

Type 2 diabetes mellitus: a marker or a risk factor for pancreatic cancer?



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The study is a fragment of the research project «Epidemiology of oncological diseases in patients with diabetes mellitus and the effect of antihyperglycemic drugs on oncogenesis markers» (registration number 0117U005263), included into the complex research work of the SHEE «Ivano-Frankivsk National Medical University» — «Pathogenetic mechanisms of development of changes in organs of the respiratory, endocrine, nervous systems in the modeled pathological conditions and their correction» (registration number 0117U001758).

Introduction. Pancreatic cancer (PC) takes a special place in the structure of oncological diseases as it has an asymptomatic aggressive course and is characterized by high mortality and low patients survival [1].

The prevalence of PC varies across regions and populations. The highest incidence is in Europe (7.7 per 100 000 people), North America (7.6 per 100 000 people), and the lowest is in Africa (2.2 per 100 000 people). Men suffer from this disease more often but the indicators also differ in different regions [2]. In Ukraine, about 4500 primary cases of PC are diagnosed annually. Morbidity is 6.6 per 100 000 people, mortality is 5.2 per 100 000 people. About 73% of patients die within 1 year of diagnosis. This type of cancer ranks ninth in prevalence and sixth among the causes of death from malignant diseases [3].

Despite the advances in the diagnostics and treatment of cancer of this localization, the 5-year survival of patients is still only 6—9%. The causes of PC are not yet well known, although there are certain risk

factors that can be subdivided into unchangeable ones and those that can be corrected. Among the unchangeable factors are: age, sex, ethnicity, blood group 0 (I), diabetes mellitus (DM), hereditary predisposition, genetic disorders. The risk factors that can be corrected are obesity, smoking, alcohol abuse, chronic pancreatitis, *Helicobacter pylori* infection [4, 5].

There are two major common types of PC: adenocarcinoma from exocrine cells (85 % of cases) and neuroendocrine tumour (less than 5 % of cases) [6]. 10% of patients are diagnosed with genetically induced PC, which is associated with the BRCA 1-2, DPC4, PP16 gene mutations. It should be mentioned that BRCA gene mutations are also characteristic of ovarian and breast cancer [7].

The results of clinical observations and epidemiological studies suggest an increased risk of PC in patients with type 2 DM [8, 9, 10]. It has been found that about 25 % of patients with PC have diabetes and about 40 % have prediabetes [11].

Hyperinsulinemia, increased activity of insulin-like growth factor-1 (IGF-1), obesity and hyperglycaemia are recognized as factors of oncogenesis in type 2 diabetes [12]. These factors affect intracellular regulatory systems. It was proved that hyperinsulinemia and increased IGF-1 activity activate PI3K/Akt/mTOR and RAS/RAF/MAPK/mTOR signaling pathways involved in cancer pathogenesis. In obesity, the oncogenic effects of proinflammatory cytokines are realized: tumor necrotic factor — alpha (TNF- α), interleukin-6 (IL-6) and impaired immunological control of oncogenes on the background of chronic

Table 1

Age characteristics, BMI, and DM duration of study patients (x ± SD)

Parameters	Group I, control n = 10	Group II, patients with type 2 DM n = 13	Group III, patients with PC n = 11	Group IV, type 2 DM + PC n = 8
Age, years	59.00 ± 8.17 ^a	58.83 ± 6.21 ^a	60.18 ± 11.8 ^a	61.00 ± 8.15 ^a
BMI, kg/m ²	26.10 ± 3.18 ^a	28.06 ± 2.10 ^a	26.10 ± 2.58 ^a	24.91 ± 2.62 ^a
Duration of DM, years	— [#]	8.96 ± 5.17 ^a	— [#]	2.80 ± 1.64 ^a

Note. Different letters indicate values, which reliably differed one from another within one line of table according to the results of comparison using Bonferroni correction, # — the duration of DM for patients without diabetes was not determined.

immunosuppression. Besides, hyperglycaemia and involvement of pathological ways of glucose metabolism cause intracellular oxidative stress, accumulation of reactive oxygen species (ROS), stimulate mytogen-activated protein kinase (MAPK) and activate the ROS/MAPK/mTOR pathway. The mTOR protein kinase plays a key role in regulating the processes of apoptosis, proliferation, and cell survival.

Currently, two hypotheses about diabetes as a risk factor for PC and as a marker of this disease are being studied [13].

The aim of the study was to investigate the role of pathogenetic factors of type 2 diabetes in the development of pancreatic cancer.

