SERUM COMPONENTS AND LIFESTYLE FACTORS - III

Association of Serum Retinol and Carotenoids with Insulin-like Growth Factors and Insulin-like Growth Factor Binding Protein-3 among Control Subjects of a Nested Case-control Study in the JACC study

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Abstract

Insulin-like growth factor (IGF)-I and its main binding protein, IGFBP-3, modulate cell growth and survival, and thus are thought to be important for tumor development. Carotenoids and retinol have been linked to the prevention of several cancers. We here evaluated associations of serum levels of carotenoids and retinol with IGF-I, IGF-II, and IGFBP-3 within the context of the JACC Study. The study subjects were 924 controls (578 men and 346 women) of a nested case-control study of lung and colorectal cancer risk . Using frozen-stored sera, serum levels of α-carotene, β-carotene, lycopene, β-cryptoxanthin, zeaxanthin/lutein, and retinol were separately determined using high-performance liquid chromatography. Serum levels of IGF-I, IGF-II, and IGFBP-3 were measured by immuno-radiometric assay. Confounding factors-adjusted least squares mean levels of serum IGF-I, IGF-II, and IGFBP-3 for each quartile of serum levels of carotenoids and retinol were estimated. Serum IGF-I, IGF-II, and IGFBP-3 levels increased with increasing serum retinol levels. Moreover, serum IGF-I levels were significantly higher in highest quartile of serum provitamin A, such as α-carotene, β-carotene, and β-cryptoxanthin, among women. Serum IGFBP-3 levels decreased with increasing serum lycopene levels in women and with increasing serum zeaxanthin/lutein levels in men. The current study indicates that positive associations exist for serum retinol levels with serum levels of IGF-I, IGF-II, and IGFBP-3 independent of age, BMI, smoking habits, drinking habits, and intake of energy and protein among Japanese healthy men and women.

Keywords: Japan Collaborative Cohort Study - retinol - carotenoids - IGF-I/II - IGFBP-3

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Introduction

Insulin-like growth factors (IGFs) and their binding proteins play important roles in cell proliferation and differentiation. IGF-binding proteins are essential modulators of the biological actions of IGF (Clemmons et al., 1991). In recent studies, the IGF system has been implicated as a major cancer risk factor. Thus, circulating levels of IGF-I and IGF-binding protein-3 (IGFBP-3) have been shown to be associated with risk of several cancers, such as lung (Yu et al., 1999), colorectal (Ma et al., 1999), breast (Hankinson et al., 1998), and pancreastic cancer (Lin et al., 2004).

The IGF system itself is regulated by various factors, including the nutrition status. Vitamin A and its retinoid derivatives are essential micronutrients for vision, immune function, reproduction, maintenance of epithelial tissue, and differentiation (De Luca, 1991). Vitamin A intake was found to be positively associated with circulating IGF-I (Maskarinec et al., 2005) and vitamin A deficiency reduced IGF-I gene expression in tissue of Japanese quail (Fu et al., 2001). It has further been reported that dietary intake of lycopene is negatively

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associated with serum IGF-I and positively associated with IGFBP-3 (Voskuil et al., 2005). Various biological effects have been attributed to carotenoids. One possible mechanism of action is via their antioxidant activity, but other mechanisms may also contribute to their beneficial effects (Bendich, 1989). Epidemiologic studies (van Poppel, 1996; Holick et al., 2002; Ito et al., 2003; Ozasa K et al, 2005) have shown an inverse relationship between various cancers and dietary carotenoids or blood levels of carotenoids. However there was little information regarding the association of serum levels of carotenoids and retinol with serum IGFs levels.

