Biochemical Effects of Levothyroxine Withdrawal in Patients with Differentiated Thyroid Cancer

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Abstract. *Background: Patients with differentiated thyroid carcinoma (DTC) are submitted to withdrawal of levothyroxine (LT4) aftter thyroidectomy, in order to undergo radiodine (^{131}I) treatment. Patients and Methods: A total of 345 patients with a history of DTC were enrolled in the study. Their biochemical profile and serum free triiodothyronine (FT3), free thyroxine (FT4) and thyrotropin (TSH) levels were measured during withdrawal of LT4 treatment, and several months after restarting LT4. Results: During withdrawal, the intra-individual percentage increase in total cholesterol, low density lipoprotein-cholesterol, very low density lipoprotein-cholesterol and triglycerides was of the order of 60-80% and that for high density lipoprotein-cholesterol 30%. Creatinine increased by 30%, whereas Na and K levels decreased by 1%. The increase for creatine phosphate kinase was around 200-300%, for aspartate aminotransferase and alanine aminotransferase 50-80%, for γ-glutamyl transpeptidase 10-20%, and for lactate dehydrogenase 25%. Glucose decreased by 1-4%. Conclusion: Short-term, acute hypothyroidism in patients with DTC induces significant alterations in several biochemical parameters. The presence of other deteriorating diseases should be considered before submitting these patients to LT4 withdrawal.*

Thyroid hormone affects almost every system of the human body, from fetal development and growth during childhood to normal organ function throughout life. Hypothyroidism is well-known to alter many biochemical parameters, leading to relative functional derangement occurring in many organs and metabolic pathways. Lipids (1), liver enzymes (2), renal function tests (3) and electrolytes (4) are all affected. Nevertheless, the degree of changes that should be expected in these parameters in athyreotic patients during levothyroxine (LT4) withdrawal is not clearly defined.

Many patients with DTC are treated with radiodine (^{131}I) after thyroidectomy, while they are hypothyroid and all are submitted to withdrawal of LT4 periodically for the evaluation of their disease state. Among the tests used for follow-up is serum thyroglobulin (Tg) as a tumor marker, and occasionally, total body scan with ^{131}I. Maximal sensitivity of the aforementioned tests is established in the hypothyroid state, under elevated thyrotropin (TSH) concentrations, achieved with LT4 withdrawal (5). In recent years recombinant human TSH (rhTSH) has been available and patients frequently undergo radiodine treatment or follow-up with the administration of rhTSH without the need for withdrawal of LT4 (6) However, we continue to administer radioiodine and follow-up patients while hypothyroid, unless major other clinical comorbidities are present (advanced chronic renal failure, coronary artery disease, or poor health status).

The aim of the present study was to determine the degree of change in several biochemical parameters due to a short-term but acutely supervening hypothyroidism, estimating thus the overall effect of hypothyroidism and differentiate it from other, possibly co-existent diseases.

Patients and Methods

This study was conducted at the Outpatient and Inpatient Departments of the Endocrinology Unit of a tertiary cancer center (Metaxa Anticancer Hospital). The study was approved by the Scientific Committee of our hospital.

In our study, we enrolled patients submitted to total thyroidectomy for DTC that were rendered hypothyroid with LT4 withdrawal in order either to receive radiodine for thyroid remnant ablation or to undergo follow-up.

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Table I. *Values of various biochemical parameters off and on levothyroxine (LT4) in the entire study population.*

Parameter (N=345)	Reference range	Off LT4 (mean±SD)	On LT4 (mean±SD)	*p*-Value
Glucose (mg/dl)	70-100	94.7±25.2	101.6±29.1	<0.001
Creatinine (mg/dl)	0.6-1.1	0.97±0.23	0.75±0.15	<0.001
Uric acid (mg/dl)	2.6-6.0	6.0±1.9	5.3±2.9	<0.001
t-Cholesterol (mg/dl)	<200	316.1±73.5	203.5±41.2	<0.001
TGL (mg/dl)	<150	201.1±155.4	116.9±56.2	<0.001
HDL-c (mg/dl)	>40	66.6±16.2	50.6±12.4	<0.001
LDL-c (mg/dl)	<130	208.9±62.7	129.5±36.5	<0.001
VLDL-c (mg/dl)	<32	41.6±32.5	24.0±14.3	<0.001
AST (U/l)	10-40	33.8±16.2	19.1±8.2	<0.001
ALT (U/l)	10-35	36.8±29.6	22.8±15.6	<0.001
γ-GT (U/l)	<30	33.5±60.1	28.0±48.5	<0.001
LDH (U/l)	125-245	231.0±51.1	189.0±42.6	<0.001
CPK (U/l)	38-174	399.9±697.6	91.6±68.7	<0.001
K (mmol/l)	3.5-5.1	4.19±0.38	4.27±0.38	0.001
Na (mmol/l)	136-145	138.6±2.2	140.0±3.6	<0.001
Albumin (g/dl)	3.5-5.5	4.35±0.33	4.24±0.34	<0.001

