Changes in the Tumor Marker Concentration in Female Patients with Hyper-, Eu-, and Hypothyroidism

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Abstract

The levels of 6 circulating tumor markers were evaluated in a total of 131 female subjects with altered thyroid states; 36 normal subjects, 46 hyperthyroid patients with Graves' disease, and 49 primary hypothyroid patients.

The mean CEA concentration was observed to be significantly higher ($p < 0.02$) in hypothyroid patients than in normal and hyperthyroid patients (1.1 ± 0.1 ng/ml, 0.8 ± 0.1 ng/ml and 0.8 ± 0.1 ng/ml, respectively). Similarly, the mean serum CA 125 concentration in hypothyroid patients was higher ($p < 0.02$) than in normal and hyperthyroid patients (13.0 ± 2.6 U/ml, 7.6 ± 1.1 U/ml and 5.5 ± 0.8 U/ml, respectively), and the mean serum CA 15-3 concentration in hypothyroid patients was significantly higher than in normal subjects ($p < 0.01$) and hyperthyroid patients ($p < 0.001$) (16.2 ± 0.9 U/ml, 13.9 ± 0.6 U/ml and 10.6 ± 0.5 U/ml, respectively). No statistical difference was found in mean CA 19-9 in the three subject groups. AFP in the hypothyroid patients (3.6 ± 0.3 ng/ml) was significantly higher ($p < 0.05$) than in normal subjects (2.6 ± 0.2 ng/ml) and hyperthyroid patients (1.7 ± 0.2 ng/ml) ($p < 0.01$). On the other hand, serum ferritin was low in the hypothyroid patients (65.9 ± 8.0 ng/ml) and significantly increased (69.1 ± 9.0 ng/ml) ($p < 0.02$) with the normalization of thyroid function. In hyperthyroidism, serum ferritin (70.2 ± 7.0 ng/ml) was significantly higher than in the hypothyroid patients ($p < 0.01$).

A significant inverse correlation was found between AFP, CEA, CA 15-3, and CA 125 with T_3 , T_4 , FT_3 and FT_4 . There was a significant positive correlation between ferritin and FT_3 and FT_4 in hyperthyroid patients. Further, the same positive correlation was observed in all subjects. Our data suggest that when patients are suffering from hyper- or hypothyroidism, caution should be taken when reading the tumor marker concentration.

In recent years, several tumor markers have been developed and used in clinical studies.

Although increased circulating carcino-embryonic antigen (CEA) in hypothyroidism (Amino *et al.*, 1981) and ferritin in hyperthyroidism (Chamel, Macaron and Macaron, 1982; Takuno *et al.*, 1988) have been reported, little information is available regarding other tumor markers in patients with no tumors but altered thyroid states. We consider it is very important to eva-

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luate the concentration of circulating tumor markers, in addition to a comparison with CEA, and ferritin, in patients with altered thyroid states.

Materials and Methods

Thirty-six normal female subjects (aged 23 ± 2), 46 female hyperthyroid patients with Graves' disease (aged 24 ± 4) and 49 female patients with primary hypothyroidism (aged 27 ± 5) were selected. All were non-smokers. No patients had diseases with tumors or any clinical or laboratory evidence of hepatic, gastrointestinal or pancreatic diseases. We measured the serum hormone concentration with commercially available kits by immunoradiometric assay or radioimmunoassay as follows [Hashimoto, Migita and Matsubara, 1986]:—Free T_3 (FT_3) and Free T_4

(FT_4) using Amerlex kits (Amersham, UK); T_3 , T_4 and TSH using EIKEN kits (EIKEN ICL JAPAN); CEA and α -fetoprotein (AFP) using Dainabot kits (Dainabot Co. JAPAN); ferritin using an LPIA kit (DIA-IATRON Co. JAPAN). Serum carbohydrate antigens (CA 15-3, CA 125 and CA 19-9) were measured with Fujirebio kits (Fujirebio INC. JAPAN), as described previously (Hashimoto *et al.*, 1989). Serum was separated by centrifugation at 4°C and stored at -20°C until the assay was undertaken. All the samples were measured in the same assay in order to avoid interassay variations. Precision of within-run of CEA, CA 125, CA 15-3, CA 19-9, AFP and ferritin was less than 3.5%, 4.3%, 5.6%, 4.4%, 3.8%, and 4.1% respectively.

Statistical methods

Data are expressed as the mean $\pm$ standard error. The significance of the difference between mean values was evaluated by Student *t*-test.