The Japan Collaborative Cohort Study (JACC Study) for Evaluation of Cancer Risk sponsored by the Ministry of Education, Science, Sports and Culture of Japan (Monbu-sho) is a cohort study initiated between 1988 and 1990 when apparently healthy residents aged 40-79 years were enrolled as a basic cohort population from 45 areas throughout Japan (Ohno et al., 2001; Tamakoshi et al., 2005). Peripheral blood samples were collected from 39,242 registered subjects between 1988 and 1990 in the JACC study. Nested case-control studies were conducted to evaluate the association of serum levels of carotenoids and retinol with risk of lung and colorectal cancer. Serum levels of carotenoids and retinol were measured using sera from death cases of lung and colorectal cancers and their control subjects. Serum IGF-I, II, and IGFBP-3 were also measured in all cases of deaths and known incident cancers and in their controls to elucidate the association of IGF-related factors with various sites of cancer and other diseases in the JACC Study.

Table 1. Characteristics of the Study Subjects

Variables	Men	Women
Number	578 (100)	346 (100)
Age (years)[1]	64.8±7.5	62.1±8.6
Smoking habits[2]		
Current	271 (46.9)	9 (2.6)
Ex	182 (31.5)	7 (2.0)
Non	125 (21.6)	330 (95.4)
Drinking habits[2]		
Current	433 (74.9)	73 (21.1)
Ex	23 (4.0)	3 (0.9)
Non	122 (21.1)	270 (78.0)
BMI (kg/m^2)[1]	22.2±2.7	22.9±3.0
Serum data[1]		
Cholesterol (mg/dl)	191.9 ± 36.4	212.0 ± 38.7
IGF-I (ng/ml)	139.2 ± 57.0	128.4 ± 49.9
IGF-II (ng/ml)	564.5 ± 122.3	624.5 ± 117.1
IGFBP-3 (μg/ml)	2.94 ± 0.83	3.24 ± 0.77
Carotenoids (μmol/l)[3]		
β-carotene	0.415 (0.235-0.748)	0.787 (0.529-1.217)
α-carotene	0.063 (0.042-0.105)	0.102 (0.070-0.157)
Lycopene	0.126 (0.060-0.256)	0.235 (0.117-0.461)
β-cryptoxanthin	0.213 (0.115-0.371)	0.375 (0.259-0.543)
Zeaxanthin/lutein	1.016 (0.754-1.259)	1.097 (0.800-1.435)
Retinol	2.485 (2.047-3.071)	2.210 (1.785-2.718)
Provitamin A	0.740 (0.439-1.268)	1.337 (0.939-1.951)

[1]Mean ± standard deviation; [2]Number and percentage; [3]Data expressed as geometric mean and 25-75 percentiles in parentheses; IGF-I, insulin-like growth factor-I; IGF-II, insulin-like growth factor-II; IGFBP-3, insulin-like growth factor binding protein-3

We evaluated the association of serum levels of carotenoids and retinol with IGF-I, IGF-II and IGFBP-3 using control subjects in nested case-control study for lung and colorectal cancer of the JACC study.

Subjects and Methods

Study subjects were 924 controls (578 men and 346 women) in a nested case-control study for risk of lung and colorectal cancer in the JACC Study. At the baseline, information on life-style was collected using self-administered questionnaires, featuring a 40-item food frequency questionnaire (FFQ) to calculate the intake amounts of energy and nutrients. Details of calculation were reported elsewhere (Date et al., 2005).

Sera were stored in -80˚C until analyses. Serum levels of α-carotene, β-carotene, lycopene, β-cryptoxanthin, zeaxanthin/lutein, and retinol were separately determined using high-performance liquid chromatography (Ito et al., 1987; Ito et al., 1990) in 2001 and 2002. Serum provitamin A levels were calculated as the sum of serum α-carotene, β-carotene, and β-cryptoxanthin levels. Serum levels of IGF-I, IGF-II, and IGFBP-3 were measured by immuno-radiometric assay, using commercially available kits (Daiichi Radioisotope Lab., Tokyo) by trained staff blind to case and control status at a single laboratory (SRL, Tokyo) in 1999 and 2000. Details of measurement of serum IGF-I, IGF-II, and IGFBP-3 are described elsewhere (Ito et al., 2005).

