–40	41–50	51–60	61–70	71–80	81–90
676 women (43.06 years)	26	106	169	171	129	63	11	1
156 men (43.35 years)	0	35	39	34	29	15	4	0

treatment, and correlated these data with serum T4, serum T4/thyroid binding globulin (TBG) and 24 h urine free T3.

MATERIALS AND METHODS

Urinary Free Triiodothyronine

Since the publication of "Urinary Thyroxin Excretion as Index of Thyroid Function" [1], by Vivian Chan, and her later publication "Urinary Triiodothyronine Excretion as Index of Thyroid Function" [2], much work has been done to examine the extent, feasibility and reliability of this most interesting procedure. Thorough work, however, was done by Professor I. Orden (Urinary Triiodothyronin Excretion) [3]. She not only disclosed all previous errors in this field, usually owing to inappropriate techniques, but she also demonstrated the usefulness of urinary free T3 excretion measurement for the assessment of thyroid disease, thus allowing her to distinguish clearly between thyroid gland hyper-, euthyroid and hypofunction.

The present study was performed on a large group of individuals, using a procedure comparable with that of Professor Orden, to assess the correlation between symptoms, treatment and urinary excretion of free T3.

Subjects

A large-scale retrospective study was undertaken, using patients data from May 1984 (the moment we started using the 24 h urine free T3 test) to July 1997 (the closure of the study). From the case notes of several hundreds of hypothyroid patients only those compliant patients were selected of whom sufficient objective and reliable data were available. Eight hundred and thirty-two Caucasian adult patients were involved in this study. For practical reasons we considered women over 18 and men over 21 years of age as mature adults.

These 832 hypothyroid patients had not used any thyroid treatment at their first visit. Eighty-one per cent were women and 19% men. Their ages ranged from 18 (21) to 79 (mean 43) years. Table 1 shows their age and sex distribution. From this group 287 patients could be followed up during treatment.

We will now successively study symptoms, 24 h urine free T3, treatment and their mutual correlations.

Symptoms of Hypothyroidism

Patients had clinically been considered as hypothyroid if they presented with an impressive accumulation of accepted symptoms of hypothyroidism. These signs and symptoms are as shown in Table 2.

Patients had been considered hypothyroid only on clinical grounds. At the beginning of this study we determined the frequency with which symptoms appeared. From the many signs and symptoms of hypothyroidism, the following eight as shown in Table 3 appeared most frequently. They are relevant as well as easy to appreciate in a non-hospital environment.

TABLE 2. Symptoms of hypothyroidism

Familial	Thyroid disease; Cholelithiasis; Hypercholesterolemia; Tuberculosis; Mycosis; Allergy; Hay fever; Diabetes mellitus; Arteriosclerosis; Myocardial infarction; Xanthelasmata; Vitiligo; Psoriasis; Deafness; Pernicious anemia.
Paediatrics	Elderly look; Wide epicanthus; Turned-up nose owing to a short skull base; Cretinism; Growth and intellectual retardation; Delayed ossification and dentition; Slowness, physical as well as mental; Drowsiness in daytime, but sleeplessness at night. On the contrary Hyperkinesis; Longstanding enuresis (over 2 years of age).
General	Fatigue; Impaired memory; Dullness and slow cerebration; Depression; Repeated infections of sinus, respiratory and urinary tract; Weight gain but also weight loss; Low basal temperature ($<36.7°C$); Sensation of coldness; Intolerance to cold but also to heat.
Head	Pallor; Hertoghe eyebrow sign; Hair loss; Lock of bleached hair; Sparse hair; Prematurely grey; Hair of poor quality; Dry; Thick or thinly structured; Red hair; Incapable of taking a curl; Headache; Palpebral oedema; Pouched eyes; Swelling and paraesthesia of hands and wrists; carpal tunnel syndrome; Myxoedema; Repetitive sneezing; Allergy; Bronchospasm; Teeth in staggered rows; Aphtosis; Macroglossia with indentations.
Neck	Thyroid hyperplasia; Lingual thyroid; Lack of any thyroid tissue; Hoarseness; Stridor; Tirage; Sensation of constriction of the throat.
Cardiovascular	Bradycardia but palpitations; Constrictive pain over the heart; Microvoltage on ECG; Enlarged heart on X-ray; Bad circulation in the limbs; Cyanosis; Dead finger; Hypertension with elevated diastolic pressure.
Gastrointestinal	Dysphagia; Slow digestion; Lack of appetite; Constipation; Atonic digestive tract; Piercing anal pain; Protuberant abdomen; Umbilical hernia; Weight gain unrelated to food intake but also weight loss.
Urogenital	Premenstrual tension; Spaniomenorrhea; Dysmenorrhea; Polymenorrhea; Amenorrhea; Delayed fertility; Weight gain of more than 12 kg during pregnancy; Heavy babies of more than 4.5 kg at birth.
Orthopaedics	Generalized weakness; Arthritis; Muscle cramps; Burning or tingling pain in the extremities; Carpal tunnel syndrome.
Neurology	Prolonged Achilles' reflex.
Dermatology	Lack of perspiration; Dry skin, coarse, crackled, with cracks in thick heel and finger skin; Scaling; Hyperkeratosis of the extensor side of the limbs; Chipped nails.

