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Thyroid Hormone Abnormalities in Haemodialyzed Patients: Low Triiodothyronine as well as High Reverse Triiodothyronine Are Associated with Increased Mortality

JIŘÍ HORÁČEK[1], SYLVIE DUSILOVÁ SULKOVÁ[2,3], MICHAELA KUBIŠOVÁ[3], ROMAN ŠAFRÁNEK[3], EVA MALÍŘOVÁ[4], MARTA KALOUSOVÁ[5], IOANNIS SVILIAS[1], JAROSLAV MALÝ[1], LUBOŠ SOBOTKA[3], PAVEL ŽÁK[1]

[1]Department of Internal Medicine II, Charles University in Prague, Faculty of Medicine and University Hospital Hradec Kralove, [2]Department of Nephrology, Institute of Clinical and Experimental Medicine Prague, [3]Department of Gerontology and Metabolism, Charles University in Prague, Faculty of Medicine and University Hospital Hradec Kralove, [4]Department of Nuclear Medicine, Charles University in Prague, Faculty of Medicine and University Hospital Hradec Kralove, [5]Institute of Clinical Chemistry and Laboratory Diagnostics, First Faculty of Medicine and General University Hospital Prague; Czech Republic.

JH and SDS have equally contributed to the paper.

Corresponding author:

Prof. Jiri Horacek, MD, PhD, Charles University in Prague, Faculty of Medicine and University Hospital Hradec Kralove, Department of Internal Medicine II, Sokolska 581, 50005 Hradec Kralove, Czech Republic. Phone: +420 495834673, Fax: +420 495832011, E-mail: horacek9@gmail.com

Short title:

Low T3 and high rT3 in ESRD patients

Summary

Numerous abnormalities of thyroid hormones in end-stage renal disease (ESRD) have been described. Our aim was to analyze the impact of these abnormalities on survival. In 167 haemodialyzed ESRD patients, TSH and thyroid hormone levels (T4, fT4, T3, fT3, rT3) were determined. The patients were then prospectively followed up for up to 5 years and the possible impact of any observed abnormalities on their mortality was studied. Only 16.8 % patients had all six tests within the reference range. The pattern of nonthyroidal illness syndrome was found in 56.3 %. Low T3 was particularly common (44.3 %), and clearly associated with increased 6- and 12-month mortality and decreased overall survival (log rank test, $P = 0.007$). Independent of T3 levels (Spearman correlation, NS), increased rT3 was more frequently observed (9.9 %) than expected from the literature, and was also related to increased mortality and decreased survival (log rank test, $P = 0.021$). Increased rT3 may be more common in ESRD patients than previously described, and together with decreased T3 it may serve as an indicator of poor prognosis in subsequent months.

Key words

Thyroid – Triiodothyronine – Reverse triiodothyronine – Haemodialysis – Survival

Introduction

The high mortality of end-stage renal disease (ESRD) patients on maintenance haemodialysis is believed to be a function of complex metabolic and regulatory disorders (Go *et al.* 2004. In particular, numerous abnormalities in endocrine regulation have been described. Thyroid homeostatic regulation may be affected at several levels (Kaptein 1996, Lim 2001, Iglesias and Diez 2009). Hypothyroidism seems to be more common in chronic

kidney disease patients (Lo *et al.* 2005), and its association with increased mortality has been reported (Enia *et al.* 2007). Moreover, patients with ESRD and hypothyroidism share some common symptomatology, e.g. asthenia, pallor and hypothermia; therefore correct interpretation of their thyroid status is essential, though this is complicated by both pathophysiological processes and methodological difficulties (Witzke *et al.* 2007).

In particular, ESRD may be viewed as a severe nonthyroidal illness, leading to nonthyroidal illness syndrome (NTIS), with a decrease in triiodothyronine (T3), and in more severe cases also in thyroxine (T4) levels, not accompanied by the usual feed-back increase in thyroid-stimulating hormone (TSH) (Docter *et al.* 1993, Adler and Wartofsky *et al.* 2007). However, it has been assumed that an increase in reverse triiodothyronine (rT3), a common abnormality in NTIS, does not occur in ESRD (Kaptein 1996, Iglesias and Diez 2009).