t-Cholesterol, total cholesterol; TGL, triglycerides; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein chlolesterol, VLDL-c, very low density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CPK, creatine phosphate kinase; K, potassium; Na, sodium.

Table II. *Values of various biochemical parameters off and on levothyroxine (LT4) and the relative percentage variation, in patients with normal thyrotropin while on LT4.*

Parameter (N=184)	Reference range	Off LT4 (mean±SD)	On LT4 (mean±SD)	*p*-Value
Glucose (mg/dl)	70-100	96.6±28.5	103.0±31.5	0.001
Creatinine (mg/dl)	0.6-1.1	0.99±0.26	0.77±0.16	<0.001
Uric acid (mg/dl)	2.6-6.0	6.3±2.1	5.2±1.5	<0.001
t-Cholesterol (mg/dl)	<200	307.9±68.7	204.0±42.8	<0.001
TGL (mg/dl)	<150	213.5±173.4	122.1±61.0	<0.001
HDL-c (mg/dl)	>40	64.7±15.0	49.6±12.6	<0.001
LDL-c (mg/dl)	<130	199.3±58.4	130.4±36.6	<0.001
VLDL-c (mg/dl)	<32	43.5±36.2	25.3±17.2	<0.001
AST (U/l)	10-40	34.3±16.2	19.5±8.7	<0.001
ALT (U/l)	10-35	37.7±32.9	23.7±16.8	<0.001
γ-GT (U/l)	<30	37.8±75.2	29.6±38.7	0.001
LDH (U/l)	125-245	234.4±54.0	190.3±39.7	<0.001
CPK (U/l)	38-174	579.6±1118	109.7±99.1	<0.001
K (mmol/l)	3.5-5.1	4.22±0.38	4.29±0.38	0.015
Na (mmol/l)	136-145	138.6±2.3	139.8±4.3	<0.001
Albumin (g/dl)	3.5-5.5	4.36±0.33	4.29±0.33	0.008

t-Cholesterol, total cholesterol; TGL, triglycerides; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein chlolesterol, VLDL-c, very low density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CPK, creatine phosphate kinase; K, potassium; Na, sodium.

We measured a series of biochemical parameters at different time points: while the patients were hypothyroid (off LT4), and at several months after the initiation of LT4 treatment (on LT4). We did not advise our patients to strictly adhere to a low iodine diet given the risk of developing hyponatremia (7, 8) and the questionable advantage on thyroid ablation (9). They were instructed verbally to avoid seafood, iodine-containing drugs and restrict their salt intake. During LT4 withdrawal, patients remained hypothyroid for 20-25 days and any disordered biochemistry might be the consequence of the hypothyroidism or it might indicate another primary disease.

A total of 345 patients were enrolled between January 2013 and May 2015, 60 males (17%) and 285 (83%) females. Their mean age (±SD) was 54.7±13.6 years (range=17-83 years).

Glucose, creatinine, uric acid, Na, K, total cholesterol, high density lipoprotein-cholesterol (HDL-c), triglycerides (TGL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GT), lactate dehydrogenase (LDH), creatine phosphate kinase (CPK) and albumin levels were measured after overnight fasting with photometric and turbidimetric methods, Abbott's ARCHITECT c16000 Clinical Chemistry Analyzer, Abbott Diagnostics, North Chicago, Illinois, USA. Very low density lipoprotein-cholesterol (VLDL-c) and low density lipoprotein-cholesterol (LDL-c) were calculated using the Friedewald formula when total triglyceride was less than 400 mg/dl (10). We also measured serum levels of free thyroxine, free triiodothyronine and TSH with immunoassay testing using ElectroChemiLuminescence (ECL) technology, Roche's cobas 6000 Analyzer, Roche Diagnostics USA.