To provide a certain gradation within these 8 symptoms we quantified them as follows:

"0" indicates the absence of the symptom, coinciding with the normal status,
"2" means the clear presence of it, while
"1" represents an intermediate state.

TABLE 3. Eight main symptoms

Fatigue	Unusual, persistent, especially on awakening, less toward the evening, with slow recovery.
Depression	Psychological melancholia, with tendency towards suicide.
Coldness	Deep as well as peripheral (forehead, nose, hands, feet and knees), cyanosis, dead finger, chilblains.
Headache	Migraine, tension headache.
Muscle cramps	In calves, toes, fingers, diaphragm, also in thighs and upper arms.
Constipation	Hard bowel movement at most every 2 days.
Arthritis	Rheumatoid pain, joint, tendon and muscle swelling and stiffness.
Neurology	Prolonged Achilles' tendon reflex.

We accept that the higher the score of symptoms, the more pronounced the disease is. So the sum of the scores of all 8 parameters represents the degree of hypothyroidism, the highest score being 16. It is upon these 8 data only that we established our statistics in this study. Of course, hypothyroidism can exist in the absence of any of these symptoms, but 97% of our patients presented with these symptoms. Indeed, 3% of the involved hypothyroid patients didn't present with any of our 8 main symptoms, but had enough of the symptoms on the general list to be ranked as hypothyroid patients.

Laboratory Techniques

The following analyses were performed: 24 h urine free T3, serum T4-RIA and TBG. The analyses were performed in Central Laboratory, Antwerp, by the following technique outlined below.

Determination of Free T3 in 24 h urine

Extraction procedure. 10 ml aliquots of the urine samples were dispensed into plastic tubes. The pH was adjusted to ± 3.5 with a few droplets of concentrated HCl. 2.5 ml urine were transferred in 10 ml glass extraction tubes. 4 ml ethylacetate were added to each tube. The tubes were mixed in a shaker (150–200 rpm) for 10 min. The organic and the aqueous phases were centrifuged for 15 min at ± 1000 g. The organic phase was transferred into a new glass tube with a pipet. Again 4 ml ethylacetate were added to the first glass tube and the tubes were mixed in a shaker (150–200 rpm) for 10 min. This organic layer was transferred to the first organic fraction. The total organic phase was evaporated to dryness with nitrogen at 40°C and the residue was dissolved in 500 ml PBS-buffer. This solution was incubated at 30°C, mixed in a vortex (for complete solution) and used in the RIA-procedure. T3 values were determined with the Amerlex-M T3 RIA kit from Ortho-Clinical Diagnostics Amersham, Catalog No.: 829 5545.