Haemodialysis strategy as well as dialysis demography has changed completely since 1980s (Lameire *et al.* 2009, Cavalli *et al.* 2010), when most of the descriptive studies on thyroid hormone patterns in ESRD were published (Lim *et al.* 1977, Faber *et al.* 1983, Kaptein *et al.* 1983a,b) and therefore some conclusions derived from those studies may not now be valid.

In several studies of ESRD, low T3 levels have been reported as an unfavourable prognostic factor for survival (Zoccali *et al.* 2006, Enia *et al.* 2007, Carrero *et al.* 2007); moreover, pretransplant low T3 levels may be associated with higher risk of kidney graft failure (Rotondi *et al.* 2008). A similar prognostic link with rT3 has not yet been published.

In this study we performed a cross-sectional survey of thyroid hormone levels in haemodialyzed ESRD patients, and we found numerous abnormalities, including high rT3. In addition, these patients were prospectively followed up for up to 5 years, and the possible impact of any observed abnormalities on their mortality was studied.

Methods

Patients with ESRD included in the chronic haemodialysis programme at our university hospital were sampled for thyroid function tests in 2006, 2008 and 2010. None of them had a history of thyroid disorders, and they were not treated with any drugs known to affect thyroid function. Patients were dialyzed three times weekly, using a two needle system, low-flux polysulphone dialyser 1.6-1.8 m^2, bicarbonate dialysis solution with dialysate flow 500 ml/min and blood flow rate 300 ml/min. Equilibrated Kt/V was checked monthly and targeted above 1.2, in accordance with K/DOQI guidelines (National Kidney Foundation 2006). The dialysis population studied was unselected but patients with severe acute complications requiring hospitalization at the time of sampling were not included in the analysis. As the possible impact of thyroid hormone abnormalities on survival may be time-dependent (i.e. more significant in the shorter interval), only the last sample before the last follow up or death was used for calculations in those who were tested repeatedly. Altogether in 167 patients, (97 male, 70 female, median age 64.9 years) thyroid hormone levels were analyzed, and the patients were followed up for at least 540 days unless they died earlier. The study was in accordance with the Declaration of Helsinki (2000) of the World Medical Association, and was approved by the institutional ethics committee.

As heparin may interfere with competitive assays, blood was drawn just before the start of haemodialysis procedure from the inserted dialysis needle or from the arterial port of dialysis circuit, before contact of blood with dialyser and before heparin administration. This ensured that there was an interval of at least 48 hours since the last heparin application.

Thyroid function tests were performed in our radioisotope laboratory as described previously (Horacek *et al.* 2010); in addition, total T4, total T3 and reverse T3 were also assayed by radioimmunoassays (RIA). The battery of tests thus included: (a) TSH determined

by immunoradiometric assay (IRMA, Immunotech, Beckman Coulter, Prague, Czech Republic), reference range (RR) 0.15-5.0 mIU/l, inter-assay variation (CV) 5.5%; (b) FT4 measured by RIA (Immunotech, Beckman Coulter), RR 11.0-23.0 pmol/l, CV 8.4%; (c) FT3, RIA (Immunotech, Beckman Coulter), RR 2.5-5.7 pmol/l, CV 6.4%); (d) T4, RIA (Immunotech, Beckman Coulter), RR 70.0-140.0 nmol/l, CV 8.6 %); (e) T3, RIA (Immunotech, Beckman Coulter), RR 1.0-3.0 nmol/l, CV 7.7 %); and (f) rT3, RIA (Adaltis, Casalecchio di Reno, Italy), RR 0.14-0.54 nmol/l CV 8.7 %).

The descriptive results were tentatively summarized in terms of proportions of various abnormalities, namely hypothyroidism, hyperthyroidism and NTIS, although the links between thyroid hormone levels and the typical patterns of these syndromes are less clear in chronic renal failure (Kaptein 1996), and subject to some debate. Spearman correlation was used for quantifying possible associations between the thyroid hormones. Patients surviving more than 6 and 12 months after the sampling were compared with those having died within the respective period using Mann-Whitney test, and for significantly different parameters (i.e. T3 and rT3), survival analysis using Kaplan-Meier curves and log rank test was performed. For statistical analysis, NCSS software package was used.

