〈Original Article〉

Relation between serum levels of thyroid hormone and serum β-carotene concentrations in patients with thyroid disorders

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Summary Hyper-β-carotenemia has been observed in various diseases (i.e., liver disease, diabetes mellitus, nephrotic syndrome, anorexia nervosa, and hypothyroidism) other than cases involving excessive consumption of carotenoid-rich foods. The aim of this study was to investigate how thyroid hormone levels relate to serum concentrations of β-carotene in patients with thyroid disorders. All subjects, including patients with thyroid disorders ($n = 101$) and healthy adults ($n = 20$), were classified based on TSH and fT4 data. Patients with high TSH and low or normal fT4 (i.e., primary or subclinical hypothyroidism) showed elevated levels of serum β-carotene compared with other patients and healthy adults. In all subjects, serum β-carotene concentrations showed a poor negative correlation with serum concentrations of fT4 ($r = -0.181$) and fT3 ($r = -0.185$). However, hyper-β-carotenemia was not observed in all patients with thyroid disorders, occurring in only five in patients with high TSH and low or normal fT4. In patients with hypothyroidism, we observed both elevated and normal serum β-carotene concentrations. Our results indicated that the prevalence of hyper-β-carotenemia was 8.0% in patients with high TSH and low fT4 (primary hypothyroidism), and 6.5% in patients with high TSH and normal fT4 (subclinical hypothyroidism). In both cases, the severity of hyper-β-carotenemia was not related to serum fT4 levels.

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1. Introduction

Aurantiasis cutis, also known as hyper-β-carotenemia, is a symptom that manifests as a yellowish skin pigmentation (i.e., carotenodermia), and usually results from consuming excessive amounts of foods containing carotenoids, such as green leafy vegetables and citrus fruits. The most prevalent dietary carotenoids are α-carotene, β-carotene, lycopene, lutein, zeaxanthin, and β-cryptoxanthin. However, only α-carotene, β-carotene, and β-cryptoxanthin can be converted into retinol (i.e., vitamin A) via retinal. Therefore, these carotenoids are known as provitamin A carotenoids[1]. Carotenoids are fat-soluble nutrients that are absorbed into duodenal mucosal cells together with dietary lipids. The majority is cleaved by the intestinal mucosal enzyme β-carotene 15,15'-monooxigenase 1 (BCMO1: EC 1.14.99.36) into two molecules of retinal, with 15% of β-carotene absorbed intact without conversion into retinal[2]. Within the intestinal absorptive cells, retinal is catalyzed by retinol dehydrogenase (EC 1.1.1.105) to retinol, which is then converted to retinyl esters by acyl-CoA retinol acyltransferase (ARAT: EC 2.3.1.76) and lecitin:retinol acyltransferase (LRAT: EC 2.3.1.135)[2]. The retinyl esters and intact absorbed β-carotene are incorporated into chylomicrons and secreted into lymph for delivery to the blood.

Hyper-β-carotenemia can occur without the consumption of carotenoid-rich foods, such as in patients with liver disease, diabetes mellitus, nephrotic syndrome, anorexia nervosa, and patients with hypothyroidism[3]. However, almost all reports of aurantiasis cutis involve subjects who consumed pumpkin, carrot or orange, whereas subjects with the aforementioned disease, especially hypothyroidism, are relatively few in the world[4,5,6]. Hyper-β-carotenemia is often overlooked until the patients manifest yellow pigmentation of the skin. It is not certain whether serum β-carotene levels are latently elevated in patients with hypothyroidism. Therefore, the aim of this study was to investigate the relation between serum concentrations of β-carotene and thyroid hormone in patients with thyroid disorders, i.e., patients with hypo- and hyperthyroidism.

2. Materials and methods

2.1. Subjects

A cross-sectional study was conducted in 101 patients with thyroid disorders (38 men and 63 women aged from 26 to 95 y, median 70 y). The subjects were randomly selected from patients visiting the Thyroid Clinic at Toho University Ohashi Medical Center. Approximately half of the patients were being treated with a thyroid hormone preparation. The controls consisted of 20 self-reported healthy adults (9 men and 11 women aged from 23 to 61 y, median 32 y) that were selected from the hospital staff.