Data were analyzed using SPSS analytical software 22 (SPSS Inc.-IBM Corp,, New York, NY, USA). Paired *t*-test was used for comparisons between means on and off LT4 and χ^2 for comparisons of categorical parameters. Intraindividual percentage changes in each biochemical parameter off LT4 in relation to those while on LT4 were calculated. Pearson's coefficient of correlation was used for correlations between variables. Logarithmic transformation was carried out for quantitative variables with non-Gaussian distribution. Differences with *p*-values of less than 0.05 were considered significant.

Results

There was a significant increase in TSH concentration and a significant decrease in FT3 and FT4 concentrations off LT4. TSH off LT4 was 92.68±49.24 mU/l (median=81.90, IQR= 58.21-115.05 mU/l) and on LT4 0.78±0.99 mU/l (median=0.31, IQR=0.07-1.22 mU/l; $p<0.001$), FT3 concentration off LT4 was 0.78±0.61 pmol/l (median=0.40, IQR=0.40-0.90 pmol/l) and on LT4 was 4.67±0.69 pmol/l (median=4.60, IQR= 4.20-5.10 pmol/l; $p<0.001$) and FT4 concentration off LT4 was 1.54±1.50 pmol/l (median=1.10, IQR=0.40-2.20 pmol/l) and on LT4 was 19.16±3.81 pmol/l (median=18.50, IQR=16.10-21.90 pmol/l; $p<0.001$). The levels of various biochemical parameters measured off and on LT4 are shown Table I. There was a significant change in all measured parameters while the patients were off LT4 *versus* while on LT4.

Table III. *Percentage change of parameters in the whole patient cohort while off levothyroxine (LT4) in relation to those while on LT4.*

Parameter (N=345)	Mean	SD	Median	IQR
Glucose	−4.94	18.75	−6.32	−15.21-2.35
Creatinine	29.48	22.39	28.57	14.28-42.85
Uric acid	18.82	27.42	16.19	2.36-34.25
t-Cholesterol	57.45	32.88	54.46	38.00-71.28
TGL	79.02	99.01	58.97	23.61-104.34
HDL-c	33.75	24.07	31.37	18.60-47.16
LDL-c	71.56	119.32	63.00	36.32-85.81
VLDL-c	82.01	102.61	61.65	27.49-106.80
AST	88.15	89.63	65.83	35.92-115.48
ALT	89.08	171.52	52.94	12.31-116.91
γ-GT	23.98	62.07	11.11	−5.00-33.33
LDH	24.38	25.13	21.42	8.59-36.17
CPK	301.3	251.4	236.4	112.8-403.7
K	−1.36	10.27	0.00	−8.88-5.26
Na	−0.89	2.24	−0.71	−2.07-0.00
Albumin	2.77	8.17	2.38	−2.32-7.50

t-Cholesterol, total cholesterol; TGL, triglycerides; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein chlolesterol, VLDL-c, very low density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CPK, creatine phosphate kinase; K, potassium; Na, sodium.

Table IV. *Percentage change of parameters off levothyroxine (LT4) in patients with normal values for each parameter while on LT4.*

Parameter	Mean	SD	Median	IQR
Glucose (N=228)	−0.89	15.83	−3.38	−9.93-3.84
Creatinine (N=338)	30.00	22.10	28.57	14.28-42.85
Uric acid (N=237)	22.94	25.86	18.33	6.32-37.84
Cholesterol (N=160)	65.82	34.65	60.54	44.89-82.69
TGL (N=249)	83.77	89.06	66.27	30.52-109.71
HDL (N=255)	30.59	22.81	29.26	14.89-43.33
LDL (N=176)	87.00	154.60	69.91	45.68-99.92
VLDL (N=222)	89.06	101.87	68.32	31.59-116.50
AST (N=333)	90.63	89.35	66.66	37.79-117.42
ALT (N=297)	102.61	179.09	61.53	22.25-129.70
γ-GT (N=254)	24.01	53.16	13.33	0.00-34.19
LDH (N=292)	25.93	24.62	22.12	10.50-38.25
CPK (N=310)	291.75	235.31	226.60	110.37-387.00
K (N=334)	−1.04	10.10	0.00	−8.02-5.40
Na (N=328)	−0.87	1.69	−0.71	−2.07-0.00
Albumin (N=314)	2.93	8.06	2.43	−2.28-7.50

t-Cholesterol, total cholesterol; TGL, triglycerides; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein chlolesterol, VLDL-c, very low density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CPK, creatine phosphate kinase; K, potassium; Na, sodium.

