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SIGNIFICANT FACTORS ASSOCIATED WITH INSULIN-LIKE GROWTH FACTOR 1 AND ITS BINDING PROTEIN 3 IN COLORECTAL CANCER – MULTIPLE REGRESSION ANALYSIS

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მნიშვნელოვანი ფაქტორები, რომლებიც დაკავშირებულია ინსულინის მსგავს ზრდის ფაქტორ 1-თან და მის შემაკავშირებელ პროტეინ 3-თან კოლორექტალური კიბოს დროს - მრავლობითი რეგრესიული ანალიზი

შინაგან დაავადებათა პროპედევტიკის დეპარტამენტი, თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი; ფრიდონ თოდუას სამედიცინო ცენტრი

რეზიუმე

მიზანი: *ჩვენი კვლევის მიზანს წარმოადგენდა ინსულინის მსგავსი ზრდის ფაქტორი 1-ის და მისი შემაკავშირებელი პროტეინი 3-ის მაჩვენებელთა კავშირის შესწავლა კრკ-ის რისკ-ფაქტორებსა და სიმპტომებთან მრავლობითი რეგრესიული ანალიზის საფუძველზე.*

მეთოდები: *იმზფ-1-ის ლაბორატორიული ტესტი ჩატარდა ECLIA-ს მეთოდით. ინსულინის და გლუკოზის დონის შეფასება წარმოებდა ორალურ გლუკოზტოლერანტული ტესტით (ოგტტ) უზმოდ და გლუკოზის დატვირთვიდან (40გ/1მ²) 120 წუთის შემდეგ. გამოსავალზე (**იმზფ-1**-ისა და **იმზფშპ-3**-ის დონეები) სხვადასხვა პარამეტრის ერთობლივი ზეგავლენის შესწავლის მიზნით ჩატარდა მრავლობითი რეგრესიული ანალიზი.*

შედეგები: *მრავლობითი რეგრესიის საფუძველზე საბოლოოდ მოდელში დარჩა სარწმუნო ცვლადები (ფაქტორები), რომლებიც ერთობლივ ზეგავლენას ახდენენ გამოსავალზე (IGF BP3-ის მნიშვნელობაზე). წრფივი მრავლობითი რეგრესიის ფუნქციამ მიიღო შემდეგი სახე: X1 - სქესი (პირდაპირი); X4 - ოპერაციის კოდი (უკუ); X7 - ჩივილი A29 სხვა ზოგადი სიმპტომი/ჩივილი (უკუ); X13 - ჩივილი D08 მეტეორიზმი/გაზები/ბოყინი (უკუ); X20 – ქიმიოთერაპიის ან სხივური თერაპიის კურსი ოპერაციამდე (უკუ); X27 - HOMA-S (პირდაპირი); X28 - HOMA-IR (პირდაპირი); X31 - კრეატინინი (პირდაპირი).*

დასკვნა*: მიმდინარე კვლევის შედეგებზე დაყრდნობით დავასკვენით, რომ CRC არის მულტიფაქტორული და მის განვითარებაზე მრავალი მნიშვნელოვანი ფაქტორია პასუხისმგებელი. მისი განვითარების ერთ-ერთი შესაძლო მექანიზმი არის ინსულინის/IGF-1 სასიგნალო გზის ცვლილება სხვა მნიშვნელოვან ბიოლოგიურ და არაბიოლოგიურ ფაქტორებთან.*

Introduction

According to GLOBOCAN 2018 statistics, among all localized cancers worldwide, colorectal cancer (CRC) ranks third in terms of incidence, followed by mortality in second place despite better screening programs for early detection and therapeutic achievement [1]. Statistics indicate an increase in CRC incidence and mortality rates above the age of 50 years. Approximately 90% of worldwide incidence and mortality was reported in this age group. It is also noteworthy that the incidence rate in men is higher (by 30%) than in women, with a wider variation for rectal cancer (more than 60%) than for colon cancer (more 30%) [2]. Among the top 5 localizations of cancer registered in women in Georgia, CRC ranks 3rd among women and 4th among men. The risk of CRC development in 2015-2019 was 4.2% in both men and women [3].

Higher concentrations of cellular insulin-like growth factor-1 (IGF-1) and decreased concentrations of its cellular binding protein 3 IGF BP3 are significantly associated with increased risk of CRC [4,5]. Potential linkage between serum IGF-1 concentrations and their tissue expression (including various mRNA isoforms) have been reported in some papers about colorectal carcinogenesis [6,7].