A diet history questionnaire (doctor's interview) noted that none of the subjects consumed carotenoid-rich foods and dietary supplements containing β-carotene. Severe anemia, liver disease, digestive organ disorders, renal dysfunction, diabetes mellitus, and anorexia nervosa were not observed in the subjects. Only a single patient exhibited yellowish staining of the skin.

In accordance with the Helsinki Declaration, informed consent was obtained from the subjects, and the study protocol was approved by the Protection of Human Subjects Committee of Toho University Ohashi Medical Center (Ethics Committee approval number 14-54, Oct 14, 2014).

2.2. Assays

Serum concentrations of free thyroxine (fT4), free triiodothyronine (fT3), and thyroid stimulating hormone (TSH) activity were determined by an automated method based on the electro-chemiluminescence immunoassay (Elecsys; Roche Diagnostics, Basel, Switzerland). The reference ranges provided by the manufacturer were 12.0-22.0 pmol/L for fT4, 3.13-6.76 pmol/L for fT3, and 0.27-4.20 μIU/mL for TSH[7] Serum β-carotene concentrations were determined by high-performance liquid chromatography (HPLC), as described by Kamiyama et al.[8], on an

ACQUITY UPLC BEH C18 column (Waters) with visible detection (472 nm). Serum retinol concentrations were determined by HPLC on a Capcell pack C18 column (Shiseido) with fluorescence detection (340 nm ex and 460 nm em). Reference ranges were 0.06-2.14 µmol/L for β-carotene[3] and 1.05-2.86 µmol/L for retinol[3].

2.3. Statistics

Serum levels of β-carotene were analyzed using the Mann-Whitney U-test. The prevalence of hyper-β-carotenemia (>2.14 µmol/L) in hypothyroidism was compared with that in hyperthyroidism using the z-test. Statistical significance was defined as $p < 0.05$.

3. Results

3.1. Serum β-carotene concentrations

In the 101 patients with thyroid disorders, serum β-carotene concentrations ranged from 0.07 to 8.16 µmol/L (median 0.47 µmol/L). No cases of β-carotene deficiency (< 0.05 µmol/L) were observed, and 95% of the patients exhibited serum β-carotene levels within the reference range. Five patients exhibited elevated levels of β-carotene as higher than upper reference limit (> 2.14 µmol/L), of whom a male patient with the highest serum concentration showed yellow pigmentation of the skin. The concentrations ranged from 0.04 to 1.52 µmol/L in healthy adults. No significant relationship was observed between age and serum β-carotene concentrations both in patients with thyroid disorders and healthy adults.

3.2. Relationship between thyroid tests and serum β-carotene concentrations

When patients were classified based on TSH and fT4, patients with high TSH and low or normal fT4 (i.e., primary or subclinical hypothyroidism) showed elevated levels of serum β-carotene compared with patients with low TSH and normal or high fT4 and healthy adults (Table 1), however this was not statistically significant. Subjects with normal

Table 1. Serum levels of β-carotene, retinol, TC and CK in 101 patients with thyroid disorders and 20 healthy subjects.

fT4 (pmol/L)		TSH (µIU/mL)		
		< 0.27	0.27 - 4.2	> 4.2
< 12.0	β-Carotene (µmol/L)	0.39 (0/1)	0.40 (0/)1*	0.97 ± 1.60 (2/25)
	Retinol (µmol/L)	1.36 (0/1)	1.18 (0/1)*	2.06 ± 0.67** (2/25)
	TC (mmol/L)	4.94 (0/1)	4.86 (0/1)*	5.25 ± 1.47 (3/25)
	CK (U/L)	35 (0/1)	134 (0/1)*	124 ± 131 (2/25)
12.0 - 22.0	β-Carotene (µmol/L)	0.53 ± 0.37 (0/12)	0.54 ± 0.42 (0/17)*	0.88 ± 0.89 (3/46)
	Retinol (µmol/L)	1.91 ± 1.22 (3/12)	1.85 ± 0.48 (0/17)*	1.98 ± 0.75** (7/46)
	TC (mmol/L)	4.85 ±1.19 (1/12)	4.80 ± 1.40 (3/17)*	4.55 ± 1.06 (1/46)
	CK (U/L)	56 ± 40 (0/12)	91 ± 39 (0/17)*	92 ± 70 (5/46)
> 22.0	β-Carotene (µmol/L)	0.59 ± 0.50 (0/17)	0.54 ± 0.36 (0/2)*	(0/0)
	Retinol (µmol/L)	1.51 ± 0.39 (0/17)	1.48 ± 0.22 (0/2)*	(0/0)
	TC (mmol/L)	4.72 ± 0.66 (0/17)	3.89 ± 0.05 (0/2)*	(0/0)
	CK (U/L)	71 ± 46 (0/17)	66 ± 18 (0/2)*	(0/0)

