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Obesity, hyperinsulinemia, IGF-1, and hyperglycemia as risk factors for colorectal cancer in patients with type 2 diabetes mellitus

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The latest studies prove an increased risk of colorectal cancer in patients with type 2 diabetes mellitus. The pathogenetic factors of type 2 diabetes have been recognized as mechanisms of association between these diseases.
The objective: **to investigate the effects of obesity, hyperinsulinemia, IGF-1 and hyperglycemia on the development of colorectal cancer in patients with type 2 diabetes.**
Materials and methods**. 36 patients were divided into groups: I – healthy (control group), II – patients with type 2 diabetes mellitus, III – patients with colorectal cancer without diabetes, IV – patients with a combination of two diseases. Using the method of enzyme-linked immunosorbent assay were determined levels of insulin and insulin-like growth factor-1 (IGF-1). DM compensation was assessed by the level of glycosylated hemoglobin (HbA1c) that was determined by immuno-exchange chromatography. The data obtained were analyzed using Statistica 12.0 (StatSoft Inc., USA). Differences between the values in the control and experimental groups were determined by the Student's t-test. The differences were considered significant at $p<0.05$.**
Results**. According to the data obtained, colorectal cancer was diagnosed in patients with the age of over 60 years old with obesity. The body mass index (BMI) in patients of all study groups was higher than 30 kg/m^2. Patients of group IV with a combination of type 2 diabetes and a circle of rectal cancer had significantly higher BMI compared to the control group ($p<0.05$). Significant hyperinsulinemia and increased IGF-1 levels were detected in patients in all study groups ($p<0.05$). Most patients with diabetes in both groups had HbA1c levels higher than 7.5%.**
Conclusions**. Obesity, hyperinsulinemia, increased bioavailability of IGF-1, and hyperglycemia are pathogenetic factors in the risk of colorectal cancer in patients with type 2 diabetes. Patients over the age of 55 with diabetes, obesity, and hyperinsulinemia are advised to be screened for colorectal cancer.**
Key words: *diabetes, obesity, hyperinsulinemia, IGF-1, cancer.*

Вплив ожиріння, гіперінсулінемії IGF-1 та гіперглікемії у розвитку колоректального раку у хворих на цукровий діабет 2-го типу

Т.С. Вацеба

Новітні дослідження доводять підвищений ризик розвитку колоректального раку у пацієнтів з цукровим діабетом (ЦД) 2-го типу. Механізмами асоціації між зазначеними захворюваннями визнані патогенетичні фактори ЦД 2-го типу.
Мета дослідження: аналіз впливу ожиріння, гіперінсулінемії, інсуліноподібного фактора росту-1 (IGF-1) та гіперглікемії на розвиток колоректального раку у хворих на ЦД 2-го типу.
Матеріали та методи. Обстежено 36 хворих, розподілених на групи: I (контрольна) група – 10 здорових осіб, II група – 10 хворих на ЦД 2-го типу, III група – 8 хворих на колоректальний рак без ЦД, IV група – 8 хворих з поєднанням двох захворювань. Методом імуноферментного аналізу визначали рівні інсуліну та інсуліноподібного фактора росту-1 (IGF-1). Компенсацію ЦД оцінювали за рівнем глікозильованого гемоглобіну (HbA1c), визначеного методом імунообмінної хроматографії. Аналіз отриманих даних проводили з допомогою програми Statistica 12.0 (StatSoft Inc., США). Відмінності між значеннями в контрольній і експериментальній групах визначали за t-критерієм Стьюдента. Відмінності вважали достовірними при $p<0,05$.
Результати. Отримані результати свідчать, що колоректальний рак був діагностований у хворих з ожирінням віком понад 60 років. Індекс маси тіла (ІМТ) у пацієнтів усіх досліджуваних груп становив >30 кг/м^2. Достовірно вищий ІМТ порівняно з показником контрольної групи мали хворі IV групи з поєднанням ЦД 2-го типу та колоректального раку ($p<0,05$). Достовірну гіперінсулінемію та підвищений рівень IGF-1 виявлено у пацієнтів усіх досліджуваних груп ($p<0,05$). Більшість пацієнтів з ЦД в обох групах мали рівень HbA1c > 7,5%.
Заключення. Ожиріння, гіперінсулінемія, підвищена біодоступність IGF-1 та гіперглікемія є патогенетичними факторами формування ризику колоректального раку у пацієнтів з цукровим діабетом (ЦД) 2-го типу. Пацієнтам віком понад 55 років з ЦД, ожирінням та гіперінсулінемією рекомендований скринінг на колоректальний рак.
Ключові слова: *цукровий діабет, ожиріння, гіперінсулінемія, IGF-1, рак.*