Table 1. Tumor Marker Concentrations in Patients with Altered Thyroid States and Normal Subjects.

Tumor Markers	Hypothyroidism	Normal subjects	Hyperthyroidism
CEA (ng/ml)	1.1 ± 0.1	0.8 ± 0.1	0.8 ± 0.1
CA 125 (U/ml)	13.0 ± 2.6	7.6 ± 1.1	5.5 ± 0.8
CA 15-3 (U/ml)	16.2 ± 0.9	13.9 ± 0.6	10.6 ± 0.5
CA 19-9 (U/ml)	18.3 ± 2.1	20.6 ± 2.4	17.4 ± 1.7
AFP (ng/ml)	3.6 ± 0.3	2.6 ± 0.2	1.7 ± 0.2
Ferritin (ng/ml)	65.9 ± 8.0	69.1 ± 9.0	$70.2 \pm 7.0^{**}$
+ $P < 0.05$, * $P < 0.02$, ** $P < 0.01$, *** $P < 0.001$			

Results

Tumor Marker Levels in Altered Thyroid States

As shown in Table 1, the mean CEA level was significantly higher ($p < 0.02$) in the hypothyroid patients than in the normal and hyperthyroid subjects. The values in the hyperthyroid and normal patients were similar.

The mean serum CA 125 concentration in hypothyroid patients was found to be significantly higher ($P < 0.02$) than in normal and hyperthyroid subjects. The CA 125 values in the normal and hyperthyroid subjects were not significantly different.

The CA 15-3 concentration in the hypothyroid patients was significantly higher than in the normal subjects ($p < 0.01$) and hyperthyroid subjects ($p < 0.001$).

No statistical difference in CA 19-9 in hypothyroid, euthyroid and hyperthyroid patients was found.

The AFP concentration in the hypothyroid patients was significantly higher ($p < 0.05$) than in normal subjects and hyperthyroid patients ($p < 0.01$). On the other hand, serum ferritin was low in the hypothyroid patients and significantly increased ($p < 0.02$) with the normalization of thyroid function. In hyperthyroidism, the serum ferritin concentration was significantly higher than in the hypothyroid subjects ($p < 0.01$).

Table 2. Regression Analysis between Tumor Markers and Thyroid Related Hormones in Patients with Altered Thyroid States.

n=number of patients;

r=coefficient of correlation;

p=statistical significance (p value; < means less than);

ns=not significant

Tumor markers	hormones	T ₃	T ₄	FT ₃	FT ₄	TSH
CEA	n	81	82	86	86	89
	r	-0.243	-0.271	-0.226	-0.153	0.465
	p	<0.05	<0.02	<0.05	ns	<0.001
CA 125	n	80	81	86	99	87
	r	-0.282	-0.304	-0.244	-0.264	0.128
	p	<0.02	<0.02	<0.05	<0.01	ns
CA 15-3	n	81	82	85	98	87
	r	-0.467	-0.496	-0.411	-0.423	0.357
	p	<0.001	<0.001	<0.001	<0.001	<0.001
CA 19-9	n	81	82	86	99	89
	r	-0.068	-0.076	-0.012	-0.026	0.041
	p	ns	ns	ns	ns	ns
AFP	n	79	80	85	97	87
	r	-0.432	-0.444	-0.402	-0.367	0.565
	p	<0.001	<0.001	<0.001	<0.001	<0.001
Ferritin	n	81	82	86	99	89
	r	0.146	0.108	0.231	0.277	0.049
	p	ns	ns	<0.05	<0.01	ns

Correlation between tumor markers and thyroid function

The correlation between the tumor markers and thyroid hormones and TSH are shown in Table 2. There was a significant inverse correlation between AFP, CEA, CA 15-3, and CA 125 with T_3 , T_4 , FT_3 and FT_4 . Also, a significant positive correlation was found between AFP, CEA and CA 15-3 with TSH and between ferritin with FT_3 and FT_4 . No correlation between CA 19-9 and thyroid hormones was found.

It can be seen that the coefficients of correlation (r) between tumor markers and thyroid hormones ranged from $r = -0.226$ to $r = -0.496$. The coefficients of correlation between tumor markers and TSH were all less than $r = 0.565$.