Values are mean ± SD. *Healthy subjects.
Number of subjects with elevated levels of β-carotene (> 2.14 µmol/L), retinol (> 2.86 µmol/L), TC (≥ 6.60 mmol/L) or CK (≥ 187 U/L) / number of subjects classified by TSH and fT4 are in parenthesis.
**Significantly higher than patients with low TSH (< 0.27 µIU/mL) and high fT4 (> 22 pmol/L).
TC, total cholesterol. CK, creatine kinase.

TSH levels were not observed in the patient group. In all subjects including healthy adults, serum β-carotene concentrations showed a poor negative correlation with serum concentrations of fT4 ($r = -0.181$, $p = 0.046$: Fig. 1A) and fT3 ($r = -0.185$, $p = 0.042$: Fig. 1B). Based on the slope of regression line, fT3 more strongly affected serum β-carotene levels than fT4.

TSH activities in five patients having elevated levels of β-carotene (> 2.14 μmol/L) were all found to be greater than 4.20 μIU/mL; two patients (59M and 61F) had low fT4 and low fT3 (or normal fT3), and three patients (88M, 87M and 67F) had normal fT4 and normal fT3 (Table 1 and Table 2). The prevalence of hyper-β-carotenemia (>2.14 μmol/L) in patients with low fT4 and high TSH (i.e., patients diagnosed as primary hypothyroidism) was 8.0% (2/25), while prevalence in patients with normal fT4 and high TSH was 6.5% (3/46) (Table 1). No significant difference was observed between these prevalences. Not all patients with high TSH and low or normal fT4 manifested hyper-β-carotenemia (>2.14 μmol/L).

3.3. Effects of administration of thyroid hormone preparation

Because approximately half of the patients were treated with a thyroid hormone preparation, the effects of administration of a thyroid drug (levothyroxine sodium hydrate) were determined. Of the 101 patients, 47 patients were being treated with thyroid drug, while the other 54 patients received no treatment. Serum β-carotene concentrations in the former group (0.71±0.78 μmol/L) were not different from the latter (0.89±1.20 μmol/L). Serum fT4 concentrations and TSH activities were not different between patients treated with or without thyroid drug; however, serum fT3 concentrations in patients treated with thyroid drug (3.88±1.33 pmol/L) were significantly ($p = 0.02$) lower than those not treated with thyroid drug (5.10±2.90 pmol/L).

3.4. Serum retinol concentrations

Overall, serum retinol concentrations ranged from 0.61 to 4.23 μmol/L in the 101 patients. In comparison, the concentrations ranged from 1.13 to 2.58 μmol/L in healthy adults. In all subjects including healthy adults, serum retinol concentrations showed a poor negative correlation with serum concentrations of fT4 ($r = -0.151$, $p = 0.098$: Fig. 2A) and fT3 ($r = -0.240$, $p = 0.008$: Fig. 2B). Based on the slope of regression line, fT3 more strongly affected serum retinol levels than fT4. Serum retinol concentrations in patients with high TSH and low fT4 (2.06±0.67 μmol/L) were significantly higher than those in patients with low TSH and high fT4 (1.51±0.39 μmol/L) (Table 1); however, no relationship was observed between serum concentrations of retinol and β-carotene ($r = 0.172$, $p = 0.411$: Fig. 3A) in these patients. This is also the case for
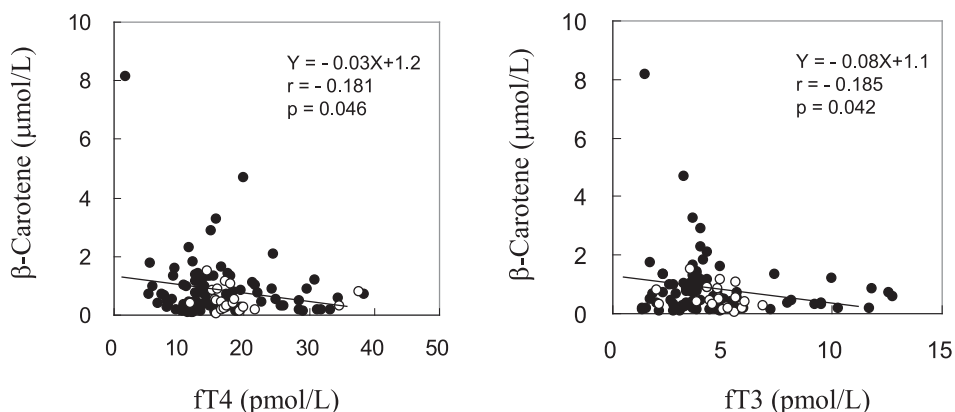

