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Alteration of Hypothalamic–Pituitary–Thyroid Axis Function in Non-Small-Cell Lung Cancer Patients

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Abstract

The aim of this study was to evaluate the hypothalamic–pituitary–thyroid (HPT) axis function in patients suffering from lung cancer. Thyrotropin-releasing hormone (TRH), thyroid-stimulating hormone (TSH), free thyroxine (FT4), interleukin (IL)-2, and melatonin serum levels were measured in blood samples collected every 4 hours for 24 hours from 11 healthy participants (H; ages 35-53 years) and 9 patients suffering from non-small-cell lung cancer (C; ages 43-63 years). Relationships between hormone levels overall and over time of day were evaluated within and among groups. A prominent circadian rhythm with peaks near midnight was present for TSH and melatonin serum levels in both H and C, indicating similar synchronization of the main body clock to the 24-hour environmental light–dark cycle. As regards 24-hour means in H and C, TSH was lower in C, whereas TRH, FT4, and IL-2 were higher in C, with no difference in melatonin levels. Simple linear regression, FT4 versus TRH, showed a positive correlation in H and a negative correlation in C, whereas FT4 versus TSH showed a negative correlation in both groups. For FT4 versus IL-2, a negative correlation was found in C but not for H, whereas TSH versus TRH showed no correlation for either group. Both groups were found to be similarly synchronized to the 24-hour sleep–wake schedule, but HPT axis function was altered in patients suffering from lung cancer. When compared with healthy controls, cancer patients showed modifications of hormone serum levels overall and a negative correlation between individual TRH and FT4 levels.

Keywords

hypothalamus–hypophysis–thyroid axis, lung cancer, circadian rhythm

Introduction

Alterations of neuroendocrine axes function and, more precisely, of the hypothalamic–pineal axis, hypothalamic–pituitary–adrenal axis, and GH/IGF1 axis, have been described in cancer patients.[1-7] Abnormalities in thyroid function have been found in cancer patients[8,9] and classified as "sick euthyroid" or "low triiodothyronine" syndrome.[10,11] Thyroid function is regulated by the thyroid-stimulating hormone (TSH or thyrotropin), synthesized and secreted by thyrotropic cells in the anterior pituitary gland, and TSH production is controlled by the hypothalamic thyrotropin-releasing hormone (TRH), which has immunomodulatory and neuroregulatory actions.[12]

Epidemiological studies have shown that people with thyrotropin levels indicating hyperthyroidism are at higher risk of lung cancer compared with others, including those with suggested hypothyroidism. The risk is elevated both in people with probable subclinical hyperthyroidism and more strongly in people with biochemically overt hyperthyroidism, whereas in relation to the prognosis, patients with cancer who develop hypothyroidism may experience longer survival, maybe in relationship to the role played by thyroid hormones in physiological processes crucial to growth, maturation, and metabolism.[13]

To study the circadian features of circulating thyrotropic cells in healthy participants and patients with lung cancer, we obtained blood samples every 4 hours for 24 hours and determined serum levels of TRH, TSH, and free thyroxine (FT4; to evaluate the function of the hypothalamic–pituitary–thyroid

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[HPT] axis); IL-2 (to evaluate immune activation); and melatonin (as a marker for the endogenous biological clock[14] to evaluate the synchronization of the participants to the 24-hour sleep–wake schedule).

Methods

Participants gave written informed consent, and the study was approved by the local scientific and ethical committee. Peripheral blood samples were collected at intervals of 4 hours for 24 hours from 11 healthy male participants (aged 35-53 years, mean ± SD = 43.6 ± 5.9 years) and 9 male patients suffering from non-small-cell lung cancer (aged 43-63 years, mean ± SD = 51.0 ± 7.2 years). Inclusion criteria for healthy participants were age <80 years, body mass index (BMI) >20 and <30, normal physical activity level, no psychiatric disorder, no alcohol intake, no chronic conditions, and normal blood pressure levels. Health status was assessed by medical history and physical examination, basal screening with blood and urine tests, ECG, chest X ray, and upper- and lower-abdominal ultrasound scans. Inclusion criteria for patients suffering from lung cancer were age <80 years, BMI >20 and <30, normal physical activity level, no treatment (surgery, chemotherapy, or radiotherapy), performance status >80% by Karnofsky performance status scale or <2 by ECOG score, no psychiatric disorder, no alcohol intake, no chronic conditions, and normal blood pressure levels. Tumor cell type (non-small-cell lung cancer) and stage of tumor were evaluated by clinical examination; bronchoscopy; computed tomography (CT) of the brain, chest, and upper abdomen; and ultrasonography of the liver.