Drugs Used

Natural desiccated thyroid (NDT), commercialized as Armour Thyroid (Thyroid tablets, USP) manufactured for Forest Pharmaceuticals, Inc., St. Louis, MO 63043, USA, by Rhône-Poulenc Rorer Pharmaceuticals, Inc., Fort Washington, PA 19034, USA was bought in local chemists by the individual patient.

Statistical Methods

All statistical calculations were executed on Excel for Windows 95. Pearson's correlation coefficients were derived between symptom scores and T4-RIA, T4-RIA/TB6 ratio, and 24 h urinary T3. Correlation coefficients were also derived between final doses of NDT and 24 h urinary T3 on the treated subgroup ($n = 287$).

RESULTS

Untreated Hypothyroid Patients

The sorted prevalence of symptoms (in 832 hypothyroid patients). Approximately 97% of our hypothyroid patients showed at least one of our eight selected main symptoms, while about 3% didn't show any. This 3% of hypothyroid patients presented with several other symptoms from the general list that proved them to be hypothyroid. The decreasing frequency of symptoms went from cold to fatigue, rheumatic symptoms, Achilles' tendon reflex, headache, depression, muscle cramps to constipation (see Fig. 1).

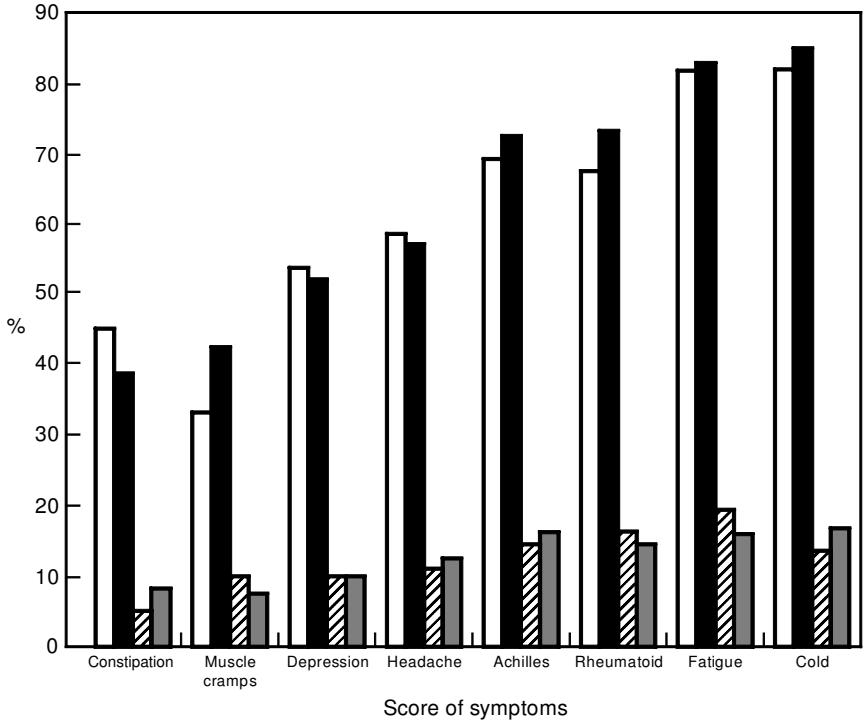

FIG. 1. Score of symptoms (detailed) before and after treatment. mean age: men, 43.35 years; women, 43.06 years; Total: 43.11 years. (□ men before; ■ women before; ▨ men after; ▩ women after).

Symptoms and 24 h urine free T3 (in 832 untreated patients). The mean number of symptoms was 10 (± 3), while the mean 24 h urine free T3 was 756 pmol (± 271).

Treated Patients

The sorted prevalence of symptoms before and after treatment. Figure 1 also shows the number of main symptoms as a percentage before and after treatment with natural desiccated thyroid (100% being the number of patients multiplied by 16, the maximum score). Under treatment, the number of the 8 selected symptoms dropped dramatically from 82.7% for cold and 41.5% for constipation, to a residual of respectively 17% and 7%. Under treatment the mean score of symptoms fell from 10 (± 3) to 2.9 (± 2.3).