Fig. 1. Correlation between thyroid hormone levels and serum β-carotene concentrations in patients with thyroid disorders and healthy adults. A: fT4 versus β-carotene, B: fT3 versus β-carotene. ● Thyroid disorders (n= 101), ○ Healthy adults (n= 20).

Table 2. Comparison of descriptive data for five patients with hyper-β-carotenemia and patients from previous reports.

	Reference range	Our study					Quoted from literatures		
Age (y) / Gender		59M	61F	88M	87M	67F	*Ref. 4*	*Ref. 6*	*Ref. 5*
Thyroid drug		(-)	(-)	(-)	(-)	(+)	(-)	nd	nd
Yellowish skin		(+)	(-)	(-)	(-)	(-)	(+)	nd	nd
TSH (μIU/mL)	0.27 - 4.20	174.39	12.96	14.78	12.27	7.88	200	<43.9±28.95	nd
fT4 (pmol/L)	12.0 - 22.0	1.78	11.46	14.93	15.70	19.82	0.77	10.7±4.8	37.33±18.66*
fT3 (pmol/L)	3.13 - 6.76	1.47	3.99	3.99	3.69	3.23	1.64	2.3±1.1	0.86±0.63**
β-Carotene (μmol/L)	0.06 - 2.14	8.16	2.29	2.89	3.27	4.71	2.93	2.05±1.30	0.14±0.05
Retinol (μmol/L)	1.05 - 2.86	2.54	1.70	3.01	2.87	2.03	nd	2.44±0.70	0.53±0.20
TC (mmol/L)	< 6.60	6.39	6.39	5.46	5.12	4.09	4.29	nd	nd
CK (U/L)	> 187	339	124	389	125	51	5236	nd	nd

Ref. 4, A Japanese male age 54 y. *Ref. 6* , Eight Austrian women average age 59 y (range 32-80 y) .
Ref. 5, 26 Indian women aged 45-50 y.
*T4 (nmol/L, reference range: 66-181 nmol/L), **T3 (nmol/L, reference range: 1.27-3.07 nmol/L).
TC, total cholesterol; for conversion to mass units (mg/dL), molar units (mmol/L) were multiplied by a factor of 38.665.
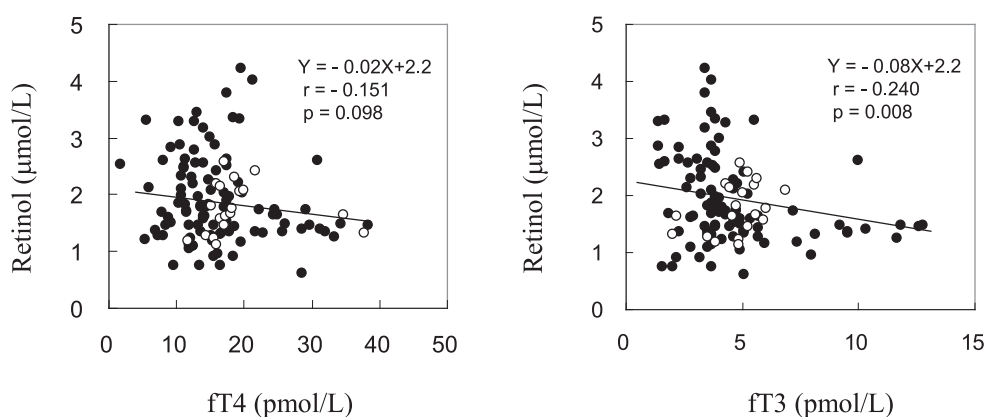CK, creatine kinase.