All statistical analyses were conducted using the Statistical Analysis System (SAS ver. 9.1, SAS Institute, USA). Since serum levels of carotenoids and retinol were distributed logarithmically, we used log-transformed carotenoids and retinol in statistical analyses and represented them as geometric means and 25th-75th percentile ranges.

Serum carotenoids and retinol levels were categorized in quartiles. Confounding factors-adjusted least squares mean levels of serum IGF-I, IGF-II, and IGFBP-3 for each quartile of serum levels of carotenoids and retinol were estimated. Age, study area, body mass index (BMI), serum total cholesterol levels, smoking habits, drinking habits, and intake amount of energy and protein were used as confounding factors in the analysis. A probability value less than 0.05 was considered statistically significant.

Results

Table 1 shows baseline characteristics of study subjects. Men were older and had a lower BMI than women. The proportions of current smokers and current drinkers were higher in men than in women. Serum levels of all carotenoids and provitamin A were significantly higher and serum retinol levels were significantly lower in women than in men. Serum IGF-I levels was significantly higher and serum levels of IGF-II and IGFBP-3 were significantly lower in men than in women.

The associations of serum carotenoids and retinol levels with serum levels of IGF-I, IGF-II, and IGFBP-3 are shown in Tables 2 and 3. In both sexes, serum IGF-I, IGF-II, and IGFBP-3 levels increased with increasing

Table 2. Comparison of Serum IGF-I, IGF-II, and IGFBP-3 Levels according to Categories of Serum Levels of Carotenoids and Retinol among Men