Results

In our sample of 167 unselected ESRD patients, thyroid abnormalities were very common (Table 1), and only 16.8 % patients had all the six tests within the reference ranges employed. The most common abnormalities were low T4 and low T3, occurring in 45.5 % and 44.3 % of cases, respectively.

Though rT3 was mostly normal, there were still 9.9 % patients with levels above the reference range, considerably more than expected from the literature (Kaptein 1996, Witzke *et al.* 2007 while decreased levels were exceptional (2.8 %).

As the competitive assays for free hormones (fT3 and fT4) generally give less reliable results in CRF, due to methodological problems (Kaptein 1996), we put more emphasis on the more robust total hormone assays but even then there were only 28.7 % patients with all the four tests (i.e. TSH, T4, T3 and rT3) within normal ranges. Patients with higher TSH and normal or lower T4 and T3 are normally classified as having subclinical or overt hypothyroidism, respectively; in our sample there were 19/167 (i.e. 11.4 %) patients in this category. Similarly, patients with suppressed TSH and normal or higher T4 and T3 are usually classified as having subclinical or overt hyperthyroidism; in our sample they comprised 6/167, i.e. 3.6 %. The remaining 94/167 (56.3 %) patients were classified as NTIS; they had normal TSH levels together with (a) lower T3 and/or (b) lower T4 and/or (c) higher rT3.

The Spearman correlation analysis (Table 2) demonstrated some expected associations, e.g. significant inverse correlations between TSH and thyroid hormones, though they were rather weak (ρ coefficients ranging from -0,190 to -0,294) and did not include T3 (ρ = -0,072), probably reflecting the frequent incidence of NTIS, or positive correlations between total and free hormones, again less prominent in T3/fT3 (ρ = 0,269) than in T4/fT4 (ρ = 0,575). Unexpectedly for such prevalent NTIS, no significant inverse correlation was found between T3 and rT3 (ρ = -0,148, NS). Conversely, an unexpectedly strong positive correlation between rT3 and both T4 (ρ = 0.448; $P<0.001$) and fT4 (ρ = 0.544; $P<0.001$) was revealed.

Within one year of sampling, 48 patients (28.7%) died. Their T3 and rT3 levels were clearly different from those having survived longer than one year while there was no significant difference in any other hormone levels (Table 3). Similar findings were seen for

the shorter 6 month period (Table 4), together suggesting an association of mortality at 6 to 12 months with lower T3 and higher rT3.

These associations were confirmed by survival analysis. The patients with T3 below RR (<1 nmol/l) had significantly worse survival than those within it (log rank test, $P = 0.007$; Kaplan-Meier, Figure 1). When median was used as the discriminator then patients with T3 values below median (<1.06 nmol/l) had worse survival than those above median (log rank test, $P = 0.042$). Similarly for rT3, the patients with values above RR (>0.54 nmol/l) had significantly worse survival than the rest of the sample (both within and below RR; log rank test, $P = 0.021$; Kaplan-Meier, Figure 2). Also, those above median (>0.29 nmol/l) had worse survival than those below it (log rank test, $P = 0.020$).

Discussion

Normal thyroid status was found only in a minority of our ESRD patients, and more than a half of our sample fulfilled the criteria for NTIS. In addition, we have used TSH values out of the reference range as markers of hypo/hyperthyroidism in the traditional way (Jameson and Weetman 2008), and in accord with the classification used in population studies (Lo *et al.* 2005, Hollowell *et al.* 2002) though in chronic renal failure a minor increase or decrease in TSH may also be attributed to NTIS (Kaptein 1996). If some of those classified as hypo/hyperthyroid actually had NTIS instead then the proportion of patients with the syndrome would have even been higher.