Comparing the Available Tests

Correlation between symptoms and serum T4-RIA. There was only a slight correlation (0.35) between the score of symptoms and serum T4-RIA ($R^2 = 0.12$). (See Fig. 2.)

Correlation between symptoms and the serum T4-RIA/TBG ratio. To exclude the influence of proteins we introduced TBG. The score of symptoms correlates better with the serum T4-RIA/TBG ratio 0.44 ($R^2 = 0.19$). (See Fig. 3.)

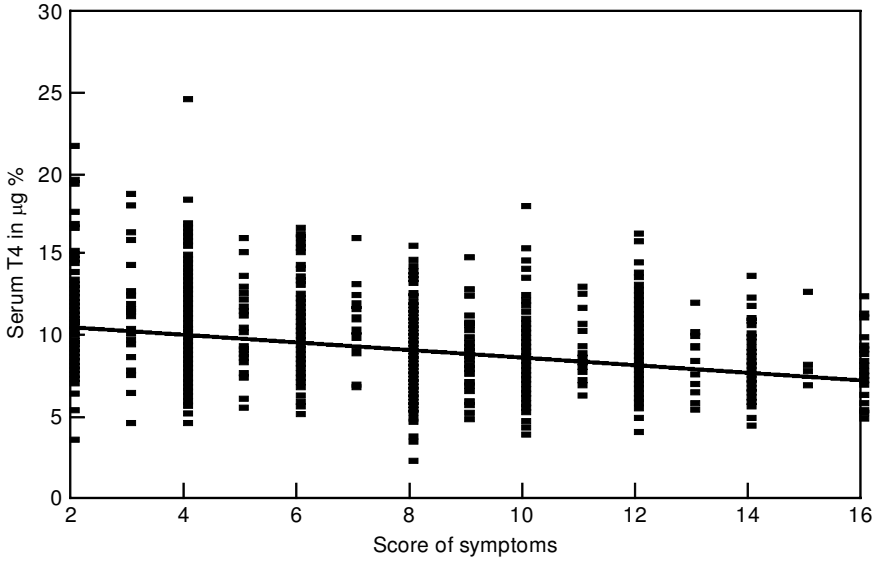

FIG. 2. Correlation serum T4 versus score of symptoms. $y = -0.2322x + 11.073$. $R^2 = 0.1219$.

Correlation between symptoms and 24 h urine free T3. During treatment, the score of symptoms and 24 h urine free T3 correlates clearly (-0.56), ($R^2 = 0.32$). From this figure it also appears that the score of zero symptoms corresponds with 2000 pmol/24 h urine T3. (See Fig. 4.)

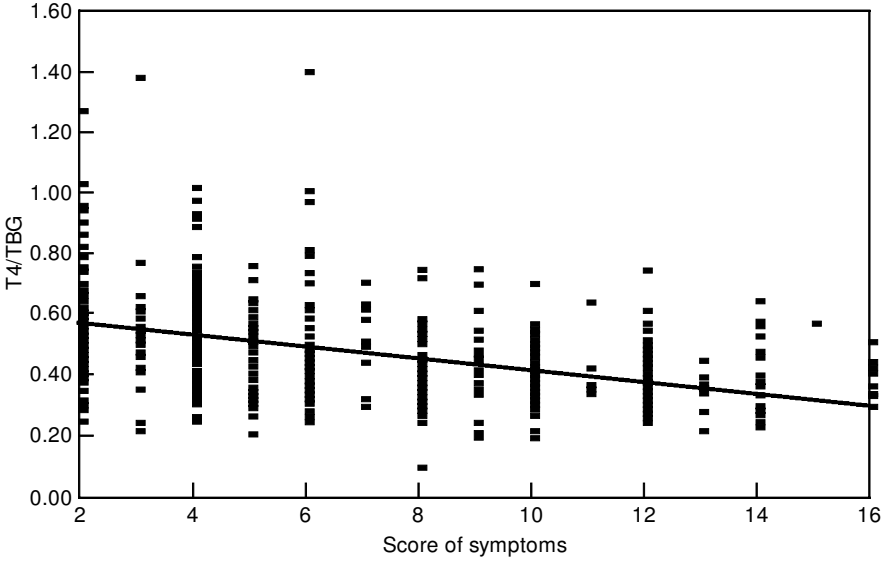

FIG. 3. Correlation score of symptoms versus T4/TBG. $y = -0.0178x + 0.589$. $R^2 = 0.1929$.