		n	Serum IGF-I (ng/ml)		Serum IGF-II (ng/ml)		Serum IGFBP-3 (μg/ml)	
			Crude	Adjusted*	Crude	Adjusted*	Crude	Adjusted*
Serum β-carotene levels (μmol/l)								
Q1	0.004-0.235	145	129.1±4.7	133.9±5.1	547.7±10.1	577.4±13.1	2.79±0.07	2.97±0.08
Q2	0.236-0.441	146	143.3±4.7	140.5±5.0	568.1±10.1	588.5±12.8	2.96±0.07	3.02±0.08
Q3	0.442-0.748	143	139.3±4.7	141.0±4.8	563.4±10.2	564.0±12.3	2.89±0.07	2.90±0.08
Q4	0.749-3.432	144	145.0±4.7	146.1±5.0	578.8±10.2	578.4±13.0	3.14±0.07	3.13±0.08
p for trend			0.039	0.126	0.051	0.705	0.001	0.373
Serum α-carotene levels (μmol/l)								
Q1	0.003-0.042	151	134.5±4.6	135.0±5.0	544.8±9.9	579.8±12.9	2.81±0.07	2.98±0.08
Q2	0.043-0.065	142	138.1±4.8	140.0±4.8	564.2±10.2	578.7±12.3	2.87±0.07	2.98±0.08
Q3	0.066-0.105	141	140.4±4.8	141.5±5.3	558.9±10.2	565.6±13.5	2.93±0.07	2.94±0.08
Q4	0.106-0.689	144	143.9±4.7	145.2±4.9	590.8±10.1	581.1±12.5	3.15±0.07	3.09±0.08
p for trend			0.149	0.173	0.003	0.911	<0.001	0.395
Serum lycopene levels (μmol/l)								
Q1	0-0.060	145	133.4±4.7	134.5±5.1	559.5±10.1	587.4±13.1	2.86±0.07	3.01±0.08
Q2	0.061-0.122	145	140.5±4.7	139.4±5.3	553.3±10.2	563.0±13.6	2.94±0.07	2.97±0.09
Q3	0.123-0.256	146	137.4±4.7	144.1±4.6	557.9±10.1	567.5±11.8	2.85±0.07	2.93±0.07
Q4	0.257-1.960	142	145.5±4.8	142.3±4.6	587.7±10.3	587.2±11.7	3.11±0.07	3.08±0.07
p for trend			0.149	0.218	0.059	0.895	0.038	0.560
Serum β-cryptoxanthin levels (μmol/l)								
Q1	0.012-0.115	151	128.7±4.6	134.6±5.0	555.3±10.0	590.9±12.9	2.78±0.07	2.98±0.08
Q2	0.116-0.207	140	144.0±4.8	141.5±5.0	570.6±10.4	585.9±12.9	2.97±0.07	3.05±0.08
Q3	0.208-0.307	143	139.4±4.8	141.3±4.9	557.3±10.3	571.5±12.6	2.92±0.07	2.95±0.08
Q4	0.308-5.317	144	145.3±4.7	144.6±5.0	575.2±10.2	559.2±12.7	3.10±0.07	3.02±0.08
p for trend			0.039	0.207	0.310	0.071	0.003	0.994
Serum zeaxanthin/lutein levels (μmol/l)								
Q1	0.206-0.754	147	130.7±4.7	135.6±4.7	562.5±10.2	588.8±12.0	2.91±0.07	3.06±0.07
Q2	0.755-0.983	144	142.5±4.7	144.5±4.9	562.9±10.2	579.5±12.6	2.99±0.07	3.11±0.08
Q3	0.984-1.259	143	139.2±4.8	140.2±5.5	561.8±10.3	581.2±14.1	2.91±0.07	2.98±0.09
Q4	1.260-5.435	144	144.5±4.7	141.9±5.0	570.7±10.2	558.0±12.9	2.96±0.07	2.85±0.08
p for trend			0.052	0.482	0.577	0.123	0.823	0.036
Serum retinol levels (μmol/l)								
Q1	0.802-2.047	147	120.6±4.6	127.6±5.3	500.5±9.4	525.2±13.3	2.58±0.06	2.73±0.08
Q2	2.048-2.505	146	132.7±4.6	138.9±5.0	547.1±9.4	569.7±12.5	2.75±0.06	2.85±0.08
Q3	2.506-3.071	141	147.7±4.7	142.8±4.7	587.4±9.6	585.0±11.7	3.11±0.07	3.09±0.07
Q4	3.072-5.568	144	156.4±4.6	149.7±4.7	624.7±9.5	616.7±11.8	3.33±0.06	3.26±0.07
p for trend			<0.001	0.003	<0.001	<0.001	<0.001	<0.001
Serum provitamin A levels (μmol/l)								
Q1	0.019-0.439	145	129.5±4.7	134.9±5.1	553.1±10.2	586.1±13.1	2.78±0.07	2.98±0.08
Q2	0.440-0.785	144	142.6±4.7	141.0±5.2	559.2±10.2	584.4±13.3	2.94±0.07	3.02±0.08
Q3	0.786-1.268	145	139.5±4.7	139.0±4.8	572.2±10.2	573.7±12.2	2.93±0.07	2.92±0.08
Q4	1.269-6.655	144	145.2±4.7	146.9±5.0	573.4±10.2	564.2±12.9	3.11±0.07	3.09±0.08
p for trend			0.037	0.158	0.104	0.221	0.001	0.521

*Adjusted for area, age, BMI, serum total cholesterol levels, smoking habits, drinking habits, and intake amount of energy and protein. Values were showed as least square means and standard errors.Serum provitamin A levels were calculated as the sum of serum α-carotene, β-carotene, and β-cryptoxanthin levels; IGF-I, insulin-like growth factor-I; IGF-II, insulin-like growth factor-II; IGFBP-3: insulin-like growth factor binding protein-3

serum retinol levels before and after adjustment for confounding factors.

Moreover, serum IGF-I levels were significantly higher in highest quartile of serum α-carotene, β-carotene, β-cryptoxanthin, and provitamin A than other quartiles of those even after adjustment for confounding factors in women. Serum IGFBP-3 levels tended to decrease with increasing serum lycopene levels in women and with increasing serum zeaxanthin/lutein levels in men. Although serum IGF-I, IGF-II, and IGFBP-3 levels were significantly associated with some serum carotenoids levels, there was no significant association of serum IGF-I, IGF-II, and IGFBP-3 with serum other carotenoids after adjustment for confounding factors.