The majority of CRC cases (60–65%) are sporadic (excluding CRC with family history) associated with somatic mutations and epigenetic changes due to modifiable risk factors [8]. According to the literature data, several parameters and factors are associated with such behavior of IGF-1 and IGF BP3 levels during CRC: patient age, carbohydrate metabolism parameters, obesity and overweight, blood pressure, sex hormone abnormalities, smoking, etc. [9-16]. Data about such relationships are widely variable, often controversial [14-20]. But there are no large-scale studies on how the IGF system is changed in the case of joint exposure of these factors.

Therefore, the aim of our study was to investigate the association of insulin-like growth factor-1 and its binding protein 3 levels with CRC risk factors and symptoms by multiple regression analyzes.

Methods

The research was carried out in Acad. F. Todua Medical Center. The criteria for inclusion in the study group were the presence of a colorectal malignancy and a signed informed consent to participate in the study; the criteria for inclusion in the control group were conditionally healthy individuals and a signed informed consent to participate in the study. Criteria for exclusion from the study in both groups were following: frequent alcohol consumption, drug addiction, pregnancy, as well as patients with hepatitis and AIDS. According these selection criteria, study and control groups completed by 50 and 50 participants, respectively.

The IGF-1 laboratory test was performed using the ECLIA method. Blood samples was collected in a serum flask; the blood was coagulated for 10-15 minutes; then the serum was separated from the cells, and then placed in a refrigerator at a temperature of 1-70C. Liquid Chromatography / Mass Spectrometry (LC / MS) methodology was used to perform the test, according to which the concentrations of IGF-1 and IGF BP3 were calculated.

Serum insulin and glucose levels were assessed by oral glucose tolerance test (OGTT) in fasting state and after 120 minutes of glucose loading (40g/1m2 of body surface). A highly specific radioimmunoassay was used to determine insulin with kits from CEA-SEN-SORIN (France). Determination of glucose levels was performed by enzyme colorimetric method. β-cell function and insulin resistance were assessed by Homeostasis Model Assessment (HOMA) [21].

The obtained results were statistically treated by the statistical software SPSS22.0. Quantitative parameters are presented as means and standard deviation (SD), and qualitative variables are presented as percentages. Student t-test was used to compare quantitative parameters and Chi2-test was used to compare qualitative variables. The criterion to reject the null hypothesis was $p < 0.05$.

Multiple regression analysis performed to study the mutual impact of different parameters on outcome (IGF-1 and IGF BP3). Parameters selected as variables were following: X1 – sex (male - 1; female - 2); X2 - age, year; X3 – stage of cancer (1; 2; 3; 4); X4 – code of surgery method (JFSB46 – 1; JFSB43 – 2; JFSB40 – 3; JFSB30 – 4; JGSB00 – 5; JGSB20 – 6; JGSB30 – 7); X5 - complaint A04 Weakness / fatigue in general (yes - 1; no - 2); X6 - complaint A10 Bleeding that is not specified otherwise (yes - 1; no - 2); X7 - complaint A29 Other general symptoms / complaints (yes - 1; no - 2); X8 - complaint D01 Abdominal pain / spasm in general (yes - 1; no - 2); X9 - complaint D02 Abdominal pain in the epigastric region (yes - 1; no - 2); X10 - complaint D04 Pain in the rectum / anus (yes - 1; no - 2); X11 - complaint D06 Abdominal pain of other localization (yes - 1; no - 2); X12 - complaint D07 Dyspepsia / digestive disorders (yes - 1; no - 2); X13 - complaint D08 Flatulence Gases (yes - 1; no - 2); X14 - complaint D11 Diarrhea (yes - 1; no - 2); X15 - complaint D16 Bleeding from the rectum (yes - 1; no - 2); X16 - complaint T03 Loss of appetite (yes - 1; no - 2); X17 - complaint T08 weight loss (yes - 1; no - 2); X18 - complaint P13 Encopresis / defecation problem (yes - 1; no - 2); X19 - presence of a colostomy (yes - 1; no - 2); X20 - A course of chemotherapy or radiation therapy before surgery (yes -1; no - 2); X21 - BMI, kg/m^2; X22 – waist circumference, cm; X23 – fasting glycemia, mmol/l; X24 – fasting C-peptide, ng/ml; X25 – fasting insulin, μU/ml; X26 - HOMA-B; X27 - HOMA-S; X28 - HOMA-IR; X29 – systolic blood pressure, mm.Hg; X30 - diastolic blood pressure, mm.Hg; X31 - Creatinine, mg/dl; X32 - Pain, score; X33 - ECOG, score.