Discussion

Our present results confirmed the previously obtained observations that serum CEA is increased in hypothyroidism (Ami-

no *et al.*, 1981) and that serum ferritin is increased in hyperthyroidism (Chamel, Macaron and Macaron, 1982; Takuno *et al.*, 1988). Moreover, in the same patients, we demonstrated new evidence that CA 15-3, CA 125 and AFP are also increased in hypothyroidism (Table 1). It is well known that serum CA 125 increases during menses (Mastropaolo *et al.*, 1986) therefore the results for CA 125 in premenopausal women should be interpreted with caution. Experiments in 12 patients (6 primary hypothyroidism, 6 hyperthyroidism) performed during the early follicular phase of the menstrual cycle (D_2-6), demonstrated that circulating CA 125 levels were higher in primary hypothyroid (18.1 ± 3.1 U/ml) than in hyperthyroid patients (6.4 ± 0.9 U/ml) ($P < 0.02$). These data confirmed that the serum CA 125 concentration was not affected by the menstrual cycle, but was increased in hypothyroidism. We assume that this pattern would be repeated throughout all the phases of the menstrual cycle. CA 19-9 did not change in the altered thyroid states. The difference in the CA

Fig. 1. Graphs showing the correlations between CEA, AFP and TSH concentrations in patients with primary hypothyroidism.

19-9 results as compared with the other carbohydrate antigens may be due to the Lewis blood-type.

Four of six tumor markers (67%) increased in hypothyroidism. However, ferritin increased in hyperthyroidism. Primarily, ferritin is a tissue protein with the greatest concentration in liver, spleen and bone marrow (Chiancone, Stefanini and Antonini, 1980). The increase in serum ferritin in hyperthyroidism may reflect an expansion of the iron storage induced by ineffective erythropoiesis, but the true pathogenesis is not clear. It may be a physiological pattern.

In contrast, several serum components, such as myoglobin (Kasai, 1979), creatine phosphokinase (CPK), lactic dehydrogenase (LDH) and aspartate aminotransferase (AST), etc., increase in hypothyroid patients. AFP, CEA, CA 15-3, and CA 125 similarly increased in hypothyroidism.

Amino *et al.* (1981) first demonstrated a significant inverse correlation between log serum CEA and serum T_4 in patients with

a altered thyroid state. They also discovered a positive correlation between CEA and TSH in patients with Hashimoto's disease. We confirmed their findings. In addition, we found new evidence demonstrating a positive correlation between AFP and TSH in patients with an altered thyroid state (Table 2). Furthermore, we found a positive correlation between CEA, AFP and TSH in patients with primary hypothyroidism (Fig. 1). Amino *et al.* (1981) also observed that the increase in CEA was significantly related to the estimated duration of primary hypothyroidism. We confirmed their observations, not only concerning CEA but AFP also.

As shown in Figs. 2 and 3 and Table 2, there was a significant inverse correlation between CEA, AFP, CA 125 and CA 15-3 with T_3 , T_4 , FT_3 and FT_4 . A positive correlation between CEA, CA 15-3 and AFP with TSH was also observed (Table 2).

Takuno *et al.* (1988) demonstrated a significant positive correlation between serum ferritin and FT_3 or FT_4 in patients with

Fig. 2. Graphs showing the correlations between AFP, CA 15-3 and T_3 concentrations in patients with altered thyroid states.

Fig. 3. Graphs showing the correlations between CA 125, CA 15-3 and T₄ concentrations in patients with altered thyroid states.

hyperthyroidism, which was confirmed in our study.

Recently, Westermarck *et al.*, (1988) reported the impact of the amount of thyroid hormone on the serum concentration of insulin-like growth factor 1 (IGF-I) and urinary epidermal growth factor (EGF) in hyper- and hypothyroidism. Furthermore, the oncogene concentration is also reported to be altered in hyper- and hypothyroidism (Franklyn and Sheppard, 1988; Nunes *et al.*, 1987). Considering these findings, the synthesis and/or degradation of tumor markers may be regulated by numerous factors, thyroid hormone appearing to be important.

In conclusion, in this study there was a significant inverse correlation between CEA and T₃, AFP and T₄, CA 125 and FT₃ and CA 15-3 and FT₄. This correlation, between tumor markers and thyroid hormones, has not yet been explained. It should be remembered that both endocrine (thyroid hormone) and non-endocrine factors, such as food consumption, physical activity, and

temperature-control mechanisms, may play a part in the synthesis and degradation of tumor markers. In the case of hypothyroid patients an increase in the circulation of these tumor markers may be caused by decreased tumor marker degradation. In the light of these findings, we recommend that when patients are suffering from hyper- or hypothyroidism, caution be exercised when taking tumor marker readings.

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