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Original Article

IGF-I and IGFBP-3 levels and their correlations with carcinoembryonic antigen in colorectal cancer patients

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ABSTRACT

Background: Colorectal cancer is one of the most frequently seen cancers worldwide. Currently, CEA is the most commonly used tumor marker in colorectal cancer. The changes in IGF/IGFBP equilibrium is also known to cause carcinogenesis. In this study, we aimed to monitor IGF-I/IGFBP-3 levels, the changes in IGF-I/IGFBP-3 ratio and correlations of these peptides with the common tumor marker CEA.
Materials and methods: 55 colorectal cancer patients and 35 control group patients were included in this study. Serum CEA, IGF-I and IGFBP-3 levels of all specimens were measured with chemiluminescence method.
Results: In colorectal cancer patients, IGF-I levels was found to be increased, IGFBP-3 levels decreased and IGF-I/IGFBP-3 ratio was increased; when compared to control group ($p < 0.05$). A moderately significant correlation was found between the conventional tumor marker CEA and IGF-I and IGF-BP3 ($p = 0.001$, $r = 0.533$ and $p = 0.001$, $r = -0.573$ respectively).
Conclusions: IGF-I/IGFBP-3 ratio seems to be increased in the colorectal cancer patients. When considered with the moderate correlation levels of these peptides with CEA, this increase in IGF-I/IGF-BP3 ratio may be useful in monitoring carcinogenesis in colorectal cancer patients among with CEA but more detailed and extensive studies in larger study groups needed to be carried out.

1. Introduction

The frequency of colorectal cancer in developed countries increased dramatically in recent years. Colorectal cancer is the second most common cancer in females and the third most common cancer in males worldwide. It is more common in developed countries with North America, Europe, and Australia having the highest incidence rates.[1,2] Different laboratory techniques are used in the diagnosis, treatment and follow up of colorectal cancer. Currently, carcinoembryonic antigen (CEA) is the most widespreadly used tumor marker. CEA is one of the most common oncofetal proteins to be used as a tumor marker as it functions as a homotypic intercellular adhesion molecule that promotes the aggregation of human colorectal carcinoma cells.[3] Clinical applications of CEA includes many different categories like diagnosis (distinction between benign and malignant tumors), treatment monitoring (therapeutic effect, tumor recurrence), special pathological techniques (immunohistochemistry, immunocytochemistry), localization (tumor monitoring with radiolabelled antibodies) and therapy (antibody-bound cytotoxic agents and vaccine vectors carrying the CEA gene).[4–6]

IGF-I is a 7.5 kDa, 70 aminoacid single chain polypeptide including three disulfide bonds. IGF-I mediates the growth stimulating effects of growth hormone (GH).[7,8] Studies conducted in the last two decades revealed that IGF-I is included in tumorigenesis process of various cancer types. The levels of IGF-I, IGF-II and IGF-IR are found to be elevated in malignancies like glioblastoma, neuroblastoma, meningioma and GIS, colorectal, pancreas and ovarian cancers.[9–12]

IGFBP-3 is found as a 150 kDa triple complex in circulation.[13] It serves as a depot by binding more than 90% of serum IGF-I.[14] This binding protein not only controls the level of free IGF-I, but it also blocks the effects of IGF-I and increases the half-life of IGF-I. Besides it's effects on IGF-I; IGFBP-3 plays important roles in cell survival, growth and differentiation in IGF-I independent manners.[15] Recent epidemiological studies have shown that low serum

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IGFBP-3 level is a negative risk factor for breast, prostate and colorectal cancers.[16]

Recent studies have shown that IGF/IGFBP ratio is a better predictor of disease progression.[17] IGF/IGFBP ratio alterations have proven to cause carcinogenesis in different levels and models.[18] There are also correlation studies about using IGF-I/IGFBP-3 ratio in various cancer types among with commonly used tumor markers.[19]

In this study, we aimed to detect IGF-I and IGFBP-3 levels and IGF-I/IGFBP-3 ratio changes in colorectal cancer patients. Another goal of the study is to determine the correlation of these peptides with CEA; the common tumor marker in colorectal cancer.

2. Materials and methods

Patient group was consisted of 55 newly diagnosed colorectal cancer patients who did not recieve any *anti*-cancer therapy or undergone cancer surgery, and who did not have any other malignancies, hypertension, diabetes mellitus, coronary artery disease, central or peripheric nervous system problems, liver disease, kidney failure or any other chronical illnesses and who had serum CEA levels above the reference limits and had no any other exclusion criteria. Control group was consisted of 35 healthy people with no signs of any acute or chronic diseases mentioned above and no signs of any malignancy; and who had CEA levels within the reference limits. Patient and control group subjects were all admitted to General Surgery Clinics at Ankara Numune Training and Research Hospital between August-October 2010. Blood samples were collected and allowed to coagulate for 30 min at room temperature and centrifuged at 1500*g* for 10 min. The extracted sera were aliquoted into eppendorf tubes and kept at −80 °C until the time of analysis.

