THE ROLE OF INSULIN-LIKE GROWTH FACTOR-1 AND INSULIN IN DEVELOPMENT OF COLORECTAL CANCER

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Colorectal cancer is one of the most common malignant tumors in the world. It is now ranked third-fourth worldwide in terms of oncological disorders. In 2012, 1.4 million new cases of cancer were recorded, according to the World Cancer Research Fund International [1]. In Georgia, 436 new cases of colorectal cancer were discovered in 2008, with 4 (0.9%) having the first stage, 82 (18.8%) having the second stage, 131 (30.1%) having the third stage, and almost half having the fourth stage of illness. According to the National Center for Disease Control, colorectal cancer was the third most frequent malignancy in women (10.9 per 100,000 women) and men (12.3 per 100,000 people) in 2014. In recent years, the number of people with colon cancer has been increasing every year. Despite the success of modern radiation and chemotherapy, surgery remains the primary therapeutic option for colorectal cancer. As a consequence, attention should be given to the search for variables (including hormonal-metabolic) that may change the fact that the individual is diagnosed with colon cancer. The demonstration of these factors has the potential to lead to breakthroughs in illness prevention and treatment.

Insulin-like growth factor 1 (IGF-1) was previously known as Somatomedin C. It stimulates the action of the hormone, controls it, and has an insulin-like function. Its ability to promote various cell growth in vitro and in vivo is one of its primary characteristics. IGF-1 is released in the liver and other organs and has a mitogenic impact on the paracrine mechanism. Because IGF-1 receptors are present on nearly all cell types, we may conclude that this effect is ubiquitous. IGF-1 is also found in the blood, where it circulates mainly in a complex with binding-protein 3. It binds to the insulin-like growth factor (binding-protein 3). It has been found that only approximately 5 percent of IGF freely circulates in the plasma. During the natal and neonatal periods, the quantity of IGF-1 in human plasma is very low. Its concentration increases after a certain period. Binding-protein 3 protects circulating IGF from breakdown and transports it to particular tissue destinations.

Hyperinsulinemia is characterized by elevated plasma insulin levels and an overreaction of insulin to increasing plasma glucose concentrations. Both hereditary and environmental causes may cause it. Hyperinsulinemia is a compensatory reaction that maintains glucose homeostasis in insulin-resistant people [2]. Recent experimental investigations support the role of insulin in colon carcinogenesis by linking IGF-I, a potential mediator of cell survival and proliferation, in the etiology of colon cancer [3]. Circulating insulin levels, in particular, may enhance IGF-I bioavailability as a consequence of insulin-mediated changes in IGFBP concentration [4].

As a consequence of pathophysiological alterations in circulating IGF-I and IGFBP, chronic hyperinsulinemia may indirectly lead to colon carcinogenesis. In women with diabetes, the chance of developing malignant uterine tumors is doubled. There is additional evidence that serum-circulating insulin and insulin-like growth factor (IGF) are essential in the development of uterine cancer [5].

Laboratory and epidemiological studies have established the link between IGF and cancer development in different organs [6]. These examinations confirm that high levels of IGF in the blood serum and low levels of binding-protein 3 enhance the chance of developing colorectal cancer. Our research aims to better investigate the IGF system in order to identify its involvement in the development of colorectal cancer. The IGF system is recognized to be a possible mitogenic and antiapoptotic peptide with characteristics of both classic hormones and tissue growth factors. Considering all the above mentioned, it is crucial to focus on studying this highly topical problem.

Material and methods. The study was carried out at Acad. Fridon Todua Medical Center with 38 patients chosen for the study. The patients were divided into two groups: The first group – patients with colorectal cancer, and the second group – practically healthy patients. The first group included 27 patients with colorectal cancer, 22 of whom had Diabetes mellitus in anamnesis. The second group included 11 practically healthy patients. None of the healthy controls had a history of diabetes and ranged in age from 45 to 65. We check weight (kg), height (cm), and waist and hip circumferences (cm). Trained interviewers gathered information on colorectal cancer risk factors. The investigation questionnaire included age, occupation, education, ethnic group, residence, history of benign colorectal diseases, and malignant tumors. Body measurements include height, weight, waist and hip circumferences, and blood pressure. Criteria for inclusion in the study: patients with colorectal cancer, control group - practically healthy. Exclusion criteria: alcoholism, narcomania, pregnancy, hepatitis, AIDS. Patients underwent physical and clinical-laboratory examinations: The IGF-1 laboratory test was performed using the CLIA technique. The test was carried out using the Chromatography/Mass Spectrometry (LC/MS) technique, which allowed us to determine the amounts of IGF-1 and IGF binding-protein 3.