Discussion

In this study, we found that serum levels of IGF-I, IGF-II, and IGFBP-3 were significantly associated with serum retinol levels, independent of age, BMI, serum total cholesterol levels, smoking habits, drinking consumption, and intake of energy and protein among Japanese men and women. Serum IGF-I levels were higher in the highest quartiles of serum provitamin A such as α-carotene, β-carotene and β-cryptoxanthin in women. Moreover serum IGFBP-3 levels were negatively associated with serum zeaxanthin/lutein levels in men and with serum lycopene levels in women.

The IGF system plays an important role in normal

Table 3. Comparison of Serum IGF-I, IGF-II, and IGFBP-3 Levels according to Categories of Serum Levels of Carotenoids and Retinol among Women

		n	Serum IGF-I (ng/ml)		Serum IGF-II (ng/ml)		Serum IGFBP-3 (μg/ml)	
			Crude	Adjusted*	Crude	Adjusted*	Crude	Adjusted*
Serum β-carotene levels (μmol/l)								
Q1	0.067-0.529	88	122.9±5.2	124.6±6.0	597.3±12.3	627.4±14.7	3.21±0.08	3.33±0.10
Q2	0.530-0.802	85	120.2±5.3	124.6±5.8	610.8±12.5	631.7±14.3	3.20±0.08	3.32±0.09
Q3	0.803-1.217	87	123.2±5.2	121.2±5.9	629.2±12.3	618.2±14.5	3.20±0.08	3.15±0.10
Q4	1.218-4.203	86	147.3±5.3	145.4±5.5	661.0±12.4	650.1±13.6	3.36±0.08	3.26±0.09
p for trend			0.001	0.018	<0.001	0.350	0.225	0.425
Serum α-carotene levels (μmol/l)								
Q1	0.006-0.070	96	118.3±5.0	117.7±6.0	595.7±11.8	633.5±14.6	3.15±0.08	3.30±0.10
Q2	0.071-0.103	79	125.1±5.5	131.0±6.1	614.4±13.0	633.6±14.9	3.17±0.09	3.25±0.10
Q3	0.104-0.157	85	126.3±5.3	127.6±5.6	639.3±12.5	623.4±13.7	3.30±0.08	3.24±0.09
Q4	0.158-0.916	86	144.6±5.3	140.8±5.7	651.2±12.5	639.3±13.9	3.35±0.08	3.26±0.09
p for trend			0.001	0.015	0.001	0.894	0.050	0.783
Serum lycopene levels (μmol/l)								
Q1	0.011-0.117	87	129.0±5.2	129.5±6.2	614.6±12.7	641.8±15.0	3.32±0.08	3.46±0.10
Q2	0.118-0.245	86	127.8±5.2	128.1±5.8	618.3±12.7	624.7±14.0	3.28±0.08	3.29±0.09
Q3	0.246-0.461	87	126.6±5.2	128.8±5.5	629.0±12.6	635.0±13.2	3.17±0.08	3.19±0.09
Q4	0.462-4.200	86	130.1±5.2	131.4±5.8	636.1±12.7	629.0±14.0	3.20±0.08	3.16±0.09
p for trend			0.513	0.807	0.228	0.691	0.204	0.021
Serum β-cryptoxanthin levels (μmol/l)								
Q1	0.030-0.259	88	117.4±5.1	119.5±5.7	605.8±12.5	636.9±14.1	3.17±0.08	3.33±0.09
Q2	0.260-0.364	85	131.2±5.1	131.8±5.6	638.5±12.7	642.4±13.7	3.28±0.08	3.28±0.09
Q3	0.365-0.543	87	128.8±5.1	123.9±5.9	624.3±12.6	614.6±14.4	3.23±0.08	3.13±0.09
Q4	0.544-5.324	86	136.3±5.1	143.8±6.0	629.9±12.7	634.8±14.7	3.29±0.08	3.32±0.10
p for trend			0.099	0.018	0.342	0.602	0.451	0.669
Serum zeaxanthin/lutein levels (μmol/l)								
Q1	0.274-0.800	90	129.1±5.0	132.9±5.6	611.5±12.3	637.8±13.6	3.28±0.08	3.41±0.09
Q2	0.801-1.054	83	120.7±5.2	117.2±6.3	624.3±12.9	632.5±15.3	3.25±0.09	3.24±0.10
Q3	1.055-1.435	87	123.1±5.1	125.8±5.6	614.6±12.6	613.7±13.7	3.10±0.08	3.11±0.09
Q4	1.436-5.120	86	140.3±5.1	140.2±5.8	648.2±12.6	646.2±14.2	3.34±0.08	3.30±0.09
p for trend			0.029	0.317	0.061	0.936	0.878	0.278
Serum retinol levels (μmol/l)								
Q1	0.783-1.785	88	108.6±4.9	104.8±5.3	578.5±12.3	579.1±13.2	2.87±0.08	2.86±0.08
Q2	1.786-2.168	87	124.7±4.9	122.6±5.3	626.5±12.3	632.0±13.2	3.11±0.08	3.14±0.08
Q3	2.169-2.718	85	132.5±5.0	138.2±5.6	640.6±12.4	661.6±14.1	3.36±0.08	3.41±0.09
Q4	2.719-5.756	86	148.2±5.0	155.5±5.5	653.5±12.4	664.5±13.8	3.63±0.08	3.71±0.09
p for trend			<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Serum provitamin A levels (μmol/l)								
Q1	0.111-0.939	87	120.4±5.3	119.4±5.9	593.7±12.3	615.5±14.6	3.24±0.08	3.34±0.10
Q2	0.940-1.375	86	122.5±5.3	125.6±5.6	607.4±12.4	630.3±13.9	3.09±0.08	3.19±0.09
Q3	1.376-1.951	87	126.6±5.3	125.9±5.9	642.5±12.3	641.6±14.6	3.28±0.08	3.23±0.10
Q4	1.952-7.578	86	144.0±5.3	146.5±5.8	654.4±12.4	643.0±14.2	3.37±0.08	3.30±0.09
p for trend			0.002	0.003	<0.001	0.170	0.121	0.902