Interestingly, no significant difference in survival was found between the whole group of NTIS patients and those with normal values of TSH, T4, T3 and rT3 (data not shown). When analyzed separately, low T3 as well as high rT3 were both associated with decreased survival, especially within the first year of follow-up. This suggests that low T4/normal TSH

pattern, though often considered as severe NTIS (Adler and Wartofsky 2007), may be of less prognostic importance in haemodialyzed patients.

Several authors have recently pointed out the negative prognostic value of low T3 in ESRD (Zoccali *et al.* 2006, Enia *et al.* 2007, Carrero *et al.* 2007). In our haemodialyzed ESRD patients, we confirmed these conclusions. Clearly, when low T3 is found in an ESRD patient it may serve as a warning sign of poor prognosis within the coming months. It suggests that identifying and treating any modifiable abnormalities that may cause both low T3 and increased mortality (e.g. malnutrition, inflammation, etc.) can be of benefit to the patient. Conversely, misguided attempts to replete thyroid hormone stores by exogenous supplementation may worsen the prognosis (Lim 2001).

Data on rT3 levels in haemodialyzed patients are so far scarce. The representative reviews (Kaptein 1996, Iglesias and Diez 2009) state that patients with ESRD have normal total serum rT3 rather than the elevated levels observed in NTIS, referring to earlier studies from 1983 (Faber *et al.* 1983, Kaptein *et al.* 1983a,b). Though these studies give careful and detailed description of thyroid hormone kinetics in a small sample of ESRD patients (ranging from 6 to 13, of which only 5 were chronically haemodialyzed) they do not provide relevant data on the estimated proportions of rT3 abnormalities in ESRD population. Such an estimate may be derived from a more recent paper (Witzke *et al.* 2007) comparing thyroid hormones, including rT3, in young patients with preterminal (n = 48) and terminal (n = 288) renal failure. Their haemodialyzed ESRD patients had significantly lower rT3 (0.25 ± 0.02 nmol/l; mean ± SEM) than those with preterminal renal failure (0.39 ± 0.03 nmol/l) or healthy controls (0.37 ± 0.02 nmol/l). As they also used RIA with the same RR for the rT3 assay our results should be comparable with theirs. However, when expressed in the same way, the rT3 levels in our ESRD patients were 0.36 ± 0.03 nmol/l, i.e. clearly higher than in their ESRD group, and similar to their other groups.

Most of our ESRD patients (ca. 87 %) had rT3 within the RR, in accord with the prevailing opinion (Kaptein 1996, Iglesias and Diez 2009). However, and rather unexpectedly, there were ca. 10 % patients with an increased rT3 in our sample. Moreover, the higher rT3 was clearly associated with poor prognosis. These novel findings suggest that also in ESRD (as a special case of NTIS) rT3 may be elevated, and serve as a negative prognostic marker, similar to other severe clinical conditions (Peeters *et al.* 2005).

The observed negative prognostic value of high rT3 appeared independent of low T3 since there was no significant (inverse) correlation between the variables. Conversely, a moderately tight and highly significant positive correlation was found between rT3 and both T4 and fT4. Though this would suggest parallel variations in 5'-deiodinase activity no ready explanation is currently available. If type 2 deiodinase activity fluctuations were responsible, one would expect an inverse correlation between T3 and rT3; perhaps both type 1 and type 2 deiodinases are involved (Maia *et al.* 2011, Williams and Bassett 2011). Interestingly, a similar correlation between rT3 and fT4 was found in independently living elderly men, and higher rT3 and fT4 were associated with lower levels of physical function (van den Beld *et al.* 2005), also suggestive of worse prognosis.

Conclusion

Low T3 concentrations have recently been associated with poor prognosis in ESRD. Our results are in accordance with these conclusions. Moreover, in this study we focused on a detailed description of thyroid status in a large cohort of non-selected ESRD patients and we reveal two novel findings concerning rT3: levels are higher than previously described and higher rT3 is associated with worse prognosis. These results are worthy of further investigation.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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Table 1. Thyroid function tests in 167 haemodialyzed ESRD patients (age: median 64.9 years, interquartile range (IQR) 56.2-75.7; Kt/V eq: median 1.31, IQR 1.11-1.47).

