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Influence of Low Protein Diet on Nonthyroidal Illness Syndrome in Chronic Renal Failure

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Renal failure causes alterations in thyroid hormone metabolism known as nonthyroidal illness syndrome. In the present study we have examined the effect of a low protein diet (LPD) on circulating levels of hormones of the pituitary–thyroid axis, and tumor necrosis factor alpha (TNF-alpha) in patients with chronic renal failure. Seventeen subjects with conservatively treated chronic renal failure (estimated creatinine clearance 39.5 ± 11.1 mL/min) were studied before and after 8 wk of dietary intervention (0.6 g/kg of ideal body mass protein, 30% of calories derived from fat, 62% of calories derived from carbohydrates, and 10 mg/kg of phosphorus). Body fat and fat-free mass remained unchanged. Urea and TNF-alpha serum concentrations significantly decreased, whereas T_3 and total and free T_4 serum concentrations increased significantly. Triiodothyronine level after treatment correlated negatively with baseline urea level. Changes in T_3, T_4, and fT_4 serum concentrations as well as calculated peripheral deiodinase activity correlated negatively with their baseline values. Alterations in TNF-alpha correlated positively with protein intake, whereas changes in T_4 and T_4/TSH were inversely related to vegetal protein intake. In conclusion, low protein, low phosphorus diet, which is often prescribed to patients with moderate impairment of renal function, exerts a beneficial effect on low T_3 syndrome coexisting with renal failure. The effect of low protein diet on the pituitary–thyroid axis is dependent on the degree of renal functional impairment and LPD-induced decrease in TNF-alpha may also contribute to the observed effects of dietary treatment.

Key Words: Chronic renal failure; low protein diet; thyroid; thyrotropin; triiodothyronine; thyroxine; TNF-alpha.

Introduction

Severe nonthyroidal illness, either acute or chronic, such as infections, malignancy, cardiac infarction, chronic renal failure (CRF), and trauma, evoke perturbations in hypothalamus–pituitary axis homeostatic feedback loop known as the syndrome of nonthyroidal illness (SNTI) or the sick euthyroid syndrome *(1)*. The main feature of SNTI is a decrease in T_3 plasma concentration and also T_4 in more severe cases. Thyrotropin level is usually normal or decreased. Decreases in plasma T_3 concentration have been interpreted teleologically as an attempt to conserve body energy stores by reducing metabolic rate, although there are no data indicating that SNTI is beneficial in any condition *(2)*. There are, however, data indicating that a decrease in thyroid hormone plasma concentration affects crucial body functions such as cardiac contractility *(3)* and cognitive performance *(4)*. Several studies have demonstrated a relationship between disturbances in the thyroidal axis function and a patient's prognosis. Low T_3 and T_4 states were found to be a predictor of poor prognosis in heart disease *(5)*, bone marrow transplantation *(6)*, and liver cirrhosis *(7)*. The effect of nonthyroidal illness on thyroidal axis was shown to be mimicked by elevation in the level of cytokines—interleukin–1, interleukin–6, interferon gamma, and TNF-alpha *(8–10)*. Therefore low T_3 seems to be the result of pathological conditions and maladaptation leading to decreased survival rather than a sign of physiological adaptation to energy shortage.

Hypothalamus–pituitary–thyroid axis activity is affected in many ways in CRF, including TSH secretion and clearance *(11)*, decline in both total and free T_3 and T_4 plasma concentrations *(12)*, decreased hepatic uptake of T_4, and diminished peripheral T_4 to T_3 conversion *(13,14)*. Thyroxine binding by thyroxine binding globulin is usually reduced, which is attributed to the presence of inhibitors *(15)*, although their role has never been proven. Low protein, low phosphorus diets (LPD) are commonly employed in conservative management of CRF in an attempt to retard the rate of renal function decline, although their effect is of relatively weak magnitude *(16)*. Taking into consideration the possible clinical significance of alterations in thyroid hormone levels, we sought to determine nutritional and hormonal determinants of the pituitary–thyroid axis response to LPD treatment in CRF.