Fig. 2.   Correlation between thyroid hormone levels and serum retinol concentrations in patients
with thyroid disorders and healthy adults. A: fT4 versus retinol, B: fT3 versus retinol.
● Thyroid disorders (n= 101), ○ Healthy adults (n= 20).

patients with high TSH and normal fT4 ($r = 0.200$, $p = 0.183$: Fig. 3B). However, serum retinol concentrations in the five patients with hyper-β-carotenemia were within normal limits or slightly increased (Table 2). Most hypervitaminosis A cases (retinol > 2.86 μmol/L) were observed in patients with normal β-carotene concentrations (β-carotene < 2.14 μmol/L) (Fig. 3A and Fig. 3B).

4. Discussion

Previous studies have suggested that thyroid hormone is involved in β-carotene and retinol metabolism[4,5,6]. However, not all of the evidence is consistent between studies or with our present observations. In our study, patients with high TSH and low or normal fT4 showed a trend towards elevated levels of serum β-carotene when compared with patients with low TSH and normal or high fT4.
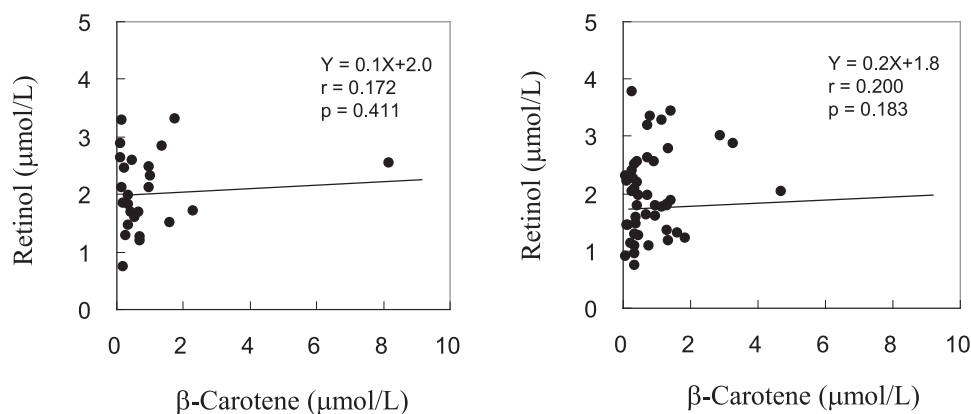
Fig. 3.   Correlation between serum concentrations of β-carotene and retinol in patients with high TSH and low fT4 (A: primary hypothyroidism, n= 24) and high TSH and normal fT4 (B: subclinical hypothyroidism, n= 46).

However, their serum retinol concentrations were significantly higher than those in patients with low TSH and high fT4.

A report of a Japanese case with hypothyroidism[4] found that the patient had an elevated serum β-carotene concentration (2.93 μmol/L) that was similar to levels observed in our five patients with hyper-β-carotenemia, however the patient's serum retinol concentration was unfortunately not investigated (Table 2).

In a report from India[5], significantly higher serum concentrations of both β-carotene and retinol were observed in female patients (ages 45-50 y) with hypothyroidism compared with hyperthyroid and normal women (Table 2). Concerning β-carotene and retinol, our observations coincide with this report. However, we cannot compare their concentrations with our patients, because their serum levels of β-carotene (0.14±0.05 μmol/L) and retinol (0.53±0.20 μmol/L) in hypothyroidism appeared to be inexplicably lower than our patients with hypothyroidism and hyperthyroidism and healthy adults (Table 2). At present, the reason for this discrepancy is not completely understood, but we can partially explain the low serum β-carotene concentrations in the Indian population by the presence of a single nucleotide polymorphism (SNP) within the *BCMO1* coding region that causes high catalytic activity in the conversion of β-carotene to retinol[9].