Variable (unit)	Reference range (RR)	Median (IQR)	Percentage (%)		
			normal	< RR	>RR
TSH (mIU/l)	0.15-5.0	1.82 (1.16-3.32)	85.0	3.6	11.4
T4 (nmol/l)	70-140	71.4 (60.9-84.4)	53.9	45.5	0.6
T3 (nmol/l)	1.0-3.0	1.06 (0.83-1.26)	55.7	44.3	0
rT3 (nmol/l)	0.14-0.54	0.29 (0.22-0.39)	87.3	2.8	9.9
fT4 (pmol/l)	11.0-25.0	11.6 (10.1-13.5)	61.7	38.3	0
fT3 (pmol/l)	2.5-5.8	3.24 (2.77-3.78)	83.8	15.0	1.2

Table 2. Spearman correlation matrix of thyroid function tests in 167 haemodialyzed ESRD patients

		fT4	T4	fT3	T3	rT3
TSH	ρ	-0,294	-0,204	-0,190	-0,072	-0,242
	P	<0,001	0,008	0,014	0,358	0,004
fT4	ρ		0,575	0,123	0,009	0,544
	P		<0,001	0,114	0,904	<0,001
T4	ρ			-0,092	0,344	0,448
	P			0,237	<0,001	<0,001
fT3	ρ				0,269	-0,109
	P				<0,001	0,195
T3	ρ					-0,148
	P					0,078

ρ = Spearman rho correlation coefficient

P = coefficient of significance

Table 3. Comparison of haemodialyzed ESRD patients surviving one year since sampling with those dying within one year.

Variable (unit)	Surviving one year n = 119	Dying within one year n = 48	*P*
TSH (mIU/l)	1.80 (1.20-3.38)	2.03 (1.10-3.00)	0.992
T4 (nmol/l)	73.2 (60.9-85.9)	70.8 (61.4-82.4)	0.570
T3 (nmol/l)	1.08 (0.89-1.27)	0.95 (0.73-1.19)	0.030
rT3 (nmol/l)	0.26 (0.21-0.35)	0.36 (0.29-0.48)	<0.001
fT4 (pmol/l)	11.8 (10.3-13.5)	11.1 (9.5-13.6)	0.299
fT3 (pmol/l)	3.27 (2.83-3.78)	3.19 (2.65-3.78)	0.366

Values are expressed as median (interquartile range).

Mann-Whitney test was used for comparison.

Table 4. Comparison of haemodialyzed ESRD patients surviving 6 months since sampling with those dying within 6 months.

Variable (unit)	Surviving six months n = 142	Dying within six months n = 25	*P*
TSH (mIU/l)	1.94 (1.20-3.40)	1.55 (0.89-2.57)	0.258
T4 (nmol/l)	72.4 (61.3-84.4)	68.0 (56.2-84.4)	0.561
T3 (nmol/l)	1.09 (0.88-1.27)	0.80 (0.71-1.06)	<0.001
rT3 (nmol/l)	0.28 (0.22-0.38)	0.39 (0.31-0.47)	0.015
fT4 (pmol/l)	11.7 (10.2-13.5)	11.4 (9.9-14.8)	0.866
fT3 (pmol/l)	3.23 (2.80-3.74)	3.50 (2.66-3.88)	0.986

Values are expressed as median (interquartile range).

Mann-Whitney test was used for comparison.