Since suppression of TSH while on LT4 (sub-clinical hyperthyroidism) may affect several of the above parameters, we repeated the analysis excluding patients with suppressed TSH (*i.e.* those with <0.27 μU/ml, the lower normal limit by our method), while on LT4. We found that patients with normal concentrations of TSH while on LT4 [N=184, mean age 53.1±14.0, 40 males (22%), 144 females (78%)] had similar alterations to those of the entire patient cohort in all the measured parameters (Table II). The respective concentrations of thyroid hormones and TSH in this subgroup of patients were: TSH: off LT4=97.07±47.27 mU/l (median=84.24, IQR=63.27-121.35 mU/l) and on LT4=1.40±1.01 mU/l (median=1.12, IQR=0.54-1.99 mU/l; $p<0.001$); FT3: off LT4=0.76±0.61 pmol/l (median=0.40, IQR=0.40-0.87 pmol/l) and on LT4=4.57±0.65 pmol/l (median=4.40, IQR=4.20-4.90 pmol/l; $p<0.001$); FT4: off LT4 was 1.52±1.41 pmol/l (median=1.10, IQR=0.42-2.10 pmol/l) and on LT4=17.62±3.22 pmol/l (median=17.15, IQR=15.32-19.67 pmol/l; $p<0.001$).

We calculated the percentage change of each parameter for the entire patient group while off LT4. There was a decrease in both the mean and median values for glucose and sodium (Na), and while for potassium (K) there was a decrease in the mean value with no change in the median value. Both the mean and median values increased for all the other parameters, with a very broad range of changes (Table III).

For the purpose of defining the expected alterations attributed to hypothyroidism exclusively, we excluded patients with abnormal values (out of the normal range) for each parameter while on LT4 and calculated the respective mean and median change. Again, both the mean and median values decrease for glucose, Na and K, while all those for all the other parameters increased (Table IV).

We compared the percentage of patients with values out of the normal range on and off LT4 for each parameter separately, and we found significant differences in most of them (Table V).

Examining for possible correlations between the various parameters and the concentrations of FT3, FT4 and TSH while off LT4, we found weak, still significant correlations both with the absolute values and the percentage change of the parameters off LT4 compared to on LT4 (Tables VI and VII). Most parameters had more sustained and strong correlations with either FT4 or FT3 than with TSH.

We compared male and female patients for any difference in the percentage change of all the parameters measured and the only significant divergence found was the degree of sodium decline. Women had a significantly higher percentage decrease in sodium concentration off LT4 in relation to that while on LT4: a decrease of 1.02±2.34% compared to men with a decrease of 0.27±1.60% ($p=0.022$).

Table V. *The percentage of values outside of the normal range for parameters while on and off levothyroxine (LT4) for the entire study population.*

Parameter (N=345)	Outside of the normal range on LT4 (%)	Outside of the normal range off LT4 (%)	χ^2	*p*-Value
Creatinine (↑)*	2	17	10.3	0.010
Uric acid (↑)*	24	47	51.5	<0.001
t-Cholesterol (↑)*	50	97	10.2	0.006
TGL (↑)*	21	53	44.5	<0.001
HDL-c (↑)*	19	62	41.9	<0.001
LDL-c (↑)*	41	89	19.3	0.001
VLDL-c (↑)*	16	47	43.2	<0.001
AST (↑)*	3	20	13.2	0.001
ALT (↑)*	13	40	14.9	0.001
γ-GT (↑)*	17	23	106.3	<0.001
LDH (↑)*	8	34	24.7	<0.001
CPK (↑)*	3	51	6.8	NS[#]
K (↓)**	1	3	43.7	0.002
Na (↓)**	3	7	6.7	0.038
Albumin (↑)*	2	3	32.2	0.001

t-Cholesterol, total cholesterol; TGL, triglycerides; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein chlolesterol, VLDL-c, very low density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CPK, creatine phosphate kinase; K, potassium; Na, sodium; (↑)*: Increase off LT4 relatively to on LT4 and higher than the upper normal limit. (↓)**: Decrease off LT4 relatively to on LT4 and lower than the lower normal limit. NS: Non significant. [#]Due to the fact that there was no patient with normal CPK off LT4 and increased on LT4. For glucose, no analysis was carried out since no patient had glucose levels lower than the lower normal limit either off or on LT4.