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Table 1
Recommended and Actual Dietary Intake of Selected Nutrients During 2 mo of Following Low Protein, Low Phosphorus Diet (Follow-up)

Nutrient	Recommended	Follow-up	*p* value
Energy (kcal/24 h)	2255 ± 222	2124 ± 150	0.002
Total protein (g/24 h)	44 ± 3	50 ± 4	<0.0001
Total protein (g/kg/24 h)	0.60 ± 0.00	0.69 ± 0.04	<0.0001
Vegetal protein (g/kg/24 h)	0.30 ± 0.0	0.41 ± 0.04	<0.0001
Animal protein (g/kg/24 h)	0.30 ± 0.0	0.28 ± 0.3	0.020
Total fat (g/24 h)	75 ± 7	72 ± 8	0.132
Total carbohydrate (g/24 h)	351 ± 373	19 ± 21	0.004
Phosphorus (mg/24 h)	808 ± 97	826 ± 58	0.445

Results expressed as mean ± SD. Statistical differences between recommendations *(33,34)* and actual dietary intake were assessed by Student's paired *t* test.

Table 2
Anthropometric and Biochemical Characteristics of the Patients Before and After 8 wk of Dietary Treatment

Variable	Baseline	After 8 wk	*p* value
BMI (kg/m^2)	26.9 ± 3.0	26.6 ± 3.0	0.043
Weight (kg)	80.8 ± 9.7	79.8 ± 9.5	0.047
Fat mass (kg)	22.7 ± 7.1	22.2 ± 6.4	0.236
Fat mass (%)	27.8 ± 6.6	27.6 ± 6.0	0.584
Fat free mass (kg)	58.1 ± 7.2	57.5 ± 7.0	0.391
Fat free mass (%)	72.2 ± 6.6	72.4 ± 6.0	0.567
Urea (mmol/L)	14.50 ± 6.75	11.52 ± 5.37	0.0005
Creatinine (μmol/L)	203.76 ± 49.64	190.41 ± 54.06	0.013
CrCl (mL/min/1.73 m^2)	39.46 ± 11.08	42.43 ± 14.04	0.047
T_3 (nmol/L)	1.22 ± 0.32	1.53 ± 0.34	0.004
T_4 (nmol/L)	117.28 ± 31.44	130.34 ± 23.08	0.018
FT_4 (pmol/L)	12.04 ± 4.13	13.77 ± 5.05	0.005
TSH (mIU/L)	1.10 ± 0.72	1.18 ± 0.66	0.526
T_3 / T_4	0.011 ± 0.004	0.012 ± 0.003	0.068
T_4 / TSH	144.56 ± 82.73	151.54 ± 91.25	0.481
FT_4 / T_4	0.104 ± 0.032	0.108 ± 0.040	0.408
G_T pmol/s	5.66 ± 2.64	6.02 ± 2.77	0.291
G_D nmol/s	11.61 ± 4.05	12.68 ± 3.82	0.070
TNF-alpha (pg/mL)	15.41 ± 11.18	9.19 ± 6.66	0.008

Results expressed as mean ± SD. Statistical differences between baseline values and after 8 wk dietary treatment were assessed by Student's paired *t* test.

Abbreviations: BMI, body mass index; CrCl, calculated creatinine clearance; T_3, triiodothyronine; T_4, thyroxine; fT_4, free thyroxine; TSH, thyrotropin; GT, calculated thyroid's T_4-secretion capacity; G_D, calculated peripheral 5'deiodinase activity.

Results

Recommended total energy, fat, and phosphorus intake targets were met during the study duration (Table 1). Total protein and vegetal protein consumption exceeded prescribed levels, whereas animal protein and carbohydrate intakes were lower than recommended (Table 1).

Before treatment, serum urea and creatinine concentrations ranged from 7.9 to 33.6 mmol/L and from 163.2 to 321.9 μmol/L, respectively. Total T_4 was in the range 64.2–202.1 nmol/L, approaching the upper normal limit in three cases. fT_4 was in the range 6.5–20.3 nmol/L (in eight cases it did not reach lower limit), T_3 ranged from 0.8 to 1.8 nmol/L (in seven cases it was below the lower normal limit). Thyrotropin level was in the range of 0.4–3.1 mIU/L.