Ожирение, гиперинсулинемия, IGF-1 и гипергликемия как факторы риска колоректального рака у больных сахарным диабетом 2-го типа

Т.С. Вацеба

Современные исследования доказывают повышенный риск развития колоректального рака у пациентов с сахарным диабетом (СД) 2-го типа. Механизмами ассоциации между указанными заболеваниями признаны патогенетические факторы СД 2-го типа.
Цель исследования: анализ влияния ожирения, гиперинсулинемии, инсулиноподобного фактора роста-1 (IGF-1) и гипергликемии на развитие колоректального рака у больных СД 2-го типа.
Материалы и методы. В исследовании приняли участие 36 больных, которые были разделены на группы: I (контрольная) группа – 10 здоровых лиц, II группа – 10 больных СД 2-го типа, III группа – 8 больных колоректальным раком без СД, IV группа – 8 больных с сочетанием двух заболеваний. Методом иммуноферментного анализа определяли уровни инсулина и IGF-1. Компенсацию СД оценивали по уровню гликозилированного гемоглобина (HbA1c), определенного методом иммунообменной хроматографии. Анализ полученных

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данных проводили с помощью программы Statistica 12.0 (StatSoft Inc., США). Различия между значениями в контрольной и экспериментальной группах определяли по t-критерию Стьюдента. Различия считали достоверными при p<0,05.

Результаты. По полученным результатам выявлено, что колоректальный рак был диагностирован у больных старше 60 лет, с ожирением. Индекс массы тела (ИМТ) у пациентов всех исследуемых групп составлял >30 кг/м^2. Достоверно повышенный ИМТ по сравнению с показателем контрольной группы отмечали у больных IV группы с сочетанием СД 2-го типа и колоректального рака (p<0,05). Достоверную гиперинсулинемию и повышенный уровень IGF-1 выявлено у пациентов всех исследуемых групп (p<0,05). У большинства пациентов с СД в обеих группах отмечали уровень HbA1c >7,5%.

Заключение. Ожирение, гиперинсулинемия, повышенная биодоступность IGF-1 и гипергликемия является патогенетическими факторами формирования риска колоректального рака у пациентов с СД 2-го типа. Пациентам старше 55 лет с сахарным диабетом, ожирением и гиперинсулинемией рекомендован скрининг на колоректальный рак.

Ключевые слова: *сахарный диабет, ожирение, гиперинсулинемия, IGF-1, рак.*

Malignant neoplasms (MN) of the colon are one of the most common cancer types. Colorectal cancer (CRC) is a tumor of the colon and rectum that originates from epithelial cells that are lining the inner surface of the indicated sections of the intestine. Currently, there is an increase in both the incidence and mortality from colon cancer. Increased risk of CRC is caused by certain factors, among which are those that determine the need for screening: the elderly age, cases of CRC in the family, precancerous conditions, such as familial adenomatous polyposis, nonspecific inflammatory bowel diseases (Crohn's disease and ulcerative colitis). At the same time, factors of oncogenesis such as obesity and bad habits are determined as those that can be corrected by a change of lifestyle [14].

Recently the spread of obesity is leading to its epidemy, causing an increase in the incidence of cardiovascular disease (CVD), type 2 diabetes mellitus (DM) and cancer. A study by Canadian scientists in 2013 shows a significant effect of obesity on the development of colon, pancreatic, gallbladder and kidney cancer (regardless of gender), endometrial, esophageal and breast cancer, leukaemia (in women), melanoma (in men) [4]. It has been proved that the risk of CRC in people, who had obesity in adolescence is 30% higher compared to those who had no obesity during teenage years [2].

Recent studies prove an increased risk of CRC in patients with type 2 DM. The pathogenetic factors of type 2 DM have been recognized as mechanisms of association between these diseases [16, 17, 11].

The objective: to investigate the effect of obesity, hyperinsulinemia, IGF-1, and hyperglycaemia on the development of colorectal cancer in patients with type 2 diabetes.

