THYROID FUNCTION IN LONG TERM HAEMOFILTRATION

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Summary

Ten patients on haemofiltration treatment for between 4 and 20 months have been screened for thyroid function. Comparing serum T3 and T4 levels at the start of haemofiltration and 5 to 20 months later, a continuous decrease was detected (T3-Ria: 92 ± 23 ng% to 68 ± 23 ng%; T4-Ria: 4.94 ± 1.79 µg% to 3.81 ± 1.21 µg%). Serum TSH-Ria values also declined in mean from 3.48 ± 0.47 µU/ml to 3.07 ± 1.26 µU/ml, yet two patients showed an increase as expected with a functioning hypothalamic pituitary-thyroid axis. During a single treatment TBG, T4 and T3 values increased in excess of the amount expected for the degree of blood volume contraction, whereas the T4/TBG ratio remained normal indicating peripheral euthyroidism. Serum TSH was found to decrease significantly after 5 hours of haemofiltration possibly by losses via the haemofiltrate. Stimulation of the pituitary gland by i.v. injection of 200 µg TRH gave a normal TSH response. Chronic haemofiltration leads to a proportional decline of thyroid hormones and their protein bound fractions: euthyroidism was proved by the normal T4/TBG ratio and the absence of clinical signs of hypothyroidism.

Patients and Methods

Ten of our 14 patients with terminal renal failure on a chronic haemofiltration programme for between 4 and 20 months were screened for thyroid gland function. All patients had had a prior period of 3 months to 7 years on haemodialysis. They were subjected to the haemofiltration procedure because of uncontrollable hypertension, severe polyneuropathy or marked signs of discomfort during regular haemodialysis treatment. The haemofiltration procedure was carried out three times weekly, and a mean 23.1 ± 1.3 L of plasma water was exchanged. Four different types of haemofilters were used. We compared T3-Ria, T4-Ria, TSH-Ria at the beginning of haemofiltration treatment and 5 to 20 months later. TBG-Ria, TSH-Ria, T3-Ria and T4-Ria were measured at the
Figure 1. Change of serum T4-Ria, T3-Ria and TSH-Ria values at onset of haemofiltration treatment and 4 to 20 months later

start and end of treatment and after injection of 200 μg TRH (Relefact®).

Results and Discussion

Peripheral thyroid gland hormone concentrations are commonly found to be in the hypothyroid area in chronic uraemic patients, whereas TSH levels are in the normal range [1,2]. In our patients we found the serum T3 levels to be subnormal, just one patient had levels in the normal range at the onset of haemofiltration. The mean T3 values were 92 ± 23 ng% with a normal range from 100–220 ng%. T4-serum levels were borderline low with a mean of 4.94 ± 1.79 μg%. T3 values are more commonly found to be in the hypothyroid range than T4, which might be caused by impaired peripheral deiodination as proposed by Lim [3]. TSH levels were all in the normal range (0–5 μU/ml)
Figure 2. Decrease of T3-Ria versus T4-Ria at onset of haemofiltration and 3 to 20 months later. Normal range is dashed.

Figure 3. Acute changes of thyroxine-binding globulin (TBG), T4, T3, TSH and T4/TBG ratio during a single haemofiltration treatment. Normal ranges are indicated by dashed lines. Post-haemofiltration values have been corrected by the percentage of volume contraction. Note the marked decline of TSH, whilst T4/TBG ratio is in the normal range throughout the treatment.
Figure 4. Per cent change of TSH-Ria, T3-Ria and T4-Ria 20 minutes post injection of 200 µg TRH (Relefact ®) i.v. Circles indicate normal TSH response, whereas squares indicate a TSH response less than 50% of starting value.

Figure 5. Absolute TSH-Ria, T3-Ria and T4-Ria levels at onset of a single haemofiltration treatment, 20 minutes post TRH stimulation (200 µg TRH i.v.) and at the end of treatment (5 h). Normal ranges are indicated by dashed lines.
with a mean of 3.48 ± 0.47 μU/ml.

During 4 to 20 months of haemofiltration treatment a continuous decrease of thyroid hormone levels was observed. T3 levels fell significantly to a mean of 68 ± 23 ng%, T4 values to 3.81 ± 1.21 μg%. The mean serum TSH values declined too (3.07 ± 1.26 μU/ml), yet two patients showed the augmentation that would be expected with a functioning hypothalamic pituitary-thyroid axis.