Insulin and glucose levels were assessed using the Oral Glucose Tolerance Test (OGGT) on an empty stomach and 120 minutes after glucose loading (40g/1m2). Additionally, the C-peptide index was determined. Insulin and C-peptide levels were determined using radioimmunoassay kits of "CEA-SEN-SORIN" (France). Enzymatic Colorimetric Methods were used to determine glucose levels. All processes were carried out following the manufacturer's specifications.

The data were statistically processed using the statistical software Epi-info version 7.2.2.6. Analyzed data were shown as mean ± SD, and the differences were considered significant when $P<0.05$.

Results and discussion. 38 patients participated in the study, 22 (57.9%) men, 16 (42.1%) women, 27 patients were included in the experimental group (71.05%), 11 - in the control group (28.95%)

Table 1. Analysis of insulin-like growth factor-1, insulin-like growth factor binding proteins 3 and serum insulin between pre and postoperative patients

Biomarkers	Control (n=11)	Preoperative Stage I-II-III	Postoperative	Stage IV
		Study group (n=27)	Study group (n=27)	
IGF-1 (ng/mL)	133.73±63.17	203.16±44.07	211.04±45.82	142.71±30.18
Binding-Protein 3 (μg/mL)	9.14±3.88	6.51±3.15	7.18±2.28	9.22±3.58
Insulin (μIU/mL)	6.21±4.65	9.68±4.55	9.99±6.08	6.58±4.68

Experimental group compared to healthy controls, P<0.001 and P<0.05

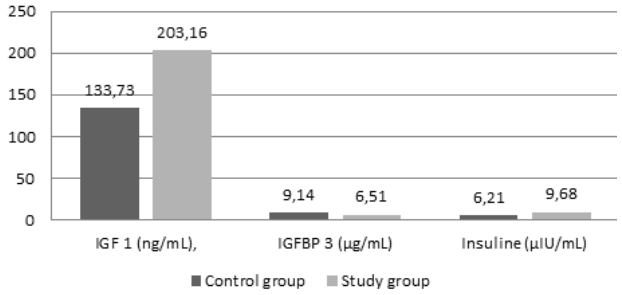

Fig. 1. Comparisons of pre-operation serum levels of biomarkers between colorectal cancer patients and healthy controls (x bar±s)

Healthy controls compared to pre- operation group of patients showed significant differences, *P*=0.015 and *P*=0.001.

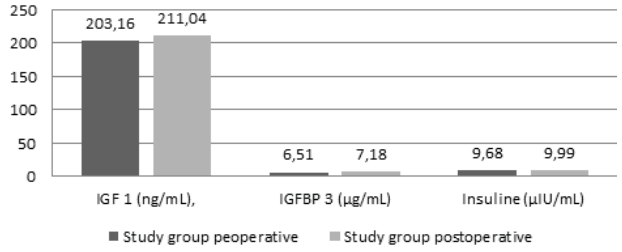

Fig. 2. Comparisons of pre-operation and post-operation serum levels of biomarkers between colorectal cancer patients

Pre-operation group of patients compared to post-operation group of patients, *P*=0.02, there were not significant difference for insulin, IGF-1: IFGBP-3.

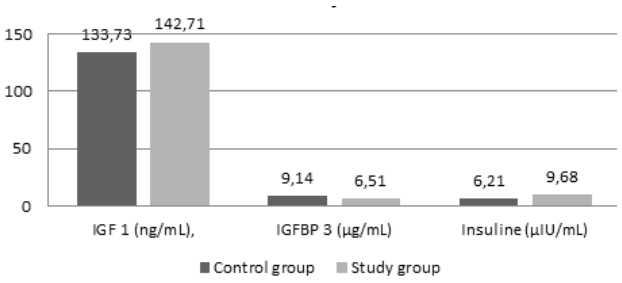

Fig. 3. Healthy controls compared to IV stage colorectal cancer patients

Healthy controls compared to IV stage colorectal cancer patients did not show significant differences, *P*=0.02.

The study showed that the levels of IGF-1 and insulin in patients with colorectal cancer increased significantly, while the level of binding-protein 3 decreased sharply, the difference between preoperative and postoperative biomarkers was negligible. Also, there was seen no difference between patients with metastatic and non-metastatic colorectal cancer.

According to various studies, a significant increase in the level of IGF-1 is predicted at an early stage of tumor development; our study additionally showed an increase in IGF-1 levels at any stage of colorectal cancer. Elevated IGF-1 levels can be used as a prognostic marker in the development of colorectal cancer.