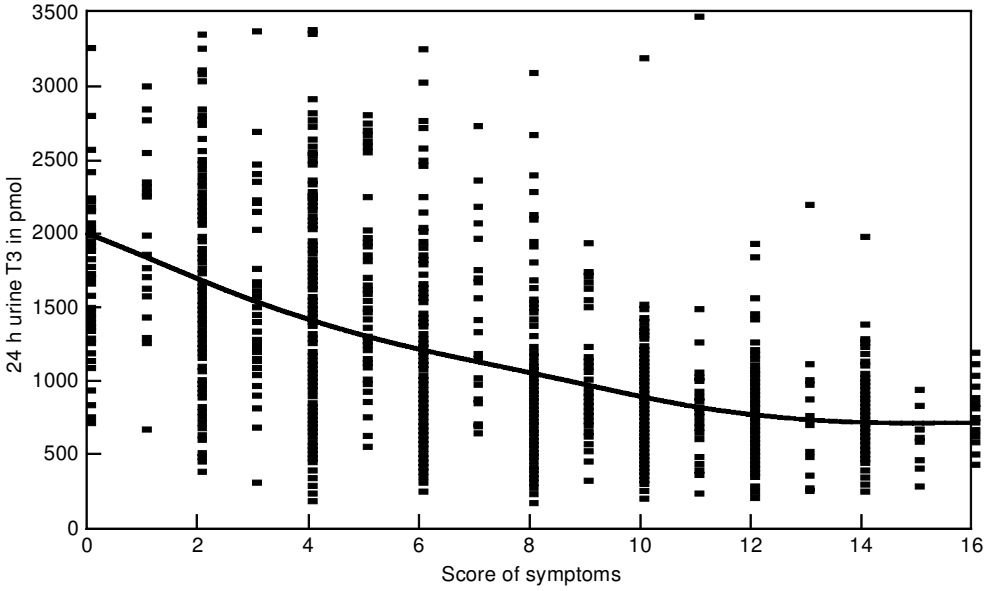

FIG. 4. Correlation 24 h urine T3 versus score of symptoms. $y = 5.8674x^2 - 175.34x + 200.6$. $R^2 = 0.3204$. 1 SD = 670 pmol.

The level of 24 h urine free T3 during treatment. Under treatment the level of the 24 h urine free T3 increased from a mean of 756 (± 271) to a mean of 1687 pmol (± 663).

Correlation between the natural desiccated thyroid dose and 24 h urine free T3. There was a direct correlation (+ 0.71) between the administered dose of NDT and the 24 h urine free T3 $R^2 = 0.50$. (See Fig. 5.)