In another report from Austria[6], β-carotene concentrations in hypothyroidism (2.05±1.30 μmol/L: Table 2) were significantly higher than in hyperthyroidism (0.56±0.19 μmol/L). Furthermore, it was reported that serum retinol concentrations were not different among hypothyroidism (2.44±0.70 μmol/L), euthyroid (2.44±0.35 μmol/L), and hyperthyroidism (2.09±0.35 μmol/L), and a significant increase was not observed in hypothyroidism.

Recent molecular biology studies revealed that triiodothyronine (T3) enhanced CMO1 (BCMO1) mRNA levels and its enzyme activity in human intestinal Caco-2 BBe cells[10]. In light of this report and the previous three studies[4,5,6] and our present observations, it is probable that accumulation of β-carotene in serum occurred in patients with hypothyroidism, caused by the lowered conversion of β-carotene to retinol. In this study, we provide the first observation of the prevalence of hyper-β-carotenemia (>2.14 μmol/L) in hypothyroidism, which has been overlooked in the previous studies. We found that hyper-β-carotenemia did not occur in all patients with hypothyroidism (i.e., patients with high TSH and low fT4 in Table 1). Moreover, hyper-β-carotenemia was also observed in some patients with high TSH and normal fT4. The prevalence of hyper-β-carotenemia (>2.14 μmol/L) in the former was 8.0% (however, the prevalence of yellowish skin pigmentation was 4.0%), and 6.5% in the latter. In these two groups, the occurrence of hyper-β-carotenemia and its severity were not related to

serum fT4 levels. Indeed, despite the presence of a patient with severely lowered fT4 (0.77 pmol/L) in the previous report[4], the patient's serum β-carotene concentration was lower than our patients (Table 2).

Excluding hypothyroidism, the prevalence of hyper-β-carotenemia (assessed by skin pigmentation) in the Japanese was reported as 13.5% (36 of 267 subjects) in diabetes mellitus[11] and 12.3% (124 of 1006 patients) in anorexia nervosa[12]. A 4.0% prevalence of yellowish skin pigmentation in hypothyroidism was not statistically lower than the prevalence observed in diabetes mellitus and anorexia nervosa. In addition, we explored whether hyper-β-carotenemia was concordant with hypercholesterolemia (Fig. 4) and/or hypercreatine kinasemia

(Fig. 5), both of which are well-documented complication of hypothyroidism[13]. In the 25 patients with high TSH and low fT4 (i.e., patients with primary hypothyroidism), only one patient (59M) showed hypercreatine kinasemia (339 U/L) accompanied by hyper-β-carotenemia (Table 2). While in the 46 patients with high TSH and normal fT4 (i.e., patients with subclinical hypothyroidism), one patient (88M) showed hypercreatine kinasemia (389 U/L) accompanied by hyper-β-carotenemia. In addition, some patients showed however hypercholesterolemia or hypercreatine kinasemia in the absence of hyper-β-carotenemia (Fig. 4 and Fig. 5). Our findings highlight the discrepancy that not all hypothyroid patients exhibit hyper-β-carotenemia despite having
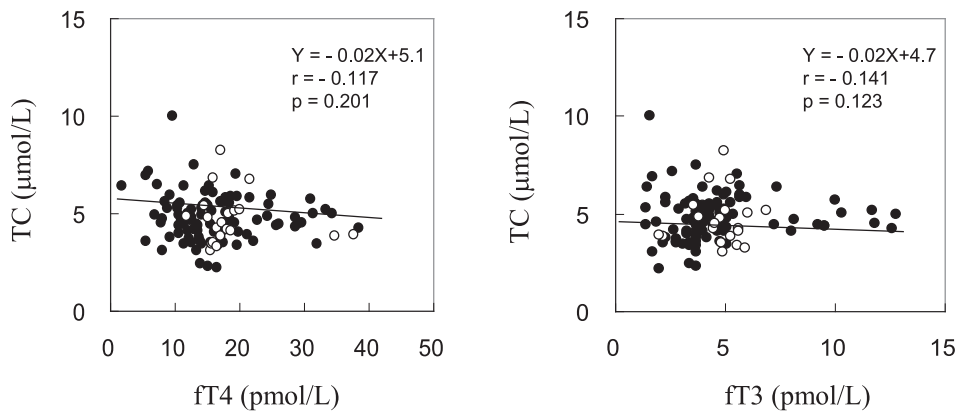