Serum CEA level detection of all specimens were made with chemiluminescence method in Beckman Coulter UniCel® DxI 800 Immunoassay System analyzers. Serum IGF-I and IGFBP-3 levels were detected with chemiluminescence immunometrical method in Siemens Immulite 1000 analyzer. The reference values for the related tumor marker CEA was accepted as 0–3 ng/mL (inter and intra-assay CV values of 6.3% and 5.8 respectively). The reference values for IGF-I was 78–222 ng/L (inter and intra-assay CV values of 7.4% and 4.5% respectively) and for IGF-BP3 was 3.4–6.9 ng/mL (inter and intra-assay CV values of 6.8% and 3.1% respectively).

3. Statistical analysis

Data analysis was made with SPSS for Windows 11.5 programme. The distribution patterns of continuous variables were checked with Kolmogorov-Smirnov test. Descriptive statistics of normally distributed continuous variables are illustrated as mean ± standard deviation. Descriptive statistics of non-normally distributed continuous variables are illustrated as median (interquartile range) values. Among group differences of normally distributed variables were analyzed with Student's *t* test while non-normally distributed variables were analyzed with Mann Whitney *U* test. Correlation analysis between CEA/IGF-I and CEA/IGF-BP3 pairs was made with Spearman's rho test and $p < 0.05$ was accepted as statistically significant.

4. Results

Age, sex, serum CEA, IGF-I and IGFBP-3 levels of patient and control groups are listed in Table 1.

IGF-I levels of control and patient groups are shown in Fig. 1, in a Box-Whiskar plot. There is a statistically significant ($p < 0.05$) difference between patient and control groups.

Table 1
The sex distribution, mean ages, CEA,IGF-I,IGFBP-3 levels and IGF-I/IGFBP-3 ratios of the study groups.

	Patient (n = 55)	Control (n = 35)	P
Age	59.4 ± 12.06	55.1 ± 10.05	0.085
Gender (%) (F/M)	36.4/63.6	40/60	0.945
CEA (ng/mL)	28.1 (10.7–144.2)[a]	1.1 ± 0.4	0.000*
IGF-I (ng/L)	84.1 (47.1–136)[a]	26 (22–38)[a]	0.000*
IGFBP3 (ng/ml)	1.56 (1.24–2.27)[a]	3.0 ± 0.84	0.001*
IGF-I/IGFBP3	58.0 ± 23.5	11.1 ± 4.34	0.001*

[a] Continuous variables that did not show normal distribution.
* Statistically significant.

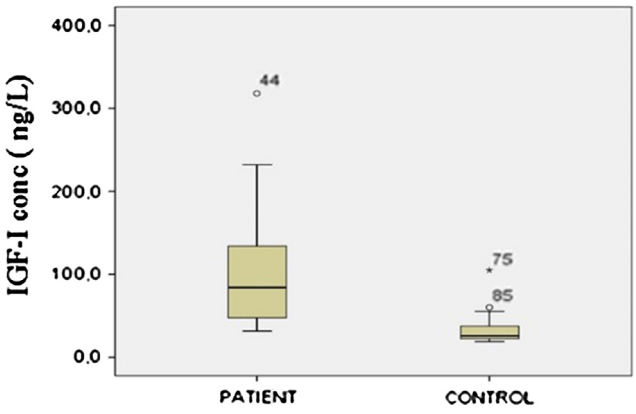

Fig. 1. Distribution of serum IGF-I levels in patient and control groups: Box-Whisker graph.

There is a statistically significant ($p < 0.05$) difference between the IGFBP-3 levels of the patient and control groups. IGFBP-3 levels of control and patient groups are shown in a Box-Whiskar plot in Fig. 2.

IGF-I/IGFBP-3 ratios of patient and control groups are shown in a Box-Whiskar plot in Fig. 3. There is a statistically significant ($p < 0.05$) difference between IGF-I/IGFBP-3 ratios of the patient and control groups.

For the correlation analysis, 5 samples with CEA levels above 1000 ng/mL were excluded as those values were exceeding analytical detection range.

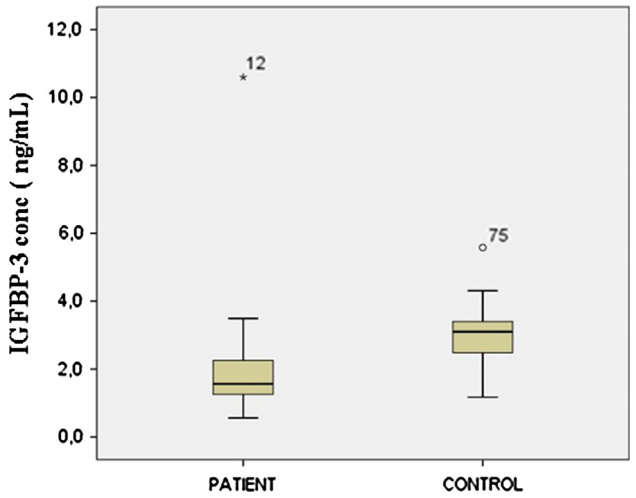

Fig. 2. Distribution of serum IGFBP-3 levels in patient and control groups: Box-Whisker graph.