There were 3 cases of squamous cell carcinoma and 6 of adenocarcinoma. The pathological diagnosis was based on light microscopy according to the WHO classification. Tumors were staged according to the TNM classification of the International Union Against Cancer staging system after reviewing the clinical, radiological, and pathological data. The numbers of pT1, pT2, and pT3 to pT4 cases were 2, 4, and 3, respectively. All 9 cases showed metastasis to regional lymph nodes. There were 5, 2, and 2 cases, respectively, of stages II, III, and IV. The groups were matched closely to avoid any bias related to sex, BMI, and/or seasonality of sampling, and all participants were subjected to the same social routine, with identical meal times and sleep/wakefulness schedules during the week preceding the sampling day (lights on at 07:00 hours and lights off at 23:00 hours. Sleep was allowed only between 23:00 hours (lights off) and 07:00 hours (lights on). During the daytime between 07:15 hours and 20:15 hours, participants stayed in the clinic, and standardized meals were provided at appropriate times for breakfast (07:30 hours), lunch (12:30 hours), and dinner (18:30 hours). During the overnight sampling period, a dim blue light (<100 lux) was used.

Blood samples were centrifuged immediately after collection and frozen at –20°C for later determination of TRH, TSH, FT4, melatonin, and IL-2. All samples were analyzed in duplicate in a single assay. The intraassay and interassay coefficients of variation were below 5% and 6% for TRH, 5% and 8% for TSH, 3% and 6% for FT4, 4% and 7 % for melatonin, and 5% and 7% for IL-2. Melatonin was measured by radioimmunoassay (RIA; Melatonin RIA kit, Buehlmann Laboratories AG, Schonenbuch, Switzerland), TRH by RIA ("Frederic Joliot-Curie" National Research Institute for Radiobiology and Radiohygiene, Budapest, Hungary), TSH by immunoassay in electrochemiluminescence (ECL; TSH Cobas Roche, Burgess Hill, West Sussex, England), FT4 by immunoassay in ECL (FT4 Cobas Roche, Burgess Hill, West Sussex, England), and IL-2 by immunoenzymatic assay (IL-2 EIA, Technogenetics, Milano, Italy).

Statistical Analysis

Statistical evaluation of hormone serum levels was performed by noninferential descriptive biometric analyses, including 1-way ANOVA performed between the time points for each variable by group using original data and values transformed to percentage of individual 24-hour means to look for a time effect, and Student's *t* test between means overall and at each time point to look for any differences between groups. Analysis of each normalized time series for circadian rhythm characteristics was accomplished by the single cosinor procedure[15] by approximation of the time series data by the least-squares linear regression of a single-component (24 hour) cosine waveform using the Chronolab statistical package.[16] A *P* value for the rejection of the zero-amplitude assumption was determined by an *F*-test of the variance accounted for by the fit of the cosine versus the variance accounted for by a straight-line approximation of the arithmetic mean. Rhythm detection was considered statistically significant if $P \leq .05$ and borderline significant if $P \leq .10 > .05$. Rhythm characteristics determined from the fitted cosine include the MESOR (the middle of the cosine representing an adjusted 24-hour average (which equals the arithmetic mean if sampling is equidistant and there are no missing data or time points), the amplitude (*A*, half the distance from the peak and trough of the best-fitting curve, with 2*A* indicating the predictable range of change), and the phase of the cosine model (φ, referred to local midnight), with the peak of the cosine termed the *acrophase* (aφ; acro = peak). A linear regression was also applied to the following hormone pairs for each group to compare the direction of relationships: TRH versus TSH, TRH versus FT4, TSH versus FT4, and IL-2 versus FT4.

Results

Results of ANOVA and cosinor analyses for time effects for each variable are listed by group in Table 1. For each variable, a time plot (chronogram) was created to show the time point means ± standard errors (SE) of serum TRH,

Table 1. Statistical Evaluation of Circadian Variations in Serum Levels of TRH, TSH, FT4, Melatonin, and IL-2 in Healthy Participants and Lung Cancer Patients[a]

