ZVIAD MAGLAPHERIDZE, VERA KAPETIVADZE, REVAZ TABUKASHVILI,
TAMAR LAZASHVILI, MARINA KUPARADZE, EREKLE GRATIASHVILI

AGE-SPECIFIC FEATURES OF ISNULIN-LIKE GROWTH FACTOR 1, ITS BINDING PROTEIN 3, AND CARBOHYDRATE HOMEOSTASIS IN PATIENTS WITH COLORECTAL CANCER

Department of Internal Disease of Propaedeutics,
Tbilisi State Medical University; Fridon Todua Medical Center

ზვიად მაღლაფერიძე, ვერა კაპეტივაძე, რევაზ თაბუკაშვილი,
თამარ ლაზაშვილი, მარინა ყუფარაძე, ერეკლე გრატიაშვილი

ინსულინის მსგავსი ზრდის ფაქტორი 1-ის, მისი შემბოჭველი პროტეინი 3-ის და ნახშირწყლოვანი ჰომეოსტაზის ასაკობრივი თავისებურებანი კოლორექტული კიბოს მქონე პაციენტებში

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

რეზიუმე

მიზანი: *კვლევის მიზანს წარმოადგენდა ინსულინის მსგავსი ზრდის ფაქტორი 1-ის, მისი შემბოჭველი პროტეინი 3-ის და ნახშირწყლოვანი ჰომეოსტაზის ასაკობრივ თავისებურებათა შესწავლა კოლორექტული კიბოს მქონე პაციენტებში.*

მეთოდები: *კვლევაში ჩართული იყო 100 პაციენტი, საკვლევი და საკონტროლო ჯგუფებში გაერთიანდა 50-50 მონაწილე, რომლებიც ასაკის მიხედვით დაიყო სამ ასაკობრივ ჯგუფად, ჯგუფი 1 (30-55წ.), ჯგუფი 2 (55-65წ.), ჯგუფი (>65წ.). პაციენტებს უტარდებოდათ იმზფ-1-ის, იმზფშ3-3, გლუკოზის და ინსულინის ტესტები.*

შედეგები: *IGF-ის საშუალო მაჩვენებლები ასაკის მიხედვით დაყოფილ ჯგუფებში იყო შემდეგი: საკვლევი ჯგუფი S1 (35-55 წწ.) - 214.5 ± 23.0 ერთ.; საკვლევი ჯგუფი S2 (55-65 წწ.) - 202.5 ± 15.5 ერთ.; საკვლევი ჯგუფი S3 (> 65 წწ.) - 190.5 ± 22.0 ერთ.; საკონტროლო ჯგუფი C1 (35-55 წწ.) - 162.3 ± 31.7 ერთ.; საკონტროლო ჯგუფი C2 (55-65 წწ.) - 150.6 ± 35.7 ერთ.; საკონტროლო ჯგუფი C3 (> 65 წწ.) - 146.1 ± 32.4 ერთ. IGF BP3-ის საშუალო მაჩვენებლები ასაკის მიხედვით დაყოფილ ჯგუფებში იყო შემდეგი: საკვლევი ჯგუფი S1 (35-55 წწ.) - 2.0 ± 0.7 ერთ.; საკვლევი ჯგუფი S2 (55-65 წწ.) - 1.6 ± 0.3 ერთ.; საკვლევი ჯგუფი S3 (> 65 წწ.) - 1.7 ± 0.6 ერთ.; საკონტროლო ჯგუფი C1 (35-55 წწ.) - 3.6 ± 1.0 ერთ.; საკონტროლო ჯგუფი C2 (55-65 წწ.) - 3.9 ± 1.0 ერთ.; საკონტროლო ჯგუფი C3 (> 65 წწ.) - 3.6 ± 0.9 ერთ.*

დასკვნა: *კოლორექტული კიბოთი დაავადებულ პაციენტებში აღინიშნა **იმზფ-1** სისტემის ასაკდამოკიდებული სარეგულაციო მექანიზმების დარღვევა. თანაც, კოლორექტული კიბოს ყველა ასაკობრივ ჯგუფში იმზფ-1 და იმზფშ3-3 მაჩვენებლების ცვლილების ხასიათის მიუხედავად შენარჩუნებული იყო რეციპროკული (უკუპროპორციული) დამოკიდებულება ამ მაჩვენებლებს შორის. თუმცა, დაბალ ასაკობრივ ჯგუფში სქესითა და ასაკით კორექტირებული IGF-1-ის კონცენტრაცია სარწმუნოდ დაბალია.*

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]. The age-specific incidence rate of CRC per 2019 per 100,000 persons decreased in both women (21.6 → 17.4) and men (23.7 → 11.0); Mortality rates were increased in both women (10.0 → 13.6) and men (12.7 → 19.2). The incidence rate in both sex groups increases with age and reaches a maximum in 70-74 yrs. age group.