MATERIALS AND METHODS

The study was conducted in accordance with the guidelines of the Declaration of Helsinki (1975) and its revised version of 1983. All patients signed informed consent for further diagnostic and research work. The study protocol was approved by the Local Ethics Committee of Ivano-Frankivsk National Medical University (№ 97/17 of October 19, 2017).

36 patients were examined. Patients were divided into groups:

I – healthy (control group) (n=10),

II – patients with type 2 DM (n=10),

III – patients with CRC without DM (n=8),

IV – patients with a combination of CRC and type 2 DM (n=8).

The study did not include patients with rectal cancer.

Groups of patients were comparable in age and BMI. Patients from the surgical and the endocrinological departments of the regional clinical hospital in Ivano-Frankivsk were involved in the study. Therapies of patients with diabetes mellitus of groups II and IV included different combinations of oral medications for lowering sugar level and insulin. Blood sampling in patients with CRC was performed before chemotherapy and radiation therapy.

The levels of insulin and IGF-1 were determined by enzyme-linked immunosorbent assay (ELISA) using a Stat fax 303+ automatic analyzer (USA) using Insulin ELISA, EIA-2935 and IGF-1 600 ELISA, EIA-4140 diagnostic kits from DRG (Germany). Compensation of DM was assessed by determining the level of glycosylated haemoglobin (HbA1c) by ion-exchange chromatography using a BIO-RAD D-10 analyzer and BIO-RAD reagents (USA). Laboratory studies were performed in the inter-departmental scientific laboratory of the Department of Internal Medicine №1, Clinical Immunology and Allergology named after Academician E.M. Neiko, IFNMU.

The data obtained were analyzed using Statistica 12.0 (StatSoft Inc., USA). The data are presented in the tables as x±SD (x ± standard deviation). Differences between values in the control and experimental groups were determined using the Student's t-test. The differences were considered significant at p<0.05.

RESULTS AND DISCUSSION

According to the results obtained, it is revealed that CRC is a characteristic of persons over 60 years of age (table 1).

The results coincide with the epidemiological study conducted by Z.P. Fedorenko and co-researchers who show that CRC cancer is widespread in individuals after 55 years of age, with a percentage of 6.7–8.0% in men and 7.1–9.3% in women [5]. Peak morbidity on CRC is observed at the age of 70–75, regardless of gender [9]. The results prove the age dependence of oncological diseases since the processes of aging of the body and tumor development processes are interrelated. Cancer is recognized as one of the diseases of aging that occur in the second half of human life, after 50–60 years of age [3].

According to the results, the BMI of patients in all experimental groups was higher than 30 kg/m2, which

Table 1

Age, BMI, and diabetes duration of study participants, x±SD

Indication	Group I, control, n=10	Group II, patients with DM, n=10	Group III, patients with CRC, n=8	Group IV, patients with DM + CRC, n=8
Age, years	58,43±7,87	56,93±4,44	67,3±10,57*	65,50±7,96*
BMI, kg/m^2	28,47±3,82	32,49±6,99	31,18±4,36	32,05±3,13*
Duration of DM, years	– #	11,25±8,78	– #	10,40±5,64

Note: * – the difference is significant in comparison with group I (p<0.05), # – the duration of diabetes for patients without diabetes was not determined.

Table 2

Insulin level, IGF-1, HbA1c of study participants (x ± SD)

Indication	Group I, control, n=10	Group II, patients with DM, n=10	Group III, patients with CRC, n=8	Group IV, patients with DM + CRC, n=8
Insulin, mIU/ml	7,70±2,24	24,50±11,27*	12,36±4,9*	16,21±1,16*
IGF-1, ng/ml	140,00±24,55	177,64±27,65*	205,21±68,43*	180,12±32,60*
HbA1c, %	– #	7,75±1,81	– #	8,02±1,31

Note: * – the difference is significant in comparison with group I ($p<0.05$), # – the duration of diabetes for patients without diabetes was not determined.

confirms the presence of obesity in patients with type 2 DM and CRC. BMI differed significantly from the control group only in patients of group IV with a combination of type 2 DM and CRC ($p<0.05$) (Table 1). The susceptibility of obese individuals to cancer of this localization has been confirmed in other studies [10, 12].