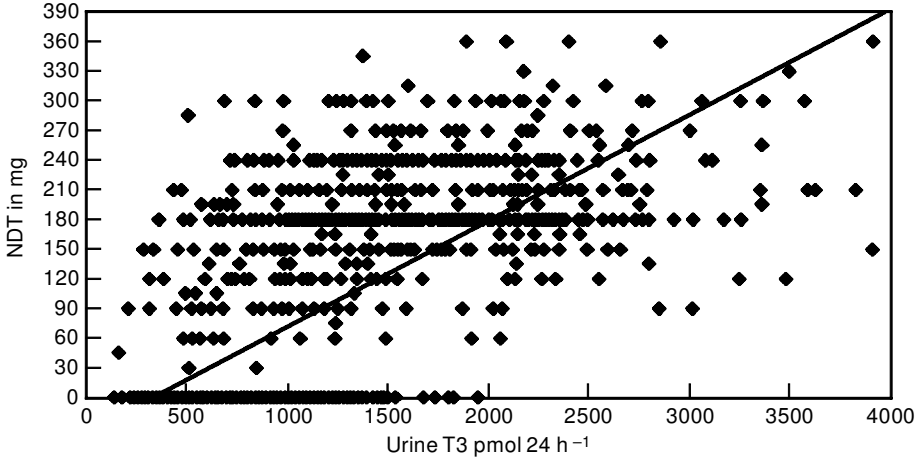

FIG. 5. Correlation urine T3 versus NDT. $y = 0.1082x - 39.683$. $R^2 = 0.4973$.

Which level of 24 h urine free T3 has to be reached to eliminate a maximum number of symptoms? As follows from an extrapolation in Fig. 4, 2000 (± 670) pmol free T3/24 h urine appears to be the target level to be reached. This is in complete concordance with the figures advanced by I. Orden, who found 2074 (± 673) pmol/24 h. It corresponds also with our clinical experience.

DISCUSSION

In 1963, Means *et al.* published an extensive list of the symptoms of hypothyroidism itemized in 177 cases [4]. Their order of frequency is roughly comparable with ours, but their percentages are slightly different. Headache, muscle cramps and Achilles' tendon reflex were not taken into account in their study.

The 8 main symptoms that we selected in our study have both a subjective and an objective aspect: the patient complains of being cold and the physician feels the patient's cold hands when shaking hands or when taking the patient's blood pressure; the patient's fatigue can be gauged by the hours he lies in bed during the day, and the number of sleeping tablets he takes at night; painful arthritis can be matched by palpation and auscultation of the articulations and by the number of NSAID tablets needed; headache is correlated with the number of tablets that the patient has to take; depression can be measured by the number of suicide attempts, or by the spells of melancholy during consultation; the degree of constipation is expressed by the number of bowel movements a week or a month, and the amount of laxative products used; muscle cramps can be quantified by the frequency, duration and potency of their attacks. The ninth most frequently noticed symptom was "dryness of the skin".

Obese patients complain less frequently about cold, as they are protected by a layer of fat. On the other hand, one has to be aware of the difficulty of estimating the underlying cold in the presence of hot flushes in insufficiently oestrogen substituted menopausal women.

It is difficult for patients to compare their symptoms from one period of time to another. They usually only recognize an important improvement or deterioration over a very short period.

The Achilles' tendon reflex has the outstanding advantage of being an expression of end-organ status, the target cells, the tissue response to changes in thyroid function, unobtainable by any other means than the ancient basal metabolism test and the basal temperature. The Achilles' tendon reflex is *absent* in diabetes mellitus, chronic alcoholism with peripheral neuropathy, and after interventions in the region of the sciatic nerve. It is *accelerated* under caffeine use. It is *prolonged* by cooling of the calves [5]. When the Achilles' tendon reflex is unreliable, the 24 h urine free T3 remains helpful.

The use of coffee, tea, coke, cacao, tonic or alcohol accelerates the Achilles' reflex, but the tendency to use these beverages is in itself a token of hypothyroidism which the patient tries to remedy. Beta-blockers, oestrogens, cotrimoxazole, psychotropes, lithium, amiodarone, and phenylbutazone decrease the T3 production by conversion inhibition from T4 into T3 in liver and kidneys.

Thyroid antibodies interfere with the production of thyroid hormones. It was also found that men seem to have a higher 24 h urine T3 production than women.

Under treatment it is useless to determine T3 in 24 h urine before the desired dose is taken for at least two months. Conversely, it takes three weeks before a new clinical steady state is obtained after stopping treatment.

The 24 h urine free T3 test appears to be reliable, and is not influenced by binding globulins. A possible problem is the collection of the total voided urine. This can be controlled by the determination of the 24 h excreted creatinine.