Results

The multiple linear regression model examined the significant factors with a mutual effect on the outcome (variables are given in the methods section). On stage I, IGF-1 was selected as the outcome (in

the model it was denoted by Y1). Non-significant variables were excluded from the model by the back-step method:
X7, X31, X32, X19, X6, X4, X10, X15, X18, X27, X2, X5, X8, X9, X25, X33, X17, X16, X30, X23, X26, X20, X12, X11.

Finally, significant variables (factors) were left in the model having mutual effect on the outcome (IGF-1 value). The linear multiple regression function took the following form:

Y = 131.9 - 27.3 X1 - 5.7 X3 + 54.0 X13 + 19.4 X14 + 3.9 X21 - 0.98 X22 - 7.3 X24 + 17.4 X28 - 0.5 X29

The coefficients for this function with significance levels are given in Table #1.

Table #1. Function coefficients obtained by linear multiple regression

	Value*	Standard deviation	t-test	P
β0	131.95	36.42	3.62	< 0.001
β1	-27.26	4.30	-6.34	< 0.001
β3	-5.74	2.32	-2.47	0.018
β13	53.96	12.80	4.22	< 0.001
β14	19.36	6.17	3.14	0.003
β21	3.88	0.76	5.10	< 0.001
β22	-0.98	0.24	-4.11	< 0.001
β24	-7.25	3.16	-2.29	0.027
β28	17.39	3.71	4.69	< 0.001
β29	-0.54	0.16	-3.28	0.002

* The "-" sign indicates a inverse correlation, and a "+" indicates a direct correlation

Hence these factors (each factor in parentheses indicates the nature of the correlation - direct or inverse): X1 - Sex (inverse); X3 - Stage (inverse); X13 - Flatulence Gases (direct); X14 - Diarrhea (direct); X21 – BMI (direct); X22 – Waist Circumference (inverse); X24 – fasting C-peptide (inverse); X28 - HOMA-IR (direct); X29 – systolic blood pressure (inverse).

On stage II, IGF BP3 was selected as the outcome (in the model it was denoted by Y2). Non-significant variables were excluded from the model by the back-step method: X33, X24, X2, X19, X32, X18, X6, X26, X11, X10, X14, X29, X17, X12, X8, X30, X9, X21, X23, X25, X3, X16, X22, X15.

Finally, significant variables (factors) were left in the model having mutual effect on the outcome (IGF BP3 value). The linear multiple regression function took the following form:

Y2 = 4.58 + 0.32 X1 - 0.06 X4 - 0.45 X5 - 1.68 X7 - 0.85 X13 - 0.50 X20 + 0.07 X27 + 0.25 X28 + 0.06 X31

The coefficients for this function with significance levels are given in Table #2.

Table #2. Function coefficients obtained by linear multiple regression

	Value*	Standard deviation	t-test	P
β0	4.57	1.40	3.25	0.002
β1	0.32	0.10	3.17	0.003
β4	-0.06	0.02	-3.12	0.003
β5	-0.45	0.13	-3.28	0.002
β7	-1.68	0.32	-5.20	< 0.001
β13	-0.85	0.36	-2.33	0.025
β20	-0.50	0.11	-4.39	< 0.001
β27	0.07	0.02	3.80	< 0.001
β28	0.24	0.11	2.24	0.030
β31	0.06	0.02	3.46	0.001

* ნიშანი "-" მიუთითებს უკუკორელაციურ კავშირზე, ხოლო "+" - პირდაპირკორელაციურზე

Hence these factors (each factor in parentheses indicates the nature of the correlation - direct or inverse): X1 - Sex (direct); X4 – Code of Surgery (inverse); X7 – other general pains/symptoms (inverse); X13 - Flatulence Gases (inverse); X14 - Diarrhea (direct); X20 – A course of chemotherapy or radiation therapy before surgery (inverse); X27 – HOMA-S (direct); X28 - HOMA-IR (inverse); X31 – creatinine (direct).

Discussion

The majority of CRC cases (60–65%) are sporadic (excluding CRC family history) associated with somatic mutations and epigenetic changes due to modifiable risk factors [8]. Approximately 35–40% of CRC cases are due to hereditary components [22,23], while family history accounts for approximately 25% of cases without disease phenotype [24].

Several other physical factors such as body mass, age, sex, body mass index (BMI) and lifestyle, smoking and etc. also are associated with juvenile CRC. Weight loss followed by fatigue and constant tiredness can be the early symptom [25]. In addition, women with a BMI greater than 30 kg / m2 had a higher risk of developing CRC (95% CI 1.15–3.25) compared to women with a normal BMI [26]. Low et al. suggest that smoking is not associated with the risk of juvenile delinquency; Neither current nor former tobacco users were at risk of developing CRC compared to non-smokers [25]. There is a higher chance of progression of CRC than juvenile CRC; Obesity is a major risk factor for colon cancer in the elderly [10,11]. The authors conclude that these differences indicate several factors associated with juvenile CRC and further studies are needed to identify the main associated risk factors.