			Analysis for Time Effect: ANOVA				Single Cosinor Model (Period = 24 hours)					
			Original Units		Percentage of Mean			Original Units	Percentage of Mean			
Variable	Group	n	F	P	F	P	24-Hour Mean ± SE	P	P	Amp(%) ± SE	aϕ ± SE	(95% Limits)
TRH	H	66	0.2	.963	1.0	.407	0.48 ± 0.07	.661	.189	13.5 ± 7.3	02:17 h ± 02:04 h	-
TRH	C	54	0.2	.944	1.8	.137	0.60 ± 0.05[b]	.684	.080	8.6 ± 3.7	23:16 h ± 01:40 h	-
TSH	H	60	2,2	.068	12.3	<.001	1.72 ± 0.11[b]	.006	<.001	30.1 ± 3.9[b]	23:32 h ± 00:30 h	(22:32, 00:32 h)
TSH	C	54	0.3	.907	4.1	.004	1.34 ± 0.13	.657	<.001	14.6 ± 4.1	01:00 h ± 01:04 h	(22:44, 03:16 h)
FT4	H	66	0.1	.995	1.6	.180	1.22 ± 0.06	.984	.835	0.41 ± 0.68	16:18 h ± 06:21 h	-
FT4	C	54	0.1	.999	0.6	.717	1.30 ± 0.03[b]	.966	.508	0.78 ± 0.67	19:36 h ± 03:16 h	-
Melatonin	H	66	1.1	<.001	36.9	<.001	37.60 ± 3.43	<.001	<.001	63.9 ± 7.4	01:35 h ± 00:25 h	(00:40, 02:28 h)
Melatonin	C	54	17.6	<.001	40.0	<.001	33.19 ± 3.94	<.001	<.001	67.7 ± 10.2	01:36 h ± 00:34 h	(00:24, 02:44 h)
IL2	H	66	0.1	.995	0.2	.961	0.44 ± 0.05	.921	.906	2.5 ± 5.7	18:18 h ± 08:36 h	-
IL2	C	54	0.5	.796	0.7	.593	0.54 ± 0.04[b]	.594	.376	11.9 ± 8.4	16:14 h ± 02:42 h	-

Abbreviations: TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; FT4, free thyroxine; IL-2, interleukin 2; SE, standard error.
[a]At each of 6 times (02:00, 06:00, 10:00, 14:00, 18:00 & 22:00 h), blood samples were obtained from 11 healthy men (H), aged 35 to 53 years, and 9 men, aged 43 to 63 years, with non-small-cell lung cancer (C). Analyses for time effect: ANOVA, analysis of variance across time point means using 66 values (6/participant) in original units and as percentage of individual mean; cosinor, least-squares fit of single or multiple component cosine to all data in original units or as percentage of individual mean; 24-hour mean, MESOR; Amp, amplitude of cosine model; *a*ϕ, acrophase (peak of cosine in hours:minute from local midnight); *a*ϕ, 24-hour cosine peak (95% limits shown if $P \leq .05$).
[b]After MESOR or amplitude indicates significant difference from controls by parameter test. No difference found for any acrophase comparison. Units: ng/mL for TRH, μU/mL for TSH, ng/dL for FT4, pg/mL for melatonin, and IU/mL for IL-2.

TSH, FT4, IL-2, and melatonin in healthy participants compared with lung cancer patients, along with the superimposed best-fitting 24-hour cosine for each group (Figure 1).

The hormone melatonin showed a prominent 24-hour oscillation in both study groups, with the highest values occurring at night (Figure 1, bottom left panel). ANOVA detected a significant time effect ($P < .001$), and cosinor analysis detected a significant 24-hour rhythm ($P < .001$) in each group, with virtually identical rhythm characteristics (mean ± SE): MESOR, 37.6 ± 2.7 versus 33.2 ± 2.8 pg/mL; amplitude, 64% ± 7% versus 68% ± 10%; and acrophases at 01:35 hours and 01:48 hours for healthy (H) versus cancer (C) participants, respectively (Table 1). There was no statistically significant difference between groups for any of these 3 parameters. The timing of this "marker" rhythm thus confirmed identical group synchronization of the main body clock (located in the suprachiasmatic nucleus of the hypothalamus) by the participants to their 24-hour environmental light–dark (sleep–wake) schedule.

Both groups also showed a significant 24-hour rhythm in TSH ($P < .001$ from ANOVA and cosinor; Table 1), with higher values at night (Figure 1, upper right panel). The timing of the TSH rhythm in both groups estimated by the acrophase (H = 23:32 hours, C = 01:00 hours) was not significantly different ($P = .228$). However, the 24-hour mean was lower by −22% in cancer patients (H = 1.72 ± 0.11; C = 1.34 ± 0.13 μU/mL; $P = .032$) and the amplitude by nearly 50% (H = 30% ± 4%; C = 15 ± 4%; $P < .001$).

No significant time effects by ANOVA or 24-hour rhythm by cosine analyses were detected in TRH, FT4, or IL-2 in either group, possibly because of the extremely low detection levels of each hormone (Table 1), although TRH values appeared to be lower during the day and higher at night for each group (Figure 1). However, significant differences were observed in 24-hour means between the 2 groups, where overall TRH, FT4, and IL-2 were higher in the cancer group: TRH (+25%: H = 0.48 ± 0.03 vs C = 0.60 ± 0.02 ng/mL; $P = .002$), FT4 (+7%: H =1.22 ± 0.02 vs C = 1.30 ± 0.03 ng/dL; $P = .030$), and IL-2 (+23%: H = 0.44 ± 0.02 vs C = 0.54 ± 0.04 IU/mL; $P = .030$).