Fig. 4. Correlation between thyroid hormone levels and serum total cholesterol (TC) concentrations in patients with thyroid disorders and healthy adults. A: fT4 versus TC, B: fT3 versus TC. ● Thyroid disorders (n= 101), ○ Healthy adults (n= 20).
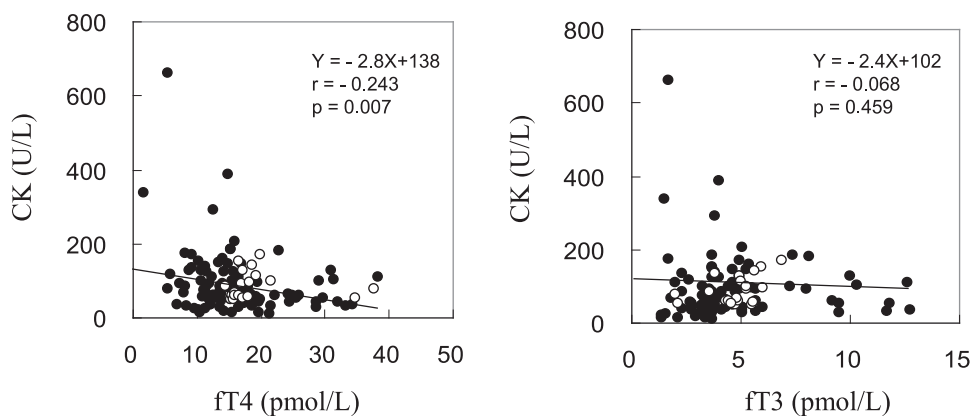

Fig. 5. Correlation between thyroid hormone levels and serum creatine kinase (CK) activities in patients with thyroid disorders and healthy adults. A: fT4 versus CK, B: fT3 versus CK. ● Thyroid disorders (n= 101), ○ Healthy adults (n= 20).

the same levels of serum TSH and fT4. In future studies, therefore, we would like to investigate which markers (including *BCMO1* polymorphisms) contribute to the manifestation of hyper-β-carotenemia in patients with high TSH and normal or low fT4. As an example, micellar solubilization of lipid facilitates access of soluble hydrolytic enzyme (BCMO1) to their substrates (β-carotene), and the enzyme requires ferrous ion (Fe^{2+}) as a cofactor[14].

Initially, we assumed that a negative relationship exists serum concentrations of β-carotene and retinol in patients with hypothyroidism, because the conversion of β-carotene to retinol would be depressed in these patients. However, our results were contrary to this assumption. Serum retinol concentrations were not negatively correlated to serum β-carotene concentrations (Fig. 3). Our observations can be explained by retinol being formed from β-carotene (i.e., vegetable food) as well as retinyl esters taken directly from animal food products. Serum retinol formed from β-carotene would decline in hypothyroidism, but retinol formed from retinyl esters would accumulate in serum. We assumed that T3 has the ability to facilitate the utilization of retinol in tissues[15]. With low levels of T3, repressed BCMO1 activity may result in accumulation of β-carotene in serum, and reduced tissue use of retinol will result in accumulation of retinol in serum. In healthy subjects, the absorption of β-carotene in the small intestine and intestinal BCMO1 activity are regulated by the retinoic acid receptor (RAR) / retinoid X receptor (RXR) heterodimer, intestine-specific homeodomain transcription factor (ISX), and intestinal scavenger class B type 1 (SRB1)[16]. With vitamin A sufficiency, ISX represses both BCMO1 activity and intestinal β-carotene absorption through SRB1. With vitamin A deficiency, ISX expression, which down-regulates BCMO1 and SRB1, is reduced due to low retinoic acid levels, leading to normal expression of BCMO1 and SRB1.

In conclusion, we revealed for the first time the prevalence of hyper-β-carotenemia in patients with high TSH and low fT4 (primary hypothyroidism) is 8.0%, thus hyper-β-carotenemia is a restricted case not observed in all patients with primary hypothyroidism. The prevalence of hyper-β-carotenemia was also observed in patients with high TSH and normal fT4 (subclinical hypothyroidism) as 6.5%. In these patients, the manifestation of hyper-β-carotenemia and its severity were not related to serum fT4 levels.

Conflicting Interests

The authors have declared that no conflict of interest exists.

Acknowledgments

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