IGF Binding-protein 3 is a causative agent of apoptosis. It regulates the concentration of IGF-1 in the blood. Due to hyperinsulinemia, the level of IGF binding-protein 3 reduces, which increases IGF-1 activity, inhibits cell apoptosis, stimulates cell proliferation, and promotes tumor cells' development [7].

Slattery et al. evaluated the effects of insulin, IGF-1 and IGFBPs on cell growth and proliferation, which played important roles in the etiology of colon cancer and breast cancer [8].

Excessive energy intake, physical inactivity, and obesity lead to insulin resistance. Consequently, plasma insulin concentrations tend to increase. Insulin resistance has been associated with increased plasma insulin levels, glucose intolerance, increased IGF-I, glucose and free fatty acids, body mass index, and increased risk for colorectal cancer [9-11]. Some studies do not explain the link between colorectal cancer and insulin levels [12,13]. And some studies suggest that hyperinsulinemia and insulin resistance may increase the risk of colon cancer [14,15].

Our study showed a significant increase of IGF-1 and insulin in patients with colorectal cancer compared to the control group and noted a substantial decrease in the levels of IGF binding-protein 3 in the experimental group compared to the control group. Our study also show that obesity could be risk factor in the development of colorectal cancer.

Our study results also showed that the levels of IGF-1, insulin, and IGF binding-protein 3 did not differ significantly in the first three stages of disease development, but there was a decline in these indexes in the fourth stage. Consequently, the role of these markers in determining the severity of the disease is negligible. However, this issue's study will be continued in our further studies, and other authors' data will be considered.

Table 2. Comparisons of body mass index ratio between colorectal cancer patients and healthy controls

Group	Body mass index
Colorectal cancer	30.5±3.2
Healthy controls	24.1±2.4

Conclusion: According to the given data from our study, it should be pointed out that an increase in insulin and IGF-1 levels, as well as a sharp decrease in the level of IGF binding-protein 3, may be a significant factor in the development of colorectal cancer, but their changes do not differ significantly in the first three stages of disease progression, but there was a decline in these indexes in the fourth stage.

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SUMMARY

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The study's goal is to discover the function of the IGF-1 factor and insulin in the development of colorectal cancer. Changes in these factors should be explored at various phases of colorectal cancer, including the preoperative and postoperative periods.

38 patients were selected for the study. Patients were divided into two groups: the first group - patients with colorectal cancer, and the second group - practically healthy. The first group included 27 patients with colorectal cancer. The second group included 11 practically healthy patients, who ranged in age from 45 to 65. The patients underwent physical and clinical-laboratory examinations: IGF-1 laboratory test: determination of IGF binding-protein 3 and Insulin levels.

The study showed that the levels of IGF-1 and insulin increased significantly in patients with colorectal cancer, while the level of IGF binding-protein 3 decreased sharply. The difference between preoperative and postoperative biomarkers was negligible.

According to our findings, an increase in insulin and IGF-1 levels, as well as a substantial reduction in IGF binding-protein 3 levels, may play a role in the development of colorectal cancer, although their alterations do not vary significantly in the first three phases of disease progression. It should be noted that these indices decreased in the fourth stage.

Keywords: Insulin; IGF 1, IGF binding protein, Colorectal cancer.

РЕЗЮМЕ

РОЛЬ ИНСУЛИНПОДОБНОГО ФАКТОРА РОСТА 1 И ИНСУЛИНА В РАЗВИТИИ КОЛОРЕКТАЛЬНОГО РАКА

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Целью исследования является определение роли инсулиноподобного фактора роста 1 и инсулина в развитии колоректального рака и изучение характера изменений этих факторов на различных стадиях заболевания, а также до операции и в послеоперационном периоде.

Для исследования отобрано 38 пациентов, которые разделены на две группы: первая группа представлена больными колоректальным раком (n=27), вторая - практически здоровыми лицами (n=11) в возрасте от 45 до 65 лет. Пациентам проводили физикальные, клинические и лабораторные исследования, лабораторный тест на инсулиноподобный фактор роста 1 (ИПФР 1) и определение концентрации связывающего белка 3 и инсулина. Исследование показало, что у больных колоректальным раком существенно возрастает концентрация ИПФР 1 и инсулина, концентрация связывающего белка 3 резко снижается, однако разница между этими показателями до и после операции несущественна.