When cancer patients were separated by stage of disease (ie, stage II, n = 5 patients; stages III and IV, n = 4 patients) and compared with controls using the *t* test, the 24-hour means for the 2 subgroups suggested more noticeable deviations from the control group than when all cancer patients were combined. Overall levels in the stage III to IV group were significantly increased for TRH by 42% (0.48 vs 0.68 ng/mL) and IL-2 by 45% (0.44 vs 0.64 IU/mL) and decreased for TSH by −41% (1.72 vs 1.01 μU/mL) and melatonin by −22% (37.6 vs 29.2 pg/ml), whereas FT4 showed an increase for the stage II group by 13% (1.22 vs 1.38 ng/dL) but was unchanged in the stage III-IV group (1.22 vs 1.20 ng/dL; Table 2).

When using simple linear regression to compare relationships between variables for each group, no significant correlation was found for TSH versus TRH in either group, whereas FT4 versus TRH showed a positive correlation in controls ($r = 0.36$; slope = +0.46; $P = .003$) and a negative correlation in cancer patients ($r = 0.49$; slope = −0.38; $P < .001$; Figure 2). When comparing FT4 versus TSH, a

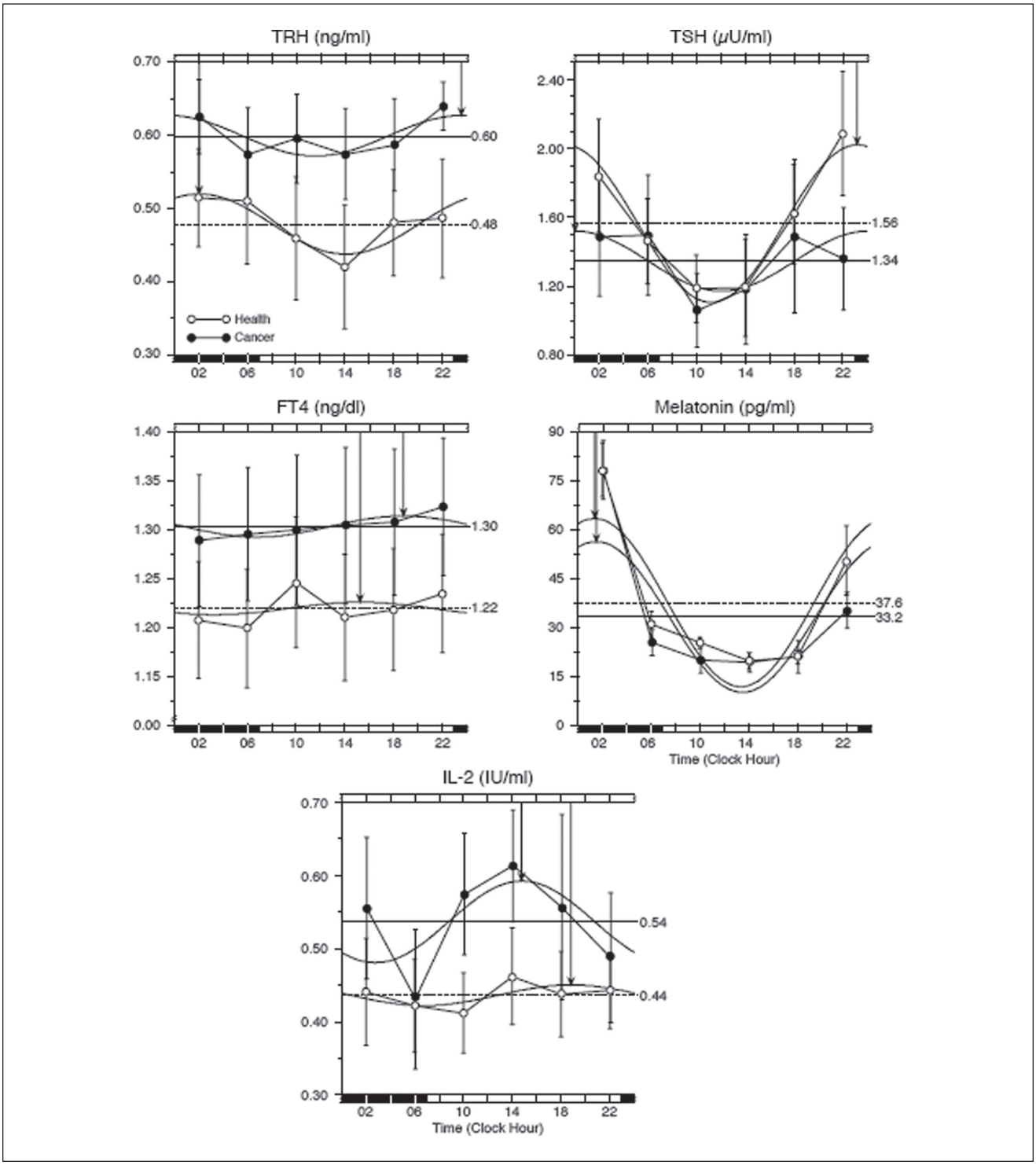

Figure 1. *x-y* Plots showing 24-hour profiles of TRH, TSH, FT4, melatonin and IL-2 in 11 healthy men (H; n = 10 for TSH) and 9 non-small-cell lung cancer male patients (C). Values of *y* are expressed as mean ± SE[a]

Abbreviations: TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; FT4, free thyroxine; IL-2, interleukin 2.