Body mass index and body weight decreased slightly, but significantly after 2 mo of dietary treatment. Body fat and fat free mass remained unchanged. Serum urea and TNF-alpha concentration decreased and calculated creatinine clearance increased significantly (Table 2). Intake of carbohydrates was directly related to creatinine clearance (r = 0.63, p = 0.008; Fig. 1). Negative correlation between changes evoked by treatment in CCr and baseline fT_4/T_4 ratio was

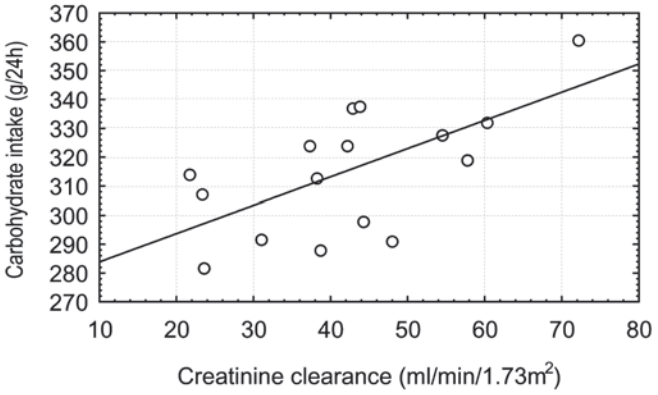

Fig. 1. Correlation between creatinine clearance and carbohydrate intake after 8 wk of low protein, low phosphorus diet (r = 0.63, $p < 0.008$).

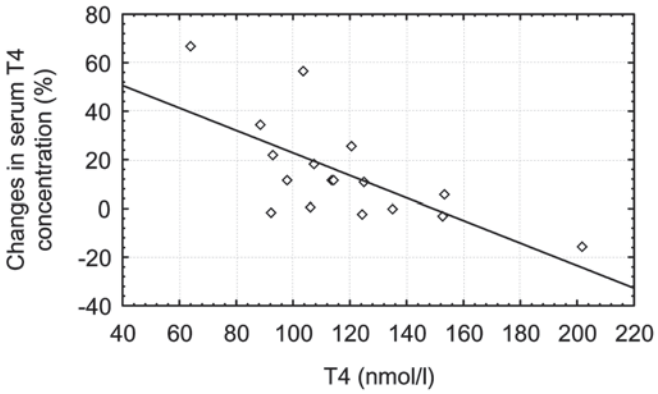

Fig. 2. Correlation between pre-treatment serum T_4 concentration and its changes after 8 wk of low protein, low phosphorus diet (r = –0.68, $p < 0.003$).

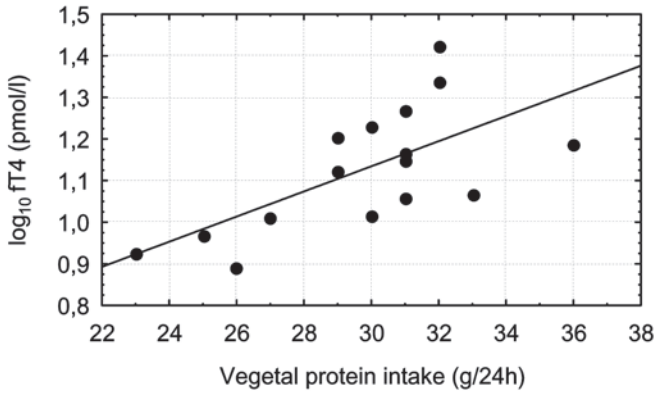

Fig. 3. Correlation between vegetal protein intake and serum log10 fT_4 concentration after 8 wk of low protein, low phosphorus diet (r = 0.66, $p < 0.005$).

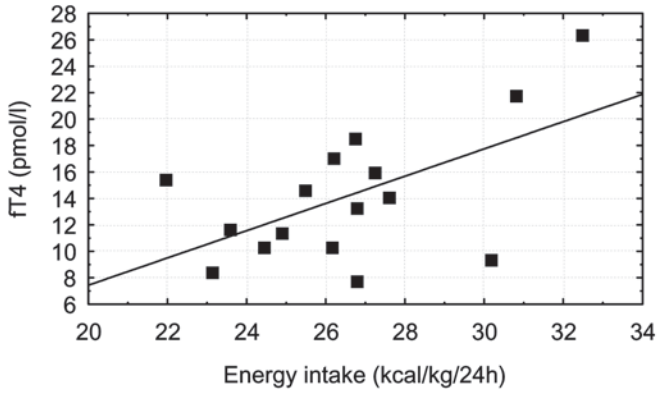

Fig. 4. Correlation between energy intake and serum fT_4 concentration after 8 wk of low protein, low phosphorus diet (r = 0.57, $p < 0.02$).

on the verge of statistical significance (r = –0.48; p = 0.059). Changes in TNF-alpha were directly related to protein intake per kilogram of body mass (r = 0.53, p = 0.04).