*Adjusted for area, age, BMI, serum total cholesterol levels, smoking habits, drinking habits, and intake amount of energy and protein. Values were showed as least square means and standard errors. Serum provitamin A levels were calculated as the sum of serum α-carotene, β-carotene, and β-cryptoxanthin levels; IGF-I, insulin-like growth factor-I; IGF-II, insulin-like growth factor-II; IGFBP-3: insulin-like growth factor binding protein-3

growth and development as well as in a variety of pathological situations, particular tumorigenesis (Khandwala et al., 2000). Several epidemiological studies (Hankinson et al., 1998; Ma et al., 1999; Yu et al., 1999) reported that higher IGF-I and lower IGFBP-3 were related to high risk of several cancers. In this study, higher retinol related to higher IGF-I, which may paradoxically suggest an increase in the risk of tumor development. Our results have to be interpreted carefully.

Serum levels of IGFs and IGFBPs are known to be influenced by dietary habits and other lifestyle factors (Voskuil et al., 2005). The decreased serum IGF-I levels observed after chronic or acute energy restriction are found to be mainly due to effects on liver IGF-I mRNA levels (Voskuil et al., 2005). Several studies have found that higher protein intake and energy are associated with higher serum IGF-I levels (Devine et al., 1998; Holmes et al., 2002). It has been reported that body mass index, smoking, alcohol intake affected IGF-I and IGFBP-3 levels (Teramukai et al., 2002). Body mass index was significantly and positively associated with IGF-I and IGFBP-3 levels. Cigarette smoking reduced IGF-I and IGFBP-3. Alcohol intake was associated inversely with IGF-I and positively with IGFBP-3.