[a](•) = $P < .05$ from *t* test comparing time point means; overall 24-hour means significantly higher in C for TRH, FT4, and IL-2 and lower for TSH (see Table 1). Circadian rhythm significant at $P < .001$ for TSH and melatonin in both groups but not for TRH, FT4, or IL-2. Arrow = acrophase (time of cosine peak); dark bar = sleep/rest from 23:00 hours to 07:00 hours.

Table 2. Comparison of 24-Hour Mean Serum Levels for TRH, TSH, FT4, Melatonin, and IL-2 in Healthy Participants and Lung Cancer Patients[a]

		Healthy Participants		Lung Cancer Stage II		Lung Cancer Stage III-IV	
Variable	Units	MESOR	±SE	MESOR	±SE	MESOR	±SE
TRH	ng/mL	0.48	±0.03	0.53	±0.03	0.68[b]	±0.01
TSH	μU/mL	1.72[b]	±0.11	1.60	±0.22	1.01	±0.08
FT4	ng/dL	1.22	±0.02	1.38[b]	±0.04	1.20	±0.02
Melatonin	pg/mL	37.60[b]	±3.49	36.41	±4.87	29.16	±5.23
IL-2	IU/mL	0.44	±0.02	0.45	±0.05	0.64[b]	±0.05

Abbreviations: TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; FT4, free thyroxine; IL-2, interleukin 2; SE, standard error.
[a]At each of 6 times (02:00, 06:00, 10:00, 14:00, 18:00 & 22:00 h), blood samples were obtained from 11 healthy men (H), aged 35 to 53 years, and 9 men, aged 43 to 63 years, with non-small-cell lung cancer (C). Analyses for time effect: ANOVA, analysis of variance across time point means using 66 values (6/participant) in original units and as percentage of individual mean; cosinor, least-squares fit of single or multiple component cosine to all data in original units or as percentage of individual mean; 24-hour mean, MESOR; Amp, amplitude of cosine model; $a\phi$, acrophase (peak of cosine in hours:minute from local midnight); $a\phi$, 24-hour cosine peak (95% limits shown if $P \leq .05$).
[b]After MESOR or amplitude indicates significant difference from controls by parameter test. No difference found for any acrophase comparison. Units: ng/mL for TRH, μU/mL for TSH, ng/dL for FT4, pg/mL for melatonin, and IU/mL for IL-2.

negative correlation was found for both healthy ($r = 0.33$; slope = –1.41; $P = .011$) and cancer groups ($r = 0.52$; slope = –2.42; $P < .001$), whereas for FT4 versus IL-2, a negative correlation was found for the cancer group ($r = 0.55$; slope = –0.74; $P < .001$) but not in healthy controls ($r = 0.04$; slope = –0.04; $P = .773$; Figure 3).

Discussion

TSH secretion is characterized by circadian rhythmicity in variation of serum levels that reach the zenith during the night.[17,18] The hypothalamic tripeptide TRH plays a central role in the regulation of pituitary TSH secretion, and TSH is the predominant regulator of thyroid growth and thyroxine (T4) and triiodothyronine (T3) synthesis and secretion. The biological functions of TRH extend far beyond regulation of the thyroid axis because greater than two thirds of immunoreactive TRH in the central nervous system is detected outside the thyrotropic zone of the hypothalamus. TRH has been implicated in the regulation of arousal, autonomic function, control of circadian rhythmicity, endotoxic and hemorrhagic shock, mood, pain perception, seizure activity, and spinal motor function.[19-30]

TRH-producing cells in the paraventricular nucleus release TRH via the hypophyseal portal system to the anterior pituitary gland, and there is insufficient evidence that serum TRH is a good reflection of this local TRH production by the paraventricular nucleus. The circulating levels of TRH may be related to the hypothalamic secretion and to the neuropeptide analogs that come from many different tissues. Because of the very short half-life of the hormone, its intracerebral/central site of action, and the presence in the peripheral blood of many TRH-like tripeptides, the data in this study regarding TRH have to be interpreted with care.