Potential link between serum concentrations of insulin-like growth factor-1 (IGF-1) and its tissue expression (including various mRNA isoforms) in colorectal carcinogenesis have been identified by some studies [4,5]. Higher concentrations of cellular IGF-1 and reduced concentrations of cellular IGF binding protein 3 (IGF BP3) were associated with an increased risk of CRC [6-8].

Comparison of serum concentrations of IGF-1 and IGF BP3 (measured by ELISA methods) in selected epidemiological studies at different stages of CRC and tissue expression of IGF-1, IGF-1R and IGF-3 are widely variable based on immunohistochemical methods [6-13]. Concentrations of serum IGF components in serum and local in vivo expression depend on studies, number of patients studied, and poor correlation with clinical data [14-19].

Therefore, the aim of our study was to study of age-specific features of IGF-1, IGF BP3, and carbohydrate homeostasis in patients with colorectal cancer.

Material and Methods.

The study was carried out in the Fridon Todua Medical Center. Inclusion criteria in study group were the presence of CRC and signed informed consent to participate in the study; participants for the control group were selected among conditionally healthy subjects after receipt of the signed informed consent. Exclusion criteria from the study for both groups were: the frequent alcohol consumption, drug addiction, pregnancy, as well as patients with hepatitis and AIDS.

The study and control groups consisted of 50-50 participants, who were divided into three age groups (see Table # 1).

Table #1. The distribution of patients in age groups

	Study group S	Control Group C
Group 1 (30-55 yrs.)	n=11	n=12
Group 2 (55-65 yrs.)	n=13	n=12
Group 3 (>65 yr.)	n=26	n=26

The study groups did not differ significantly from each other in terms of the tumor stages, the presence of a colostomy, the presence of preoperative chemotherapy and / or radiotherapy, body mass index (BMI), and waist circumference.

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 1-7^{0}C. 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 (40 g / 1 m^2 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) [20].

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 $p < 0.05$.

Results.

The mean IGF-1 values for the age groups were as follows (see diagram #1): study group S1 (35-55 yrs.) - 214.5 ± 23.0; study group S2 (55-65 yrs.) - 202.5 ± 15.5; study group S3 (> 65 yr.) - 190.5 ± 22.0; control group C1 (35-55 yrs.) - 162.3 ± 31.7; control group C2 (55-65 yrs.) - 150.6 ± 35.7; control group C3 (> 65 yr.) - 146.1 ± 32.4. Mean IGF-1 values observed in all study groups were significantly higher than in the corresponding control group ($p<0.05$). The analysis between the study groups showed that the mean IGF of study group 1 was significantly higher than mean IGF-1 of study group 3 ($p = 0.005$); The difference between the mean IGF-1 values of other groups was not significant.

After adjustment of IGF-1 values by age and sex for the age groups were as follows (see diagram #2): study group S1 (35-55 yrs.) - 1.03 ± 0.10; study group S2 (55-65 yrs.) - 1.12 ± 0.06; study group S3 (> 65 yr.) - 1.09 ± 0.09; control group C1 (35-55 yrs.) - 0.74 ± 0.15; control group C2 (55-65 yrs.) - 0.83 ± 0.20; control group C3 (> 65 yr.) - 0.81 ± 0.17. Sex-age-adjusted mean IGF values rate observed in all study groups was significantly higher ($p < 0.05$) compared to the corresponding control group. The analysis of these parameters between study groups showed that only the mean adjusted-IGF value in the study group S1 was significantly lower than in the study group S2 ($p = 0.012$); The difference between the other groups was not significant.

diagram #1. Mean IGF-1 values in age groups.