The effect of obesity on the processes of oncogenesis can be explained by the influence of cytokine imbalance. Adipocyte hypertrophy stimulates hypoxic processes in adipose tissue, leading to infiltration by its macrophages and lymphocytes, which produce an excess of cytokines with proinflammatory properties. The results of recent studies prove the role of hyperleptinemia in the development of CRC. Normally, leptin determines a person's eating behavior by affecting the hypothalamic centers of appetite regulation. By obesity, the sensitivity of these centers is significantly reduced, which causes secondary hyperleptinemia. Leptin has a structural similarity to interleukin-6 (IL-6) and C-reactive protein (CRP), has the ability to stimulate the synthesis of tumor necrotic factor-α (TNF-α) and monocyte chemotaxis proteins, also enhances the synthesis of reactive oxygen species (ROS) by endothelial cells and mononuclear cells, which causes oxidative stress (OS) and chromosomal aberrations of DNA [8].

Adiponectin (APN), an adipocytokine that is synthesized only by adipocytes and has significant anti-inflammatory, insulin-sensitizing, and antitumor effects, has opposite to leptin characteristics. Hypoadiponectinemia is considered as a cancer risk factor in obese people. APN concentration is inversely proportional to insulin levels and an amount of adipose tissue [15].

The average duration of illness of patients with type 2 DM of group II without cancer is 11.25±8.78 years, in patients of group IV – 10.40±5.64 years. There was no significant difference between the duration of DM in the compared groups ($p>0.05$) (Table 1).

The study involved the determination and comparison of insulin and IGF-1 levels in patients with type 2 DM and CRC. Based on the results obtained, significant hyperinsulinemia and increased levels of IGF-1 compared to the control group were determined in patients of all study groups ($p<0.05$) (Table 2).

Hyperinsulinemia is considered to be one of the main pathogenetic mechanisms of oncogenesis in patients with type 2 DM and obesity. Excessive insulin increases the bioavailability of insulin-like growth factor-1 (IGF-1). Due to structural similarity, both growth factors can cross-interact and competitively interact with insulin receptors (IR) and IGF-1 receptors (IGF-1R), activating intracellular signaling pathways, in particular, the «insulin» pathway PI3K/Akt/mTOR, which plays an important role in the regulation of intracellular metabolism and survival [13].

Hyperinsulinemia has been proved to reduce the expression of genes that are responsible for the synthesis of IGF-1 binding protein, which causes IGF-1 overexpression. It has been found that insulin can independently activate mitogen-activated protein kinase (MAPK), which directly affects mTOR, a key kinase involved in carcinogenesis [1, 6].

In the II group 28,6% of patients had compensated diabetes (according to HbA1c level), 14,3% – subcompensated, and 57,1% – decompensated. In group IV the comparable indicators were 10,0%, 30,0% and 60,0%, respectively.

The results confirm the mutually complicating effect of both diseases on diabetes compensation. Hyperglycemia is an important factor in carcinogenesis. There are indirect and direct pro-carcinogenic effects of hyperglycemia. The indirect effect is due to the stimulation of certain organs for the synthesis of growth factors (insulin/IGF-1) and inflammatory cytokines. A direct effect is the induction of mutations in the cell through OS and the activation of carcinogenesis-related signaling pathways.

It is proved that in adipose and muscular tissues glucose transport is carried out due to the insulin-dependent mechanism, involving the glucose transporter-4 (GLUT-4). However, the endothelium of blood vessels, mesangial cells of the kidney glomeruli, neurons contain mainly insulin-independent glucose transporters GLUT-1 and GLUT-3, which are constantly presented on the surface of cells and continually transfer glucose from the outside into the cell. The amount of these cells can increase in response to an increase in glucose concentration. These cells lack the mechanism of prevention of the transport of excess glucose from the bloodstream to the cytoplasm by hyperglycemia, which causes its accumulation. This leads to the intensification of glycolysis, a tricarboxylic acid cycle that eventually causes free radical (superoxide-anion) hyperproduction and OS, which causes oxidation of intracellular structures, including DNA, causing chromosomal aberrations. The role of dyslipidemia and excess of free fatty acids (FFA) in the activation of OS in the cells should also be noted.

Hyperglycaemia causes proliferative, antiapoptotic and metastatic effects. The proliferative effect of hyperglycaemia is caused by the increased expression of GLUT-1 and GLUT-3 in tumor cells, which promotes their nutrition [7]. The anti-apoptotic effect is the result of an increase in the level of hypoxia-activated factor -1 (HIF-1), which regulates cancer cell survival under hypoxia. The metastatic effect is realized through vascular endothelial growth factor (VEGF), which provides invasion of malignant cells beyond the localization organs.

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CONCLUSIONS

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