Physiologically, a strong correlation exists between the serum concentrations of TSH and thyroid hormones, such that the amounts of thyroid hormone available to peripheral tissues are maintained within narrow limits. The sensitivity of the thyrotrophs is such that reductions in serum T3 and T4 concentrations of as little as 10% to 15% result in 50% to 100% increases in serum TSH concentrations. These actions are mediated through TSH binding to the TSH receptor located on the plasma membrane of thyroid follicular cells, and the feedback mechanisms that regulate TRH, TSH, T3, and T4 concentrations act very rapidly (in a time varying from half an hour to a few hours).[31,32]

Data obtained in our current study confirm our previous results obtained in a smaller number of participants with a less stringent experimental design and time-related procedure[33] and show decreased nocturnal TSH serum levels with increased TRH and FT4 serum levels in lung cancer patients with respect to healthy participants. This phenomenon resembles reduced pituitary response to protirelin stimulation and enhanced sensitivity of thyroid to thyrotropin. Pituitary response to TRH is evaluated by the TRH stimulation test that measures the increase of pituitary TSH in serum in response to the administration of synthetic TRH. The magnitude of the TSH response to TRH is modulated by the thyrotroph response to active thyroid hormone and is thus almost always proportional to the concentration of free thyroid hormone in serum. The response is exquisitely sensitive to minor changes in the level of circulating thyroid hormones, and a direct correlation between basal serum TSH values and the maximal response to TRH has been observed even in the absence of thyroid hormone abnormalities, suggesting that there may be a fine modulation of pituitary sensitivity to TRH in the euthyroid state.[34-36]