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 included 42 participants that were divided into groups: I — healthy (control group) (n = 10), II — patients with type 2 DM (n = 13), III — patients with PC without DM (n = 11), IV — patients with a combination of PC and type 2 DM (n = 8). Patient groups were comparable for age and BMI. The study involved patients of the pancreatology centre based on the surgical department of the regional clinical hospital in Ivano-Frankivsk and patients of the endocrinological department of the regional clinical hospital. Therapy of patients with DM of groups II and IV included different combinations of antidiabetic pills and insulin. Blood sampling in patients with PC was performed before chemotherapy.

Insulin and IGF-1 levels were determined using the automatic analyzer Stat fax 303+ (USA) using diagnostic kits Insulin ELISA, EIA-2935 and IGF-1 600 ELISA, EIA-4140 DRG company (Germany). DM compensation was

assessed by determining the level of HbA1c by the method of ion-exchange chromatography, using the BIO-RAD D-10 analyzer. Laboratory studies were performed in the inter-departmental scientific laboratory of the Department of Internal Medicine N 1, Clinical Immunology and Allergology IFNMU.

Analysis of the data was carried out using Statistica 12.0 (StatSoft Inc., USA), ANOVA program. The data are presented in tables as x ± SD (x ± standard deviation). Differences between the values in the control and experimental groups were determined using the Bonferroni correction. Differences were considered reliable at P < 0.05 and P < 0.001.

RESULTS AND DISCUSSION

According to the obtained results, it was revealed that the PC is characteristic of persons older than 60 years (Table 1).

The duration of DM in patients with cancer-free group II was significantly higher than in patients with PC diagnosed in the background of DM (P = 0.02). In group IV, PC was diagnosed in patients with duration of DM up to 3 years (Table 1).

The obtained results coincide with the findings of other studies, which confirm the diagnosis of PC with a short history of type 2 DM [14, 15]. Other studies show an increase in the risk of PC by 1.5—2.0 times in patients with type 2 DM lasting more than 10 years or with impaired glucose tolerance for more than 5 years [16].

When collecting anamnesis of the disease in patients of group IV, it was found that patients did not have obesity in the first diagnosed diabetes. At the time of the study, patients also had normal BMI (Table 1). It is known that obesity is a risk factor for PC [17]. However, according to Ben Q. et al. investigation, the risk of PC in patients with DM is independent of BMI [18].

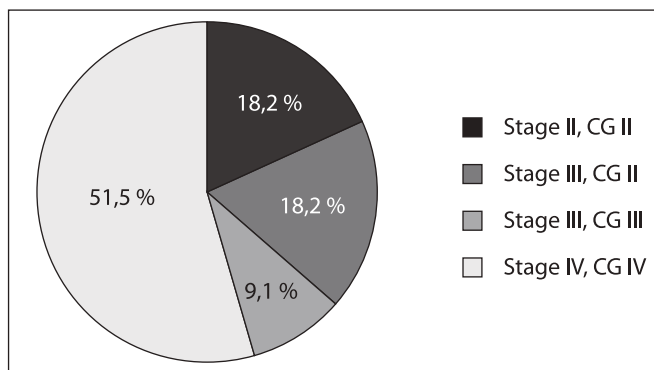


Fig. 1. Cancer stages and clinical groups of patients in group III

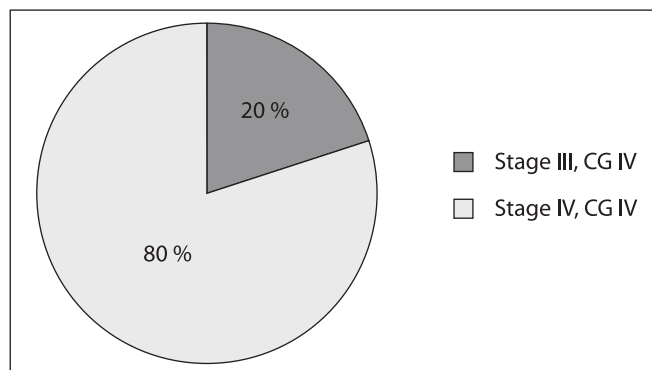


Fig. 2. Cancer stages and clinical groups of patients in group IV

The results of the studied medical cards of the patients confirm the detection of late-stage PC. In more than half of patients of group III the cancer was diagnosed at stage IV, clinical group (CG) IV (Fig. 1).

In group IV of patients with a combination of cancer and type 2 DM, the vast majority of cancer cases were