Animal experiments have shown that vitamin A deficiency decreases circulating IGF-I levels in rats (Bartlett et al., 1990) and down-regulates tissue IGF-I mRNA in Japanese quail (Fu et al., 2001). Vitamin A intake

has been reported to be positively associated with circulating IGF-I (Holmes et al., 2002; Maskarinec et al., 2005). Other studies have demonstrated the important effects of retinoic acid, a major active metabolite of vitamin A, on the expression of IGF-I, IGF-II, and IGFBP in many cell lines (Zhou et al., 1996; Gabbitas et al., 1997; Shang et al., 1999). Retinoic acid has also been shown to bind to the mannose-6-phosphate / IGF-II receptor to regulate the availability of extracellular IGF-II by speeding up receptor shuttling between cell surface and lysosomes where its broken down (Kang et al., 1998; Byrd et al., 1999). Some in vitro studies have shown that retinoic acid stimulates growth hormone gene expression (Bedo et al., 1989; Guibourdenche et al., 1997). Growth hormone mediates the production of IGF-I and also stimulates to some extent the production of IGF-II in the liver.

We found a positive association of serum IGF-I, IGF-II, and IGFBP-3 with serum retinol in this study. Serum IGF-I levels were also higher in highest quartile of α-carotene, β-carotene, and β-cryptoxanthin among women in this study, although an epidemiological study (Tran et al., 2006) showed that dietary intakes of α-carotene and β-carotene were not related to either serum levels of IGF-I or IGFBP-3. Retinol may be a major source of retinoic acid, because retinoic acid is synthesized from retinol in organs (Blomhoff et al., 2006). Carotenes, such as α-carotene, β-carotene, and β-cryptoxanthin, is known as provitamin A (precursor to vitamin A). The conversion of provitamin A is strictly regulated in the body and results in the generation of retinal, the precursor of retinoic acid. This mechanism may affect our results. We suggested that vitamin A might be a determinant of circulating IGFs and IGFBP levels.

The evidence of association between other carotenoids and IGF system is inconsistent. Consumption of tomato products or intake of lycopene may be inversely associated with IGF-I and positively associated with IGFBP-3 (Voskuil et al., 2005). Lycopene intake may affect the IGF system, possibility through an effect on IGFBPs as well as retinoids. Other studies have, however, shown no association between lycopene supplementation and circulating IGF-I levels (Graydon et al., 2007). A recent study has shown no significant associations of serum carotenoids with serum IGF-I, IGFBP-3 levels, and IGF-I/IGFBP-3 ratio in Black and White men aged 25-37 years (Kim et al., 2007). They analyzed the association of lycopene, the sum of four carotenoids (α-carotene, β-carotene, lutein/zeaxanthin, and β-cryptoxanthin), and the sum of all five carotenoids with IGF-I, IGFBP-3, and the ratio of IGF-I/IGFBP-3. We used separated carotenoids in analyses of associations of serum carotenoids levels with serum levels of IGF-I, IGF-II, and IGFBP-3 in this study. We found that negative association of serum IGFBP-3 levels with serum lycopene in women and with zeaxanthin/lutein levels in men. Further detailed study of associations between lycopene or zeaxanthin/lutein and IGF system may be required to clarify these associations.

Serum samples had been stored in deep-freezers for about 10 years until assayed. We previously investigated whether levels of serum components measured after 9 years of frozen storage are stable or not. There was no statistically significant difference in distribution of measured values of IGF-I, IGF-II, and IGFBP-3 between newly collected sera and frozen specimens stored for 9 years (Ito et al., 2005). We also found that the mean differences in serum components were less than 15% for α-carotene and β-carotene and less than 20% for lycopene, β-cryptoxanthin, zeaxanthin/lutein, and retinol (Ito et al., 2000).

In conclusion, we found healthy men and women with high serum levels of retinol had higher serum levels of IGF-I, IGF-II, and IGFBP-3.

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