Table VI. *Significant correlations between the absolute values of the various parameters and the concentrations of free triiodothyronine (FT3), free thyroxine (FT4) and thyrotropin (TSH) while off levothyroxine.*

Parameter	FT3		FT4		TSH	
N=345	r	*p*-Value	r	*p*-Value	r	*p*-Value
Glucose	0.14	0.007			–0.20	<0.001
Creatinine	–0.12	0.019	–0.25	<0.001	0.14	0.006
Uric acid			–0.20	<0.001		
t-Cholesterol	–0.12	0.019	–0.19	<0.001		
TGL			–0.11	0.041		
HDL-c	–0.11	0.029				
LDL-c	–0.11	0.036	–0.18	0.001		
VLDL-c			–0.12	0.026		
AST	–0.14	0.006	–0.15	0.004		
ALT	–0.11	0.040	–0.11	0.030		
CPK			–0.20	0.001		
Na	0.20	<0.001	0.14	0.009		
Albumin	0.12	0.026				

t-Cholesterol, total cholesterol; TGL, triglycerides; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein chlolesterol, VLDL-c, very low density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CPK, creatine phosphate kinase; Na, sodium.

Discussion

Thyroid hormone withdrawal in patients with DTC represents a unique model of acute overt hypothyroidism. Thyroid hormone, through genomic and non-genomic actions, affects every aspect of cell life, such as differentiation, migration and proliferation through to energy production, survival and function (11). In clinical practice, any deviation from normal of thyroid hormone action at the tissue and organ level can be assessed only roughly by routine biochemistry. Nevertheless, it is a useful tool for making treatment decisions and in follow-up.

In our study, we examined the effect of short-term hypothyroidism on various biochemical parameters in patients with DTC. We compared the data of our patients with those in the literature and we referred to the possible mechanisms accounting for any alteration observed. We found a statistically significant change in all the parameters examined and we will briefly report on each of them separately.

In our study there was a small, yet statistically significant decrease of glucose level off LT4 compared to on LT4, of the order of 1-4%. However, such an alteration may become clinically important in diabetic patients with frequent hypoglycemia. Serum glucose levels in hypothyroid patients are decreased and increase after replacement with thyroxine (12). Thyroid hormone stimulates hepatic gluconeogenesis and output, while concurrently it increases the expression of glucose transporters (GLUT) in the liver and the peripheral tissues (13). Although hepatic glucose production in hypothyroidism is reduced (14), the function of GLUTs is at the same time impaired (15) and hypothyroidism is considered a state of insulin resistance (16, 17). An inverse relation between FT4 levels and insulin resistance, even in the euthyroid state, has been reported (18). Reduction of insulin metabolism, as observed in hypothyroidism, may worsen the already impaired glucose production (14).

We found a significant increase off LT4 compared to on LT4 in all the lipids measured, both in patients with suppressed TSH and in those with normal TSH while on LT4. The increase of total cholesterol, LDL-c, VLDL-c and TGL levels were in the order of 60-80% and for HDL-c of 30%. Even for patients with normal concentrations of LDL-c, VLDL-c and TGL on LT4, levels may double off LT4. In contrary to glucose, lipid values off LT4 frequently exceeded the normal limits and the possible lasting impact of such

Table VII. *Significant correlations between the percentage change of the various parameters while off levothyroxine (LT4) in relation to those while on LT4, and the concentrations of free triiodothyronine (FT3), free thyroxine (FT4) and thyrotropin (TSH) while off LT4.*