Smoking, increased BMI, red meat intake, lack of regular physical activity, and poor diet are all associated with an increased risk of CRC [12]. Various studies have shown that about 12% of CRC-related deaths are caused by tobacco use. Tobacco smoke contains at least 70 chemicals that are classified as carcinogenic. Smoking in men is associated with early onset and distal location of CRC [13].

Food content is closely related to the risk of developing CRC. Some studies show a 70% reduction in risk by switching to healthier foods and acquiring healthier eating habits [27]. Patients who consume fatty foods, especially red meat, have a higher risk of developing high-grade CRC [28,29]. Meat consumption is more closely related to colon cancer than rectal cancer [30]. The mechanical association with the positive association of red meat consumption with CRC is the presence of hemi-iron in the meat [30,31]. Meat cooked at high temperatures produces heterocyclic amines and polycyclic aromatic hydrocarbons, which are considered carcinogenic compounds [30,32]. People who consume calcium-rich foods (diet and supplements), fruits, fiber and vegetables have a decreased risk of CRC development [33,34].

Overweight and obese individuals are at a higher risk of mortality, ranking fifth among the causes of cancer-related mortality. Approximately 2.8 million adults die each year from obesity-related cancer [35]. In Europe, about 11% of CRC cases are associated with obesity and overweight [35]. Researchers have found a positive association between excessive body mass and cancer in both sexes; however, it has been found that men are at higher risk. The authors attributed this to the fact that testosterone levels are significantly lower in older men than in postmenopausal women with higher estrogen levels [36]. Various studies have shown a significant positive correlation between CRC and BMI [37,38]; The total RR of BMI to predict CRC by each 1 kg / m2 increment was 1.03 (95% CI, 1.02-1.03) [39]. BMI is associated with total body fat; waist circumference - with abdominal fat; Studies have shown that an increased risk of CRC is more closely related to waist circumference than BMI [40,41].

Abdominal fat is divided into 2 categories: visceral adipose tissue and subcutaneous adipose tissue. Inflammatory pro-adipokines (e.g., TNF) at higher levels and adiponectin (insulin-sensitive hormone) at lower levels are secreted in visceral adipose tissue compared to the subcutaneous adipose tissue [42]. For any BMI, visceral obesity is more common in Asian populations than in Caucasians [43]. Evidence from one study confirms that obesity in men compared to women is strongly associated with an incidence of rectal cancer compared with colon cancer and an incidence of distal cancer compared with proximal colon cancer [44]. One meta-analysis showed an association between abdominal obesity and an increased risk of colorectal adenoma (RR, 1.42; 95% CI, 1.30-1.56) [45]. Other meta-analyzes predicted a higher risk of developing CRC in diabetic patients (21%; 95% CI, 1.02-1.42) compared with non-diabetics [46].

Obesity can also lead to hyperinsulinemia and insulin resistance (IR) [47] due to low expression of insulin receptors and decreased intracellular insulin signaling in response to the insulin receptor binding [48]. This leads to an increase in insulin secretion and a decrease in insulin sensitivity, leading to an increase of IGF-1 levels. IGF-1 is involved in the maintenance of tissue homeostasis, in the differentiation of phenotype, growth regulation, proliferation, apoptotic imbalance, angiogenesis, migration, cell adhesion, and wound healing [49]. The signaling pathway of insulin-IGF-1 promotes colorectal carcinogenesis by reducing apoptosis and increasing cell proliferation [50]. After menopause, obesity becomes a major site of estrogen production in women, protecting them from susceptibility to CRC [51,52]. Thus, cancer induced by insulin and IGF1 in older women with excess body mass or obesity may counteract the anticancer effects of estrogen [53].

Intake of dietary insoluble fibers by increased concentrations reduces the risk of colorectal epithelial carcinogenesis by increasing the fecal mass in the lumen, diluting the fecal content, and reducing the transition time [54]. One study found that rural Africans had a lower risk of developing CRC compared to Westerners due to higher fiber intake [55].

A case-control study predicted a association between CRC incidence and dietary fiber intake; authors concluded that grains with a high content of dietary fiber were significantly associated with the risk of CRC (increase by 10 g per day - RR, 0.90; 95% CI, 0.83-0.97 compared with fiber of fruits, vegetables and legumes) [56]. In their report, the World Cancer Research Foundation (WCRF) and the American Institute for Cancer Research (AICR) added fiber-containing grains to the list of possible protective agents against CRC [57].