As clinically no evident signs of developing hypothyroidism could be detected, we studied the variation of thyroid hormones and their specific binding globulin TBG during a single haemofiltration procedure. Corrections were made for the reduction of blood volume at the end of treatment, which declined by a mean of 22% measured by Indium-tagged erythrocytes [4]. We found an increase of TBG levels (statistically not significant) in excess of the expected rise caused by reduction of blood volume. TBG values were subnormal in all but one patient, indicating that liver synthesis may have been suppressed or that continuous losses via the haemofiltrate exceeded the rate of neosynthesis, though TBG is an inter-α-glycoprotein with a molecular weight of about 60,000 daltons. T4 levels increased too, but post haemofiltration values did not reach the normal range as found by other observers during haemodialysis [5]. The mean pre- and post-values of the T4/TBG ratio, which expresses the peripheral amount of active, unbound T4, do not change and are in the normal range, indicating that T4 and TBG levels are proportionally low. In one case with marked elevation of the T4/TBG ratio, caused by a disproportionately low TBG value, a transformation of binding affinity to the thyroxine-binding prealbumin fraction must be involved. T3 levels were found to increase similarly to the T4 values after 5 hours of haemofiltration treatment, but serum TSH levels declined significantly from 2.68 ± 0.73 μU/ml to 2.04 ± 0.31 μU/ml. Some authors think this phenomenon to be heparin-induced or on the other hand caused by the elevation of T4 which would lead to TSH suppression [6]. In contrast other observers have found a slight decrease at the beginning of haemodialysis induced by heparin and no change of TSH levels at the end of treatment despite the elevation of T4 [5]. In haemofiltration we think TSH is filtered, as the molecular weight of 28,000 daltons is possibly low enough to pass the filter pores in sufficient amounts to explain the decline in serum values post-treatment, though others could not detect TSH in filtrate samples [7].

Ten patients on haemodialysis, of similar age and sex distribution were also screened for thyroid gland function and compared with the haemofiltration group. No differences could be detected for T3-Ria, T4-Ria and TBG levels, and the T4/TBG ratio in the patients treated by haemodialysis also revealed peripheral euthyroidism. TSH values however were found to be markedly higher (4.31 ± 1.87 μU/ml) in the haemodialysis group when compared with the haemofiltration group (2.68 ± 0.73 μU/ml).

As the decline of T4 and T3 values in long term haemofiltration is not accompanied by TSH elevation, we tested the functional state of the hypothalamic-pituitary-thyroid-axis by stimulation with 200 μg TRH (Relefact®) i.v., and corrected the thyroid hormone levels by the percentage of volume contraction. Seven patients showed an appropriate elevation of TSH levels 20
minutes post injection ranging from 68 to 225%; in 3 cases TSH increase was less than 50% of baseline value. TSH elevation exceeding 50% of baseline value was considered to be normal. Parallel T3 levels increased from 64 ± 24 ng% to 90 ± 37 ng%, whereas T4 values declined slightly from 4.08 ± 1.20 μg% to 3.82 ± 1.22 μg%. In healthy subjects TRH stimulation via TSH-secretion primarily provokes a thyroidal release of T3 which peaks at 2 hours post injection, T4 values were found not to be influenced [8]. The observed decline of serum T4 levels 20 minutes post TRH injection may be accounted for by increased peripheral deiodination, as heparin induced changes of serum T4 values, determined by a radioimmunoassay could be excluded [9].

The three patients with an increase of TSH levels to less than 50% of baseline value 20 minutes after TRH stimulation were also shown to be euthyroid by reference to their normal T4/TBG ratio. As the kinetics of TSH secretion vary widely [10], the TSH peak may have been delayed in these patients and so remained undetected in our trial.

Despite the normal response of the pituitary gland to TRH stimulation, mean TSH values decrease in long term haemofiltration though all are within the normal range. The declining T3 and T4 values may be accompanied by decreasing TBG serum levels, as the normal T4/TBG ratio indicates a sufficient concentration of active thyroid hormones to guarantee euthyroidism.

At the present point of knowledge haemofiltration does not influence the peripheral euthyroid hormone status, yet further decrease in TSH levels could possibly lead to a disproportionate relationship between thyroid hormones and protein binding fractions.

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References