Treatment caused significant increase in T_3 as well as in total and free T_4 serum concentrations (Table 2). Triiodothyronine level after dietary treatment was inversely related to baseline urea serum concentration (r = –0.51, p = 0.04). Relative changes in T_3 level correlated negatively with baseline T_3 (r = –0.58, $p < 0.015$) and positively with initial TSH level (r = 0.86, p = 0.000). Changes in total and free T_4 were inversely related to their baseline concentrations (r = –0.68, p = 0.003, Fig. 2 and r = –0.61, p = 0.01, respectively). Changes in total T_4 and T_4/TSH ratio were inversely related to vegetal protein intake (r = –0.75, p = 0.001) and (r = –0.53, p = 0.03, respectively), whereas a reciprocal relation occurred between vegetal protein intake and log10 fT_4 level after dieting (r = 0.66, $p < 0.005$; Fig. 3). Both fT_4 concentration after 2 mo of therapy and alterations in fT_4 level correlated positively with calorie consumption per kilogram of body mass (r = 0.57, p = 0.02, Fig. 4 and r = 0.56, p = 0.02, respectively). Mean TSH serum concentration was not affected by treatment, although it should be noted that in response to treatment it increased in 12 cases, decreased in 3, and did not change in 2 cases.

Initial peripheral 5'deiodinase activity was inversely related to its change after dietary treatment (r = 0.83, p = 0.000). After therapy, thyroid's T_4-secretion capacity correlated positively with creatinine clearance (r = 0.53, p = 0.042).

Discussion

The low protein/low phosphorus diet employed in our study for CRF management caused a decrease in TNF-alpha and a small but significant increase in thyroid hormone serum concentrations. Such short-term LPD has not changed nutritional status as apparent from fat free mass and fat mass. Improvements in thyroid axis activity and TNF-alpha serum concentration were seen in spite of incomplete dietary compliance. Animal protein, fat, and carbohydrate intake determined from diet diaries were significantly lower than prescribed, while total and vegetal protein consumption exceeded recommended level. Over consumption of vegetal protein was due to distaste for low protein bread, and consumption

of nondietetic baker's goods. The direct relationship between creatinine clearance after dietary intervention and intake of carbohydrates agrees with findings of Kopple et al. *(17)*, indicating dependence of spontaneous dietary protein and energy intakes on the progression of renal insufficiency. Unfortunately, owing to technical reasons, we were unable to assess pre-intervention diet. It is, however, improbable that patients' diets were actually not changed by dietary intervention. Kopple et al. *(17)* have found that in patients with GFR in a range 21–37 mL/min (lower than in our study), protein intake estimated from diaries was 1.05 ± 0.34 g/kg/d, substantially exceeding this variable estimation from diaries in our patients. Furthermore, we observed decrease in blood urea concentration which suggests that study subjects actually decreased their protein intake. Possible limitations of this study were not only that there were no pre-test diet diaries, but also include small population, male sex of all the participants, and short study duration.