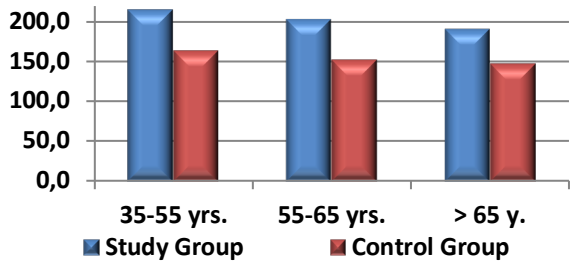
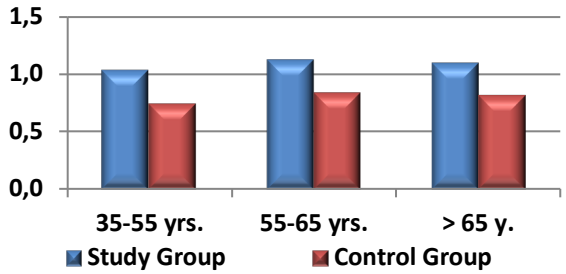


diagram #2. Mean IGF-1 values adjusted by age and sex in age groups.



The mean IGF BP3 values for the age groups were as follows (see diagram #3): study group S1 (35-55 yrs.) - 2.0 ± 0.7; study group S2 (55-65 yrs.) - 1.6 ± 0.3; study group S3 (> 65 yr.) - 1.7 ± 0.6; control group C1 (35-55 yrs.) - 3.6 ± 1.0; control group C2 (55-65 yrs.) - 3.9 ± 1.0; control group C3 (> 65 yr.) - 3.6 ± 0.9. The mean of IGF BP3 was significantly higher ($p < 0.05$) in all study groups compared to the corresponding control group. The analysis between the parameters of the study groups showed that the difference between the study groups was not significant.

After adjustment of IGF BP3 values by age and sex for the age groups were as follows (see diagram #4): study group S1 (35-55 yrs.) - 0.78 ± 0.29; study group S2 (55-65 yrs.) - 0.69 ± 0.16; study group S3 (> 65 yr.) - 0.77 ± 0.31; control group C1 (35-55 yrs.) - 1.43 ± 0.41; control group C2 (55-65 yrs.) - 1.64 ± 0.47; control group C3 (> 65 yr.) - 1.53 ± 0.46. Sex-age-adjusted mean IGF values rate observed in all study groups was significantly higher ($p < 0.05$) compared to the corresponding control group. The analysis of these parameters between study groups did not show the significant difference between the study groups.

diagram #3. Mean IGF BP3 values in age groups.

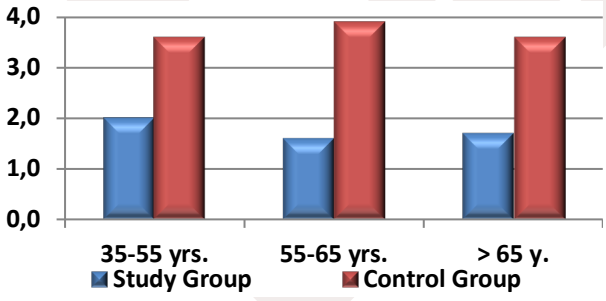
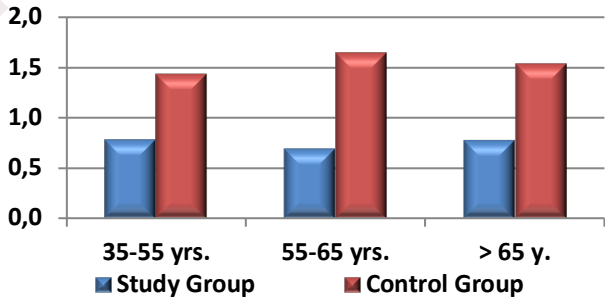


diagram #4. Mean IGF BP3 values adjusted by age and sex in age groups.



Comparison of the parameters of the carbohydrate metabolism showed the same trend in the study groups - the mean levels of fasting glycemia, C-peptide and insulin differed significantly from those of the control groups (see Table #2). The difference between these parameters between the study groups was not significant.

Comparison of the HOMA-indices of β-cell function (HOMA-B), insulin sensitivity (HOMA-S), and insulin resistance (HOMA-IR) showed the same trend - these indices of study groups were significantly differed from the indices of corresponding control groups (despite of HOMA-B of control group C2; see Table #3). Among the study groups themselves: a) the difference between the study groups S1 and S2 is close to the limit of significance ($p = 0.052$); b) the mean index of beta-cell function in the study group S1 is significantly higher than the similar indices of the group S3 ($p = 0.023$); c) The difference between the other indices was not significant (diagram #5).