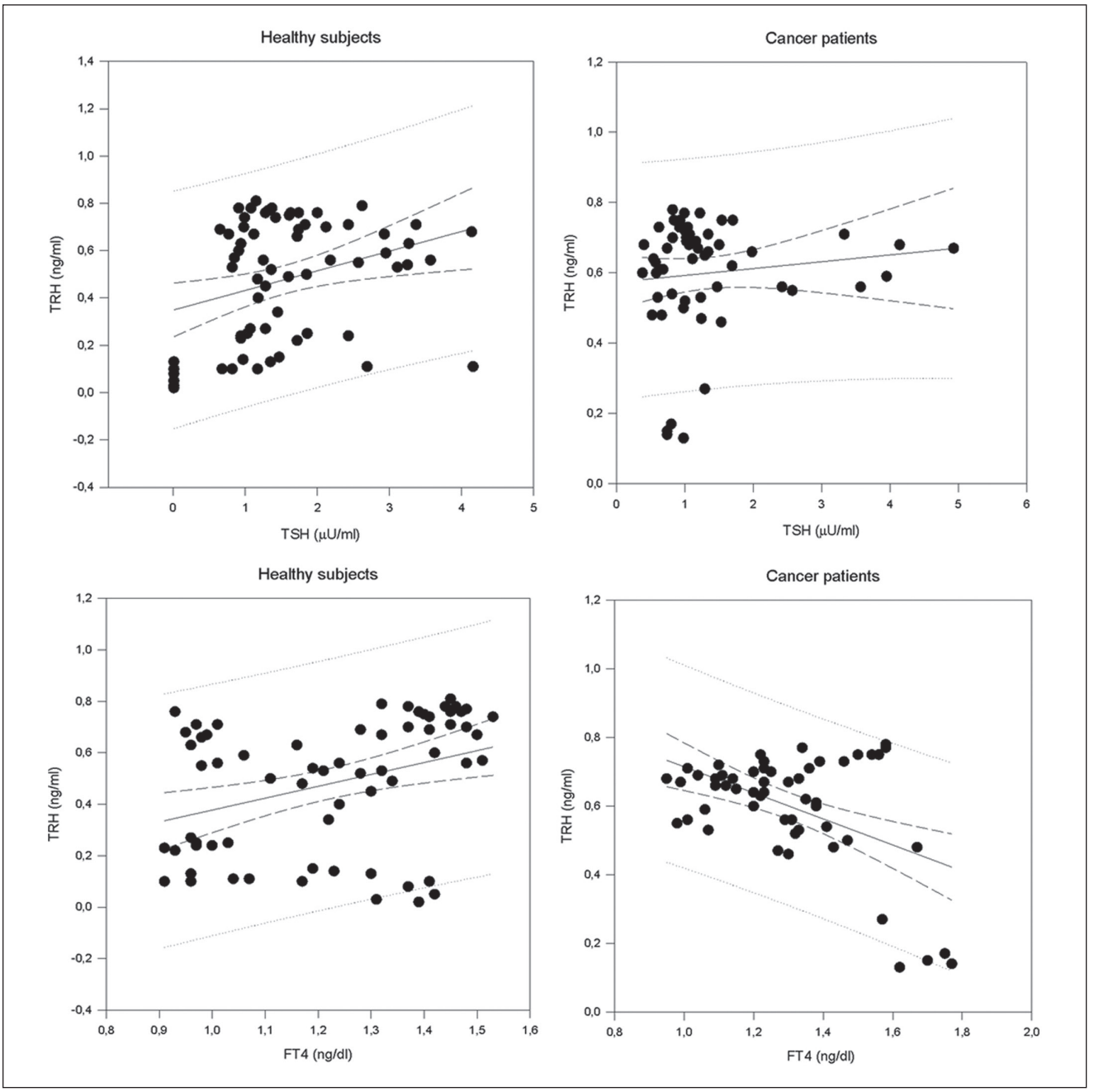

Figure 2. *x-y* Plots showing linear regression lines with 95% confidence limits between all original 4-hourly values of TRH versus TSH and TRH versus FT4 serum levels in 11 healthy participants and 9 small-cell lung cancer patients. No significant correlation was found for TSH versus TRH in either group (top panels), whereas FT4 versus TRH showed a positive correlation in controls ($r = 0.36$; slope = +0.46; $P = .003$) and a negative correlation in cancer patients ($r = 0.49$; slope = –0.38; $P < .001$)—bottom panels
Abbreviations: TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; FT4, free thyroxine; IL-2, interleukin 2.

A possible explanation of the conditions found in our study may be represented by TRH resistance in lung cancer patients. Hormone resistance syndromes can be broadly defined as reduced or absent end-organ responsiveness to a hormone. Several general mechanisms have been identified,[37-39] and a quantitative reduction in receptor or defects in postreceptor signaling pathways seem to be the more probable explanations; but a different explanation may be plausible. A subset of depressed patients demonstrated a diminished TSH response to TRH stimulation. The pathophysiological mechanisms that account for the blunted TSH response have not been elucidated, although downregulation