Changes in T_4 and T_3 serum concentrations caused by low protein diet were in agreement with published reports *(18,19)*; however, unlike Carpi et al. *(18)*, we observed an increase in serum fT_4 level. It must be noted, however, that in the study of Carpi and colleagues *(18)* proteinuria was in the nephrotic range. Increase in fT_4 was paralleled in our study by the rise in total T_4, thus the fT_4 index has not been altered. Elevation of T_3 concentration could be due both to decrease in uremic toxins level, which have been shown to interfere with intrahepatic transport of T_4 *(14)* and to the effect of low protein–high carbohydrate diet on thyroid hormone metabolism. Low protein–high carbohydrate diet has been shown in humans and rats to increase serum T_3 with concomitant decrease in T_4 concentration, mainly due to stimulation of type I deiodinase activity, which is upregulated by glucose *(20–22)*. However, in contrast to response of serum T_4 to LPD seen in healthy subjects, in CRF patients we observed an increase in mean T_4 serum concentration. This might imply that the increase in stimulation of T_4 release was also a consequence of LPD, presumably due to the increase in TSH secretion. In SNTI, central hypothyroidism is often observed. Diminished TSH synthesis in SNTI supposedly results from the decline in TRH synthesis *(23)*. However, in CRF TSH is usually in the normal range or elevated *(2,24,25)*. This was also the case in our patients, as evidenced by TSH concentrations not exceeding upper normal limit before treatment. However, taking into account the wide spread of normal TSH values (ranging from 0.05 to 4.5 IU/mL), it cannot be excluded that in some patients the TSH level was actually decreased. This may be corroborated by an increase in TSH concentration occurring in 12 cases, as well as by concomitant rise in T_4 and T_3 seen after the introduction of LPD. Positive correlation between creatinine clearance and GT may indicate the negative influence of uremic toxins on thyroid activity.

Decrease in TNF-alpha level might be one of the factors responsible for the rise in the thyroid hormone concentration. TNF-alpha has been shown to influence thyroid activity by affecting TSH secretion *(26)* and action. TNF-alpha inhibits iodide transport *(27)* and synthesis of proteins engaged in hormone synthesis—thyroid peroxidase and thyroglobulin *(28)*. Moreover, TNF-alpha was found to interfere with thyroid hormone action by impairement of T_3-dependent induction of hepatic iodothyronine 5'deiodinase gene expression *(29)*.

The effect of LPD treatment on T_3, T_4, and fT_4 serum concentrations and peripheral 5'deiodinase activity was related to their level before dietary treatment. Subjects with lowest initial T_3, T_4, fT_4, and GD had the best response to the diet. Lower initial TSH was associated with a greater increase in T_3 concentration. Moreover, the effect of a low protein diet on thyroid hormone level was not seen in patients with normal initial hormone concentration. This may suggest that, before dietary intervention, subjects with thyroid hormone concentration values within the normal range consumed a diet with an appropriate amount of protein. However, the same patients in whom T_3 or T_4 serum values did change slightly or did not change at all, LPD decreased urea concentration which indicates that these patients actually decreased protein consumption in relation to pretreatment period. Thus, normal T_3 and T_4 serum concentrations before dietary management seem to result rather from the patients' overall state than from the proper composition of their diet.

A negative correlation, which was found for protein consumption and T_4/TSH ratio, suggests an influence of protein nutrition in CRF on thyroid sensitivity for TSH stimulation. Low serum fT_4 levels before dietary intervention could also be due to metabolic acidosis *(30)*. Ingestion of normal amount of protein ingested in the setting of a loss of renal function leads to retention of hydrogen ions *(31)*. With decreased protein intake, the daily acid load is reduced. Thus, improvement of acidemia might cause an increase in fT_4 concentration, although this was not directly addressed in our study.

In conclusion, low protein, low phosphorus diet, which is often prescribed to patients with moderate impairment of renal function, exerts a beneficial effect on low T_3 syndrome coexisting with renal failure. The effect of LPD on the pituitary–thyroid axis is dependent on the degree of renal functional impairement. Response of thyroidal hormones seems to be determined by narrow limits of protein intake and sufficient calorie consumption. LPD-induced decrease in TNF-alpha may also contribute to the observed effects of dietary treatment.

Materials and Methods

Patients

Seventeen male subjects aged 63 ± 10 yr (range 40–74 yr), with conservatively treated CRF [predicted creatinine clearance 39.5 ± 11.1 mL/min/1.73 m^2 (range 19.7–60.3

mL/min/1.73 m^2)] were studied before and after 8 wk on a low protein, low phosphorus diet. The causes of CRF were chronic interstitial nephritis (n = 9) and nephrosclerosis (n = 8). All the patients were on antihypertensive medications (beta-blockers, n = 6; calcium channel blockers, n = 4; and angiotensin-converting enzyme inhibitors, n = 8). All of them were also treated with drugs commonly used in CRF such as phosphate binders and diuretics. No drug regimen was modified during the study. Exclusion criteria included diabetes mellitus, proteinuria greater than 2.0 g/24 h, use of glucocorticoids, anticoagulants, or cytotoxic agents within the last 6 mo, ongoing antibiotic therapy, or renal transplantation. The study was approved by the ethics committee of the National Food and Nutrition Institute in Warsaw, and all patients gave written informed consent.