Результаты проведенного исследования позволяют сделать вывод, что повышение концентрации ИПФР 1 и инсулина, снижение связывающего белка 3 в крови являются значимым фактором, способствующим развитию колоректального рака. Изменения этих показателей существенно не различаются по ходу прогрессирования этого заболевания на первых трех стадиях, однако на четвертой стадии выявляется снижение их концентрации.

რეზიუმე

ინსულინმსგავსი ზრდის ფაქტორის-1 და ინსულინის როლი კოლორექტული კიბოს განვითარებაში

ზ.მაღლაფერიძე, ვ.კაპეტივაძე, რ.თაბუკაშვილი, თ.ლაზაშვილი, მ.ყუფარაძე, ე.გრატიაშვილი

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, შინაგან დაავადებათა პროპედევტიკის დეპარტამენტი; ფ.თოდუას სამედიცინო ცენტრი, თბილისი, საქართველო

კვლევის მიზანს წარმოადგენდა ინსულინმსგავსი ზრდის ფაქტორის-1 და ინსულინის როლის განსაზღვრა კოლორექტული კიბოს განვითარებაში და აღნიშნული ფაქტორების ცვლილებების დადგენა კოლორექტული კიბოს სხვადასხვა სტადიაზე, ოპერაციამდე და ოპერაციის შემდგომ პერიოდებში.

კვლევაში ჩართული იყო 38 პაციენტი 45-დან 65 წლამდე. პაციენტები დაიყო ორ ჯგუფად: პირველი ჯგუფი (n=27) – კოლორექტული კიბოთი ავადმყოფები, მეორე ჯგუფი – პრაქტიკულად ჯანმრთელი პირები (n=11). პაციენტებს ჩაუტარდა ფიზიკალური, კლინიკური და ლაბორატორიული გამოკვლევები: ინსულინმსგავსი ზრდის ფაქტორის-1-ის (იმზფ-1) ლაბორატორიული ტესტი, შემაკავშირებელი ცილა 3-ის და ინსულინის დონის განსაზღვრა. კვლევამ აჩვენა, რომ კოლორექტული კიბოთი დაავადებულ პაციენტებში მნიშვნელოვნად მატულობს იმზფ-1-ის და ინსულინის მაჩვენებლები, ხოლო შემაკავშირებელი ცილა 3-ის დონე მკვეთრად კლებულობს, განსხვავება ოპერაციამდე და ოპერაციის შემდეგ ბიომარკერებს შორის უმნიშვნელო იყო.

კვლევის შედეგად მიღებული მონაცემების საფუძველზე უნდა აღინიშნოს, რომ ინსულინის და იმზფ-1-ის მაჩვენებლების მატება, ხოლო შემაკავშირებელი ცილა 3-ის დონის მკვეთრი კლება შეიძლება გახდეს კოლო-რექტული კიბოს განვითარების მნიშვნელოვანი ფაქტორი. მათი ცვლილებები მნიშვნელოვნად არ განსხვავდება დაავადების პროგრესირების პირველ სამ სტადიაზე, ხოლო მეოთხე სტადიაზე აღინიშნა ამ მაჩვენებლების შემცირება.

PSYCHOLOGICAL AND PSYCHOPATHOLOGICAL FEATURES OF PATIENTS WITH SKIN CANCER

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Oncology is one of the most pressing medical and social problems in the world [1-3]. Malignant tumors are the second major cause of death in the world and one of the most economically expensive diseases; the World Health Organization's experts predict that cancer incidence will increase 1.5 times by 2030 [4,5]. In recent decades a modern trend has developed rapidly in the intersection of clinical psychology, psychiatry and oncology - psycho-oncology, studying psychiatric and medico-psychological aspects of oncological pathology, as well as developing strategies for psychosocial care for cancer patients [6,7]. There is an urgent need to provide cancer patients with adequate psychosocial care; at the same time, the formation and development of psycho-oncology meets a number of difficulties, which requires efforts of oncologists and psychiatrists, as well as the activation of extensive scientific researches in this field [8,9]. One of the most significant groups of oncological nosologies is skin cancer, which is characterized by a high prevalence and significant social consequences [10]. In patients with skin cancer revealed a wide range of psychopathological symptoms, mainly depressive and anxiety spectrum, as well as three times higher risk of development of mental disorders compared with healthy people [11–13]. All this determines the relevance of the study of various aspects of psychopathological symptoms associated with skin cancer and finding modern methods of psychosocial care of patients with this pathology.

The aim - study of individual-psychological characteristics and spectrum of psychopathological symptomatology of patients with skin cancer taking into account gender differences.