Conclusion

Based on the results of current study we concluded that CRC is multifactorial and many significant factors are responsible for its development. One of possible mechanisms for its development is the changes insulin/IGF-1 signaling pathway with other significant biological and non-biological factors. Study results will be useful for the identification of risk groups and prevention measures. However, these results should be confirmed by other RCTs and more wide population-based studies.

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ЗВИАД МАГЛАПЕРИДЗЕ, ВЕРА КАПЕТИВАДЗЕ, РЕВАЗ ТАБУКАШВИЛИ, ТАМАР ЛАЗАШВИЛИ, МАРИНА КУПАРАДЗЕ, ЭРЕКЛЕ ГРАТИАШВИЛИ

ЗНАЧИТЕЛЬНЫЕ ФАКТОРЫ, СВЯЗАННЫЕ С ИНСУЛИНОПОДОБНЫМ ФАКТОРОМ РОСТА 1 И ЕГО СВЯЗЫВАЮЩИМ БЕЛКОМ 3 ПРИ КОЛОРЕКТАЛЬНОМ РАКЕ -МНОЖЕСТВЕННЫЙ РЕГРЕССИОННЫЙ АНАЛИЗ

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РЕЗЮМЕ

Цель: Цель нашего исследования состояла в том, чтобы исследовать ассоциацию инсулиноподобного фактора роста-1 и уровней его связывающего белка 3 с факторами риска CRC и симптомами с помощью множественного регрессионного анализа.

Методы. Лабораторный тест IGF-1 был выполнен с использованием метода Eclia. Уровни инсулина в сыворотке и глюкозы оценивали с помощью перорального теста на толерантность к глюкозе (OGTT) в состоянии натощак и после 120 минут нагрузки глюкозы (40 г / 1 м2 поверхности тела). Множественный регрессионный анализ, выполненный для изучения взаимного влияния различных параметров на результат (IGF-1 и IGF BP3).

Результаты: значительные переменные (факторы) были оставлены в модели, оказывающей взаимное влияние на результат (значение IGF BP3). Линейная функция множественной регрессии приняла следующую форму: следовательно, эти факторы (каждый фактор в скобках указывает на природу корреляции - прямой или обратный): x1 - пол (прямой); X4 - Код хирургии (обратный); X7 - другие общие боли/симптомы (обратные); X13 - газы (обратная); X14 - диарея (прямой); X20 - курс химиотерапии или лучевой терапии перед операцией (обратная); X27-Homa-S (прямой); X28 - homa -ir (обратный); X31 - креатинин (прямой).

Заключение. На основании результатов текущего исследования мы пришли к выводу, что CRC является многофакторным, и многие важные факторы ответственны за его развитие. Одним из возможных механизмов его развития является изменения сигнального пути инсулина/IGF-1 с другими значимыми биологическими и небиологическими факторами.

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SIGNIFICANT FACTORS ASSOCIATED WITH INSULIN-LIKE GROWTH FACTOR 1 AND ITS BINDING PROTEIN 3 IN COLORECTAL CANCER – MULTIPLE REGRESSION ANALYSIS

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SUMMARY

Aim: the aim of our study was to investigate the association of insulin-like growth factor-1 and its binding protein 3 levels with CRC risk factors and symptoms by multiple regression analyzes.

Methods: The IGF-1 laboratory test was performed using the ECLIA method. Serum insulin and glucose levels were assessed by oral glucose tolerance test (OGTT) in fasting state and after 120 minutes of glucose loading (40 g / 1 m2 of body surface). Multiple regression analysis performed to study the mutual impact of different parameters on outcome (IGF-1 and IGF BP3).

Results: Finally, significant variables (factors) were left in the model having mutual effect on the outcome (IGF BP3 value). The linear multiple regression function took the following form: Hence these factors (each factor in parentheses indicates the nature of the correlation - direct or inverse): X1 - Sex (direct); X4 – Code of Surgery (inverse); X7 – other general pains/symptoms (inverse); X13 - Flatulence

Gases (inverse); X14 - Diarrhea (direct); X20 – A course of chemotherapy or radiation therapy before surgery (inverse); X27 – HOMA-S (direct); X28 - HOMA-IR (inverse); X31 – creatinine (direct).

Conclusion: Based on the results of current study we concluded that CRC is multifactorial and many significant factors are responsible for its development. One of possible mechanisms for its development is the changes insulin/IGF-1 signaling pathway with other significant biological and non-biological factors.