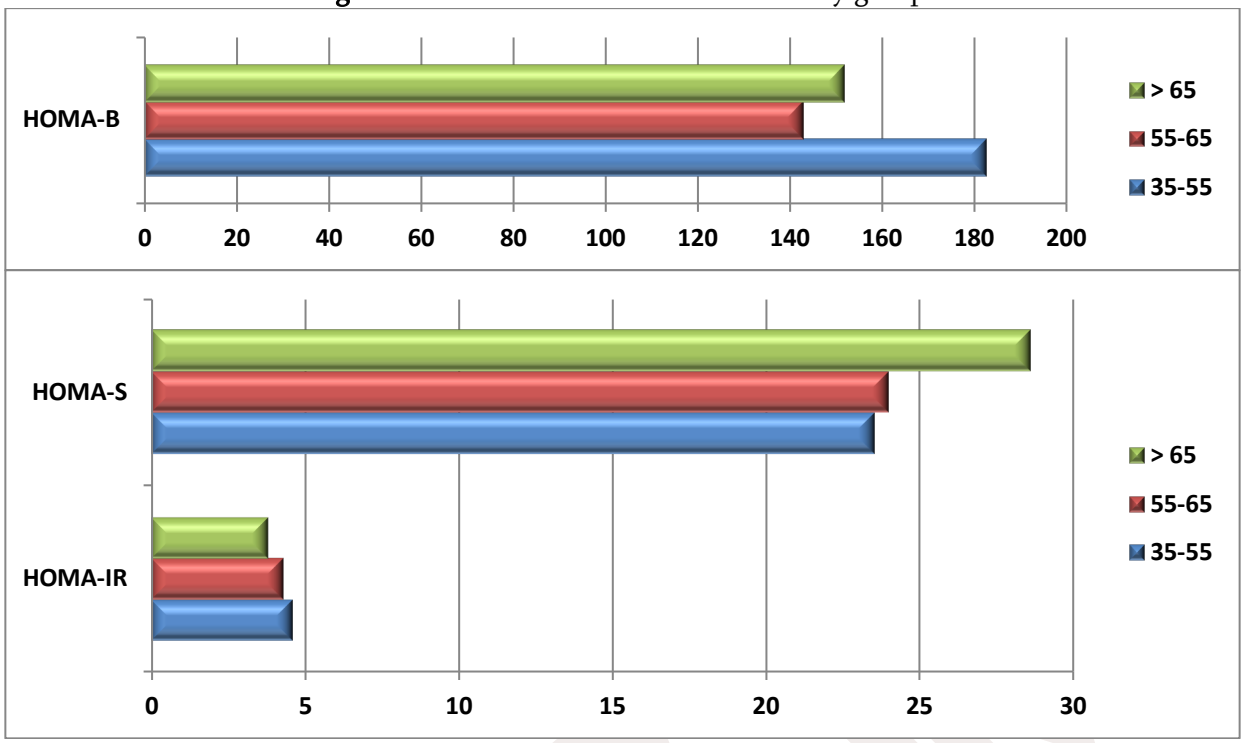
Table #2. The parameters of the carbohydrate metabolism in the study groups.

Parameter	Mean	SD	Mean	SD
	Study Group S1		Control Group C1	
Fasting glycemia, mmol/l	6.2	0.5	5.0	0.3
t-test (p)	7.052 (p<0.001)			
Fasting C-peptide, ng/ml	5.9	1.8	1.9	0.5
t-test (p)	7.407 (p<0.001)			
Fasting Insulin, μU/ml	29.5	4.7	17.7	5.5
t-test (p)	5.506 (p<0.001)			
Parameter	**Study Group S2**		**Control Group C2**	
Fasting glycemia, mmol/l	7.0	1.2	5.1	0.2
t-test (p)	7.052 (p<0.001)			
Fasting C-peptide, ng/ml	5.6	1.1	2.3	0.6
t-test (p)	6.250 (p<0.001)			
Fasting Insulin, μU/ml	30.0	2.7	17.2	4.8
t-test (p)	7.327 (p<0.001)			
Parameter	**Study Group S3**		**Control Group C3**	
Fasting glycemia, mmol/l	6.3	0.5	5.1	0.3
t-test (p)	10.228 (p<0.001)			
Fasting C-peptide, ng/ml	4.8	1.3	2.2	0.6
t-test (p)	8.977 (p<0.001)			
Fasting Insulin, μU/ml	27.7	5.0	17.8	4.6
t-test (p)	7.327 (p<0.001)			

Table #3. The HOMA-indices in the study groups.