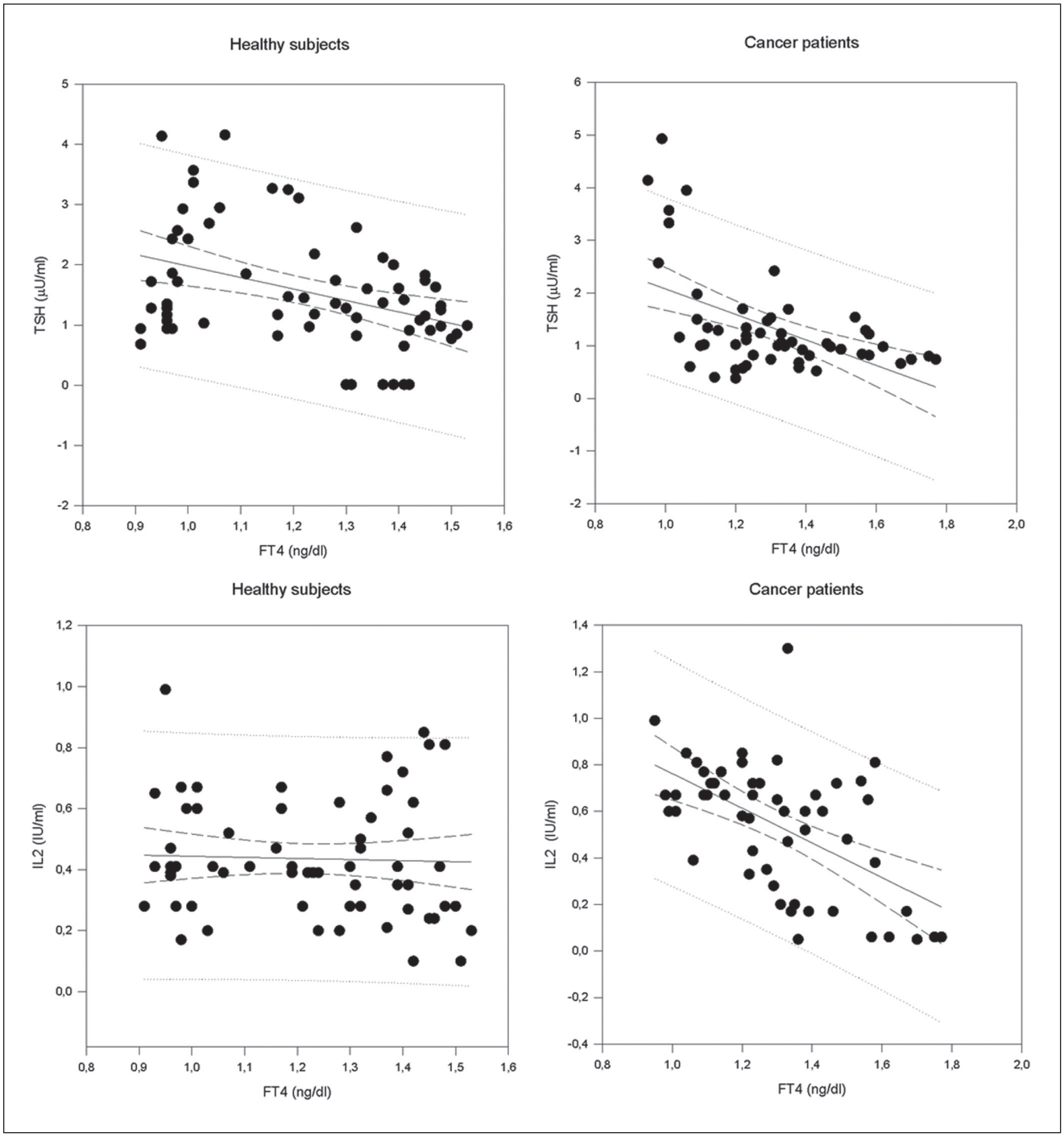

Figure 3. *x-y* Plots showing linear regression lines with 95% confidence limits between all original 4-hourly values of TSH versus FT4 and IL-2 versus FT4 serum levels in 11 healthy participants and 9 small-cell lung cancer patients. When comparing FT4 versus TSH, a negative correlation was found for both healthy ($r = 0.33$; slope = –1.41; $P = .0011$) and cancer groups ($r = 0.52$; slope = –2.42; $P < .001$)—top panels. When comparing FT4 versus IL-2, a negative correlation was found for the cancer group ($r = 0.55$; slope = –0.74; $P < .001$), but not in healthy controls ($r = 0.04$; slope = –0.04; $P = .773$)—bottom panels

Abbreviations: TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; FT4, free thyroxine; IL-2, interleukin 2.

of TRH pituitary receptors has been suggested, and particularly, thyroid axis abnormalities in depression may demonstrate a circadian component.[40] In our lung cancer patients, TRH serum levels were elevated by 25% with no significant rhythmicity, whereas TSH secretion was reduced by 22% while maintaining circadian rhythmicity. The stimulatory

effect of TRH is specific for pituitary TSH, and the magnitude of the response is greater at 23:00 hours than at 11:00 hours, in accordance with the circadian pattern of the basal TSH level, which correlates to its response to TRH.[41] This evidence seems to highlight the importance of normal nyctohemeral rhythmic variations and the dynamics of secretion for the physiological TSH action on peripheral target organs and structures. This evidence may be of particular importance in lung cancer patients considering the immunoregulatory role played by the HPT axis. TSH has been shown to have a variety of immune-regulating cytokine-like activities that enhance lymphocyte activity and can affect the magnitude of antibody and cell-mediated responses of peripheral lymphocytes.[42-45] In addition, thyroid hormones modulate lymphocyte reactivity via the regulation of protein kinase C content in lymphocytes, which could be involved in altered responsiveness to mitogen-induced stimulation of proliferative responses, independently of TSH levels.[46]

On the other hand, the changes in the pituitary–thyroid axis function may be mediated by the inflammatory cytokines, and in our cancer patients, we have documented increased levels of IL-2 by 23% overall, reflecting a global activation of immune and inflammatory mechanisms. IL-2 stimulates the synthesis of interferon-γ in peripheral leukocytes and also induces the secretion of IL-1, tumor necrosis factor (TNF)-α, and TNF-β. Altered pituitary–thyroid axis function, with increased FT4 and decreased TSH levels, has been described in lung cancer patients treated with IL-2 infusion, and reports in the scientific literature suggest that therapy with recombinant interleukin (IL)-2 may result in thyroid dysfunction, highlighting the need of tight control of thyroid function in those treated with this cytokine.[47-49] This indirect evidence may explain the negative correlation found between FT4 and IL-2 serum levels in our cancer patients (but not in controls). Also, in agreement with the observation that cancer patients with hyperthyroidism have a worse prognosis, in our small group of lung cancer patients with advanced stages III and IV of disease, we found greater pituitary suppression when compared with controls, as indicated by the 41% decrease in TSH secretion (1.72 vs 1.01 μU/mL) despite unchanged FT4 serum levels (1.22 vs 1.20 ng/dL).

Conclusion

HPT axis function is altered in lung cancer patients and is characterized by a significant overall increase, as compared with controls, of 25% for TRH, 7% for FT4, and 23% for IL-2, and a decrease of 22% for TSH. Levels of FT4 versus TRH and FT4 versus IL-2 each showed a strong negative relationship in cancer patients versus a positive or neutral one in healthy controls. In spite of overall decreased levels in cancer, both TSH and melatonin showed circadian rhythms that were identically timed with controls, indicating synchronization to the environmental sleep/wake schedule. Although thyroid hyperfunction in lung cancer patients may have a negative prognostic value, it might still be the target of a possible chronotherapeutic approach to treatment(s)[50,51] in patients who nevertheless maintain circadian rhythmicity in key body rhythm markers.

Declaration of Conflicting Interests

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