Study Design and Laboratory Methods

Dietary recommendations during the study were as follows: protein 0.6 g/kg of ideal body mass [with at least half of the protein being of high biologic value, defined as the extent to which a protein matches the amino acid composition of animal tissues *(32)*], 10 mg/kg phosphorus, 30% of calories derived from fat, and 62% of calories from carbohydrates *(33,34)*. For all the subjects an actual energy expenditure was calculated as the basic metabolic rate from the Harris and Benedict formula *(35)*, and using the "activity factor." The subjects received detailed instructions from the certified dietician (LK) on how to follow a low protein, low phosphorus diet. Hormonal and metabolic parameters, as well as weight and body composition (by bioimpedance method), were measured before and after 8 wk of dietary treatment. Patients, supervised by a dietician, recorded their food and beverage intake, including nutritional supplements if any, during an assigned 3 d period. Nutrient intake was calculated using *Dietetyk* software (JuMaR, Poznan, Poland).

All measurements, including blood sampling, were made after an overnight fasting, using standardized methods. Weight was measured to the nearest 0.1 kg, height was determined to the nearest 0.01 m. Body composition was determined by bioelectrical impedance method with BIA Akern 101/S apparatus (Akern-RJL Systems, Florence, Italy) with an operating frequency of 50 kHz at 800 μA and standard electrode locations on the right hand and foot. Fat mass was estimated using software provided by manufacturer of the apparatus.

Serum was separated after centrifugation and stored at –70°C until analyzed. Serum thyrotropin concentration was analyzed by an IRMA test, serum T_3, total and fT_4 by RIA kits (POLATOM, Warsaw, Poland). For TSH, the intraassay coefficient of variation (CV) was 1.5% and the interassay CV was 1.9%. The intraassay CV was 3.6% for T_3, 4.0% for T_4, and 4.6% for fT_4; the interassay CV was 4.8% for T_3, 3.6% for T_4, and 4.0% for fT_4. TNF-alpha level was measured by ELISA (Boehringer Mannheim, Mannheim, Germany); the within-assay CV for this test is 8.3%, and the between-assay CV is 10.8%. Serum creatinine and urea were determined by enzymatic methods using assay kits supplied by Sigma-Aldrich (Poznan, Poland). Creatinine clearance was estimated using the Cockcroft–Gault formula *(36)*. The thyroid's T_4-secretion capacity (GT) and peripheral 5'deiodinase activity (GD) were calculated using SPINAThyr v. 3.0 software *(37)*.

Thyroid's T_4-secretion capacity is determined with *(37)*:

$$G_T = \frac{\beta_T (D_T + [TSH])\,[T_4]}{\alpha_T\,[TSH]}$$

where β_T is the clearance-exponent for T_4 (1.1×10^{-6} s^{-1}), D_T is EC50 for TSH (2.75 mU/L), an α_T is the dilution factor for T_4 (0.1 L^{-1}). The sum activity of peripheral 5'deiodinase was calculated by the following equation *(37)*:

$$GD = \frac{\beta_{31} (K_{M1} + [fT_4])[T_3]}{\alpha_{31}\,[fT_4]}$$

where β_{31} is the clearance exponent for T_3 (8×10^{-6} s^{-1}), K_{M1} is the dissociation constant of Type-I-deiodinase (5×10^{-7} mol/L), and α_{31} is the dilution factor for T_3 (reciprocal of apparent volume of distribution).

Statistical Analysis

Results are expressed as means and standard deviations. p value less than 0.05 was considered statistically significant. Correlations were analyzed using Pearson's correlation coefficient. Repeated measurements were tested by Student's t-test for paired samples. Calculations were performed using *Statistica* (data analysis software system), version 6 (StatSoft, Tulsa, OK, USA).

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