Parameter	FT3		FT4		TSH	
N=345	r	*p*-Value	r	*p*-Value	r	*p*-Value
Glucose	0.12	0.024	0.10	0.046		
Creatinine	–0.14	0.006	–0.25	<0.001		
Uric acid	–0.16	0.003	–0.24	<0.001		
t-Cholesterol	–0.15	0.004	–0.26	<0.001		
TGL	–0.11	0.044	–0.11	0.043		
HDL-c	–0.15	0.005				
LDL-c			–0.16	0.005		
VLDL-c			–0.12	0.035		
AST	–0.14	0.008	–0.19	<0.001	0.15	0.004
ALT					0.13	0.016
CPK			–0.20	0.031		
Na			0.11	0.040		
Albumin	0.11	0.049				

t-Cholesterol, total cholesterol; TGL, triglycerides; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein chlolesterol, VLDL-c, very low density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CPK, creatine phosphate kinase; Na, sodium.

derangement on vascular atherosclerosis is unknown. Thyroid hormone affects both lipogenesis and lipolysis through regulation of many enzymes and receptors involved in lipid metabolism (19). In hypothyroidism, there is a decline in both lipid formation and degradation. Yet reduced lipid metabolism prevails due to impaired expression of LDL receptor (20) and decreased activity of hepatic lipase, lipoprotein lipase (21) and cholesteryl-ester transfer protein (22). Accordingly, hypothyroidism (overt or subclinical) is associated with increased total cholesterol, LDL-c, HDL-c, VLDL-c and TGL, while T4 replacement restores values towards normal (23). In summary, hypothyroidism (and sub-clinical hypothyroidism) has a detrimental effect on various cardiovascular risk factors (24), although its direct impact on cardiovascular risk is not unequivocally established (25, 26). Nevertheless, it seems that the decline of thyroid function, even within the normal range, may influence the presence and severity of coronary atherosclerosis (27, 28) or act as a pro-atherogenic factor (29).

Our data indicate an increase in serum creatinine levels of around 30% and a decrease of 1% in sodium concentration, reaching in extreme cases 2%. Still, this difference was statistically significant. The restriction of dietary salt that patients with DTC are instructed to follow may contribute to the decline of serum sodium. Thyroid hormone directly and indirectly affects the renal function. It regulates ion channels and transporters in renal tubules, modifies the action of other hormones on the kidney (aldosterone, catecholamines) and, through its action on the cardiovascular system, thyroid hormone influences hemodynamic conditions in the kidney (3). The reduction in cardiac output and its increase in peripheral resistances seen in hypothyroidism, both lead to diminished renal blood flow (RBF) and glomerular filtration rate (GFR), with consequent reduced water excretion (30). Except for the increase in creatinine level, a consequence is a decrease in sodium concentration. Furthermore, inappropriately increased anti-diuretic hormone, in relation to plasma osmolality, and increased sodium excretion may also contribute to the decline of serum sodium (31). Therefore, hypothyroidism is consistently regarded as a cause of hyponatremia. Conversely, even severely hypothyroid patients with extreme elevations of TSH have normal serum sodium concentrations or those in the lower limit of the normal range (32), and hypothyroid patients with DTC only rarely present with hyponatremia (33). This was also the case in our study. It is probable that for the development of clinically important hyponatremia, at least in short-term hypothyroidism, other factors should also concur, such as old age, female sex or use of diuretics (7, 34). These factors should be taken into account when submitting patients with DTC to LT4 withdrawal. Of note, as others have also observed, we found that the decrease in serum sodium is greater in women. The reason for such a difference is unknown. Possibly, it is related to the different sodium metabolism in women (35). Again, the presence of factors predisposing to hyponatremia should be considered when recommending LT4 withdrwal.

In contrast to a previous study (36), we found a minimal, still significant, decrease in serum potassium off LT4, of the order of 1%, whereas another study found that elevated TSH levels were associated with both hyper- and hypokalemia (4). A mild, incomplete renal tubular acidosis, as observed in hypothyroidism, accompanied by either hypokalemia or hyperkalemia (37, 38) may explain the above findings.