HOMA-indices	Mean	SD	Mean	SD
	Study Group S1		Control Group C1	
HOMA-B, %	182.5	50.9	120.7	21.1
t-test (p)	3.866 (p<0.001)			
HOMA-S, %	23.5	7.1	74.9	19.2
t-test (p)	8.357 (p<0.001)			
HOMA-IR	4.6	1.4	1.4	0.4
t-test (p)	7.601 (p<0.001)			
HOMA-indices	**Study Group S2**		**Control Group C2**	
HOMA-B, %	142.9	44.2	128.8	15.2
t-test (p)	1.088 (p=0.288 - NS)			
HOMA-S, %	24.0	4.4	63.8	14.5
t-test (p)	9.470 (p<0.001)			
HOMA-IR	4.3	0.8	1.7	0.5
t-test (p)	9.937 (p<0.001)			
HOMA-indices	**Study Group S3**		**Control Group C3**	
HOMA-B, %	151.9	28.8	123.0	18.3
t-test (p)	4.215 (p<0.001)			
HOMA-S, %	28.6	10.0	67.1	17.8
t-test (p)	9.661 (p<0.001)			
HOMA-IR	3.8	1.0	1.6	0.5
t-test (p)	9.742 (p<0.001)			

diagram #5. The HOMA-indices in the study groups.



Discussion

The main objective of our study was to evaluate the relationship between the IGF-system and insulinemia / glycemia with age of patients with CRC. A number of prospective studies have shown that the IGF-1 / IGF-3 system increases the risk of the CRC development by increasing the circulating IGF-1 concentration and decreasing the concentration of IGF BP3 [11,21]. According to our research, the decrease of the concentration of IGF BP3 in the patients with CRC indicates a weakening of its buffer properties [7,8,10]. Increased fasting insulin concentrations in the patients with CRC also indicate a significant role for hyperinsulinemia in the development of CRC [9].

Observations in the study and control groups showed a decrease in the concentration of IGF-1 and an increase in the concentration of IGF BP3 in the blood with increasing age, a similar result was obtained in a number of other studies [21,22]. A significant inverse correlation between age / IGF-1 and age / IGF BP3 has been confirmed. Such a correlation could not be established in a group of patients with colorectal cancer, which may be explained by a violation of the relevant physiological regulatory mechanisms. In our previous study, visible data were obtained between the concentrations of IGF-1 and fasting insulin and the degree of tumor invasion quality [22].

Both IGF-1 and IGF BP3 levels decline with the age after adolescence [23-25]. In one study [25], 40% of healthy elderly adults (age 60-88 years) had very low IGF-I levels. It has been suggested that impaired immune function may participate in aging-related tumorigenesis and the treatment option with growth hormone or IGF-I might reverse the immune deficiency in humans [25,26]. The results of some studies showed that, although both IGF-I and IGF BP3 levels decrease with age, IGF-I levels are higher among case subjects than among control subjects at each level of IGF BP3, independent of age [27]. The inverse association of IGF BP3 with CRC risk is also independent of age and IGF-I. Furthermore, the associations of IGF-I and IGF BP3 with risk were consistent among younger and older men. Since older men had statistically significantly lower levels of IGF-1 than younger men, older men might be at even higher risk if their IGF-1 levels were increased to levels equivalent to those at a younger age. This findings of studies of circulating IGF-1 levels and risk of prostate cancer [27,28] raise concern that administration of growth hormone or IGF-1 over long periods, as proposed for elderly men to delay the effects of aging [26], may be associated with increased risk of neoplasia. Further investigations are needed to confirm our results, to better understand the determinants of circulating levels of IGF-1 and IGF BP3, to assess the feasibility of identifying individuals with high risk of CRC based on circulating sex and age-adjusted IGF-1 and IGF BP3 levels, and to investigate potential lifestyle or pharmacologic approaches to decreasing IGF-1 bioactivity in high-risk populations.

Conclusion

Age-dependent features of the IGF-system have been reported in patients with colorectal cancer. Moreover, in all age groups of CRC patients, despite the nature of the change of IGF-1 and IGF BP3, a inverse association was maintained between these parameters. However, the concentration of sex-adjusted IGF-1 in the lower age group is significantly low compared to the old age group. Further study is needed to make stronger evidence-based conclusions.