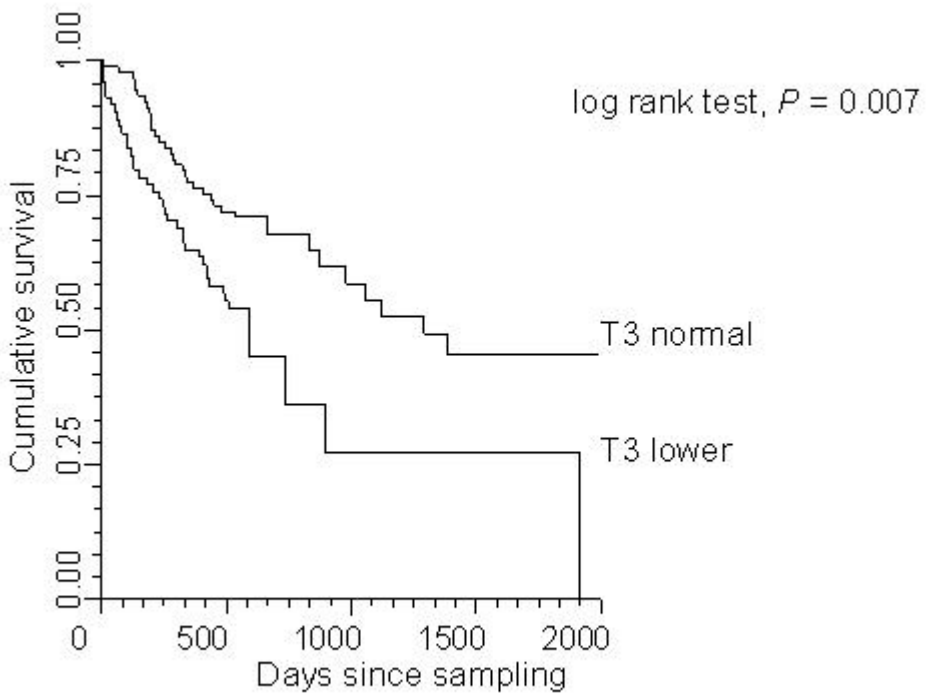

Figure 1. Kaplan-Meier survival analysis of T3 in ESRD patients.

Patients are divided into two groups on the basis of their T3 level; upper trace: values within the reference range (1.0-3.0 nmol/l); lower trace: values < 1.0 nmol/l.

Log rank test, $P = 0.007$.

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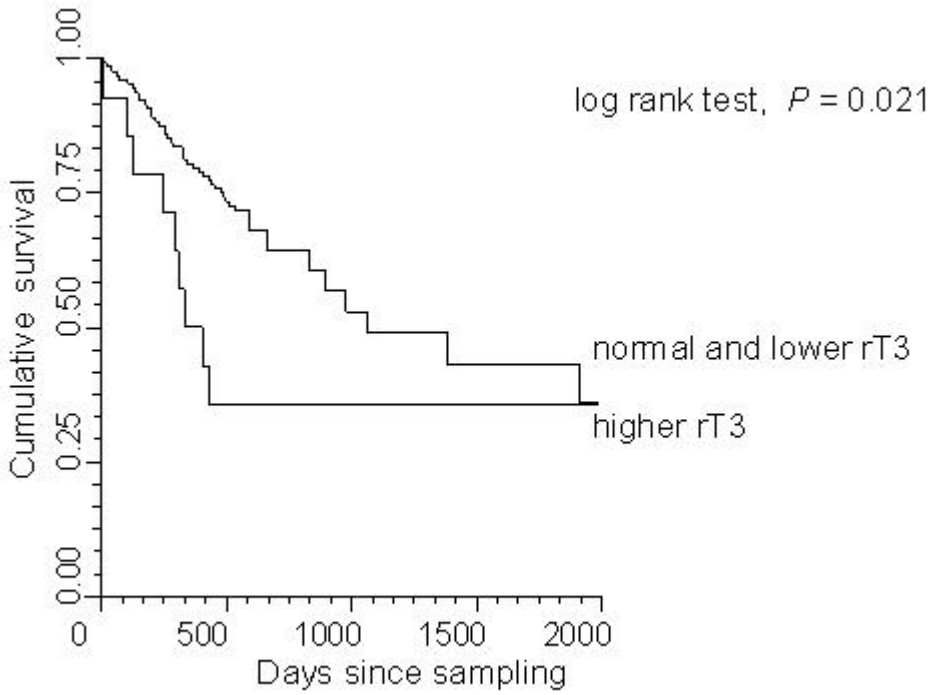

Figure 2. Kaplan-Meier survival analysis of rT3 in ESRD patients.

Patients are divided into two groups on the basis of their rT3 level; upper trace: values within the reference range (0.14-0.54 nmol/l) or below; lower trace: values > 0.54 nmol/l.

Log rank test, $P = 0.021$.