We found a significant increase in AST/ALT, LDH and γ-GT in our patients while off LT4, indicating an adverse effect of hypothyroidism on both hepatic cells and bile excretion. AST/ALT levels exhibited a very broad range of increase of around 50-90%. Even in patients with normal liver enzymes on LT4, values may double when they are off LT4. γ-GT and LDH increased to a much less extent of 10-20% and 25%, respectively. It seems that hypothyroidism has both a cytotoxic and a cholestatic effect on the liver (39). It has been implicated in the development of non-alcoholic liver disease and non-alcoholic steatohepatitis even as an independent risk factor (40), although this was not confirmed by other studies (41). It is not clear whether thyroid dysfunction is directly involved in the pathogenesis of liver disease or there is an abnormal metabolism of thyroid

hormones due to liver disease (42). However, low FT4 concentrations are associated with hepatic steatosis (43), while TSH and FT4 levels, even in the normal range, are significantly correlated to ALT and γ-GT levels (44). Additionally, hypothyroidism is a cholestatic condition resulting from impaired bile metabolism and excretion, and patients with hypothyroidism have an increased incidence of bile stones (45).

We observed a remarkable increase of CPK of the order of 200-300% with LT4 withdrawal. Hypothyroidism has a profound effect on muscle cell energy production and metabolism, and the symptoms of myopathy are among the most prominent of the disease (46). CPK is increased in hypothyroidism and directly correlated to the degree of hypothyroidism (47, 48). Several cases of rhabdomyolysis have been reported (49), either in hypothyroidism alone or in combination with other factors, such as statin co-administration (50). This should be considered in patients with DTC when LT4 is withdrawn if they concomitantly take lipid-lowering agents (25, 26). Myopathy should account in part for the elevation of both AST and LDH noted off LT4 since together these two enzymes are also secreted by muscle cells.

There was a significant increase in uric acid off LT4, of approximately 20%, as is commonly found in hypothyroidism, probably related to reduced GFR and RBF (46), while the prevalence of gout is increased in hypothyroid patients (51).

We also found a significant increase in albumin off LT4 of around 2-3%. Similarly to lipids and carbohydrates, protein synthesis and degradation are both decreased in hypothyroidism. However, due to the predominance of the effect on the latter, protein levels exhibit a mild increase (52).

In the literature, there exist several other reports on biochemical alterations associated with acutely induced hypothyroidism in patients with DTC (33, 53, 54, 55) in which most biochemical parameters remain within the normal range while off LT4, except for lipids and CPK. This was also the case in our study. It is important to note, however, the significant increase of levels outside of the normal range off LT4 in most parameters measured. In certain patients with borderline levels of these parameters, hypothyroidism may provoke a further deterioration of respective organ function. In patients with borderline renal function, hyperlipidemia, impaired liver biochemistry, increased uric acid, or those receiving diuretics or statins, hypothyroidism may impose a further strain.

Owing to the very broad range of alterations in the parameters measured, we were unable to define a precise cut-off for the percentage change off LT4 in relation to on LT4 which was attributable to hypothyroidism. Nevertheless, we believe the above mentioned percentages for the increase or decrease in the parameters during LT4 withdrawal may serve as a rough clinical guide in order to differentiate the impact of hypothyroidism from other possibly concomitant morbidities.

In our analysis we found several weak, still statistically significant, correlations between FT3, FT4, and TSH concentrations on one hand, and the levels or the percentage change of the biochemical parameters on the other. It is established that serum thyroid hormones levels do not accurately reflect their tissue level or action (56). Additionally, biochemical parameters such as those evaluated in our study are influenced by multiple factors and traits. Hypothyroidism certainly accounts for a small proportion of their levels.

Our study has certain limitations. Firstly, we submitted our patients to LT4 withdrawal if no major health problems were present. Therefore, the results are not representative of the whole patient population with DTC. Secondly, and more importantly, we did not evaluate the parameters regarding the quality of life during T4 withdrawal, which certainly deteriorates (57), nor the psychological impact of hypothyroidism. The latter, accordingly to the literature (58) and our experience, is overwhelming in some patients. Thus, we believe that it is the physician's choice to suggest either LT4 withdrawal or the administration of rhTSH in patients with DTC.

In conclusion, the present study showed that acute, short-term hypothyroidism has a significant impact on many biochemical parameters, reflecting the relative alterations in many organ functions and metabolic pathways. Finally, we determined the degree of change in these parameters that is expected in hypothyroid patients and we consider this to be useful clinical knowledge for the differentiation of hypothyroidism from other, possibly concurrent, diseases.

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