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

ИНСУЛИНОПОДОБНЫЙ ФАКТОР РОСТА-1, ЕГО СВЯЗЫВАЮЩИЙ БЕЛОК-3 И ВОЗРАСТНЫЕ ОСОБЕННОСТИ УГЛЕВОДНОГО ГОМЕОСТАЗА У БОЛЬНЫХ КОЛОРЕКТАЛЬНЫМ РАКОМ

Тбилисский Государственный Медицинский Университет, Департамент пропедевтики внутренних болезней, Медицинский центр им.Придона Тодуа

РЕЗЮМЕ

Цель: Целью исследования было определение инсулиноподобного фактора роста-1, его связывающего белка-3 и возрастные особенности углеводного гомеостаза у больных колоректальным раком.

Методы: Участие в исследованиях приняло 100 пациентов, 50-50 участников были объедены в исследуемую и контрольную группы. Возраст был расспределен на три возрастные группы: 1 группа (30-55лет), 2 группа (55-65 лет), 3 группа (>65лет). У пациентов исследовали инсулиноподобный фактор роста-1, его сязывающий белок-3, тесты количества глюкозы и инсулина.

Результаты: Средние показатели IGF – в возрастных группах были следующие: Исследуемые группы S1(30-35 лет) – 214,5±23,0 ед., S2 (55-65лет) – 202,5±15,5 ед., S3 (>65 лет). Контрольные группы – C1(30-35 лет) – 162,3±31,7 ед., C2 (55-65 лет) - 150±35,7 ед., C3(>65 лет)- 146,1±32,4 ед. Средние показатели ICF BP3 в возрастных группах были следующие: Исследуемые группы S1 (30-35 лет) – 2,0±0,7 ед., S2 (55-65 лет) – 1,6±0,3 ед., S3 (>65 лет) – 1,7±0,6 ед. Контрольные группы –C1 (30-35 лет) – 3,6±1,0 ед., C2 (55-65 лет) – 3,9±1,0 ед., C3 (>65 лет) – 3,6±0,9.

Выводы: у пациентов с колоректальным раком наблюдалось нарушение инсулиноподобного роста фактора-1 в возрастных регуляторных механизмах. Во всех возрастных группах несмотря на разность показателей инсулинподобного роста фактора-1 и его связывающего белка-3 отмечалась обратнопропорциальность этих величин, хотя у пациентов низкой возрастной группы концентрация ICF-1 была достоверно низкая.

ZVIAD MAGLAPHERIDZE, VERA KAPETIVADZE, REVAZ TABUKASHVILI,
TAMAR LAZASHVILI, MARINA KUPARADZE, EREKLE GRATIASHVILI

AGE-SPECIFIC FEATURES OF ISNULIN-LIKE GROWTH FACTOR 1, ITS BINDING PROTEIN 3, AND CARBOHYDRATE HOMEOSTASIS IN PATIENTS WITH COLORECTAL CANCER

Department of Internal Disease of Propaedeutics,
Tbilisi State Medical University, Fridon Todua Medical Center

SUMMARY

Aim. The aim of our study was to study of age-specific features of IGF-1, IGF BP3, and carbohydrate homeostasis in patients with colorectal cancer.

Methods: The study and control groups consisted of 50-50 participants, who were divided into three age groups, **Group 1** (30-55 yrs.); **Group 2** (55-65 yrs.); **Group 3** (>65 yr.). IGF-1, IGF BP3, Serum insulin and glucose levels were performed.

Results: The mean IGF-1 values for the age groups were as follows: study group S1 (35-55 yrs.) - 214.5 ± 23.0; study group S2 (55-65 yrs.) - 202.5 ± 15.5; study group S3 (> 65 yr.) - 190.5 ± 22.0; control group C1 (35-55 yrs.) - 162.3 ± 31.7; control group C2 (55-65 yrs.) - 150.6 ± 35.7; control group C3 (> 65 yr.) - 146.1 ± 32.4. The mean IGF BP3 values for the age groups were as follows: study group S1 (35-55 yrs.) - 2.0 ± 0.7; study group S2 (55-65 yrs.) - 1.6 ± 0.3; study group S3 (> 65 yr.) - 1.7 ± 0.6; control group C1 (35-55 yrs.) - 3.6 ± 1.0; control group C2 (55-65 yrs.) - 3.9 ± 1.0; control group C3 (> 65 yr.) - 3.6 ± 0.9.

Conclusion. Age-dependent features of the IGF-system have been reported in patients with colorectal cancer. Moreover, in all age groups of CRC patients, despite the nature of the change of IGF-1 and IGF BP3, a inverse association was maintained between these parameters. However, the concentration of sex-adjusted IGF-1 in the lower age group is significantly low compared to the old age group.