A patient, showing a score of 5/16 or more of the main symptoms, with a 24 h urine free T3 of 1400 pmol and less, is likely to have hypothyroidism. If a patient under maximum

treatment still presents with a score of symptoms of 5/16 or more, drug compliance being certified, unsatisfactory intestinal absorption or inactivity of the drug has to be suspected.

The determination of free T3 in the 24 h urine has a far better correlation with the clinical thyroid status of a patient than any other classical test. The determination of free T3 in 24 h urine collection provides a logical and practical answer to the many clinicians who are anxiously looking for laboratory confirmation of their clinical diagnosis in thyroid disease. In a study recently undertaken in 80 clinically hypothyroid patients [6], a group of investigators saw in only 6% of their clinically diagnosed hypothyroid patients a corroboration of their clinical diagnosis by a serum free T4 below the classical reference values, and in only 5% of their hypothyroid patients a confirmation of their clinical diagnosis by TSH values above the classical reference values. Other investigators didn't find any correlation between their symptoms score and TSH in 50 overt hypothyroid patients [7]. The correlation presented in this study between our symptoms score and the 24 h urinary free T3 is about 0.55 ($R^2 = 0.32$).

Under treatment, TSH measurements are of little value [8]. Under long-term treatment, even a third generation TSH-test drops to undetectable values. In comparison with the 24 h urine free T3 we consider TSH a poor indicator of the thyroid status. In secondary and tertiary hypothyroidism the determination of TSH is, of course, useless. But conversely, even under treatment with natural desiccated thyroid (T3 + T4), the level of 24 h urine free T3 continues to correlate closely with the patient's clinical status. The explanation is that TSH is grossly in feedback with serum T4 only, not so much with serum T3, while the patient's wellbeing depends on the free T3 that is disposable inside the cells. As hypothyroid patients are usually unable to convert inactive T4 into active T3, owing to a lack of 5′-deiodinase in the liver and kidneys, the administration of T4 can eventually correct the serum TSH level, but rarely provides the patient with the T3 needed to be relieved of his symptoms.

The determination of 24 h urine free T3 will prevent patients, suspected of hyperthyroidism, based on a low TSH rather than on clinical findings, from being treated unnecessarily with thyroidectomy, radioactive iodine or thyreostatics.

CONCLUSION

The 24 h urine free T3 test seems to be a reliable test, more accurate than the serum T4, serum free T4 and serum TSH test in the diagnosis of thyroid diseases and their follow-up under treatment. It correlates well with the clinical status of the patient, and is not influenced by binding globulins. A series of 8 main symptoms can be used as an efficient tool in the discovery of thyroid disease.

REFERENCES

[1] Chan V, Landon J. Urinary thyroxin excretion as index of thyroid function. Lancet 1972; 4–6.
[2] Chan V, Landon J, Besser GM, Ekins RP. Urinary triiodothyronin excretion as index of thyroid function. Lancet 1972; 253–6.
[3] Orden I, Pié J, Juste MG, Giner A, Gomez ME, Escanero JF. Urinary triiodothyronin excretion. Rev Esp Fis 1988; 44: 179–84.
[4] Means JH, De Groot LJ, Stanbury JB. The Thyroid and its Diseases. McGraw-Hill, 1963, 321–2.
[5] Nuttall FQ. The Achilles Reflex in Thyroid disorders. A Critical Evaluation. Ann Int Med 1964; 61: 269–88.
[6] Skinner GRB. Thyroxin should be tried in clinically hypothyroid but biochemically euthyroid patients. BMJ 1997; 314: 1764.
[7] Zulewski H, Müller B, Exer P, Miserez AR, Staub JJ. Estimation of tissue hypothyroidism by a new clinical score: evaluation of patients with various grades of hypothyroidism and controls. J Clin Endocrinol Metab 1997; 82/3: 771–6.
[8] Franklyn JA, Black EG, Bitteridge J, Sheppard MC. Comparision of second and third generation method for measurement of serum thyrotropin in patients with overt hyperthyroidism, patients receiving thyroxine therapy, and those with nonthyroidal illness. J Clin Endocrinol Metab 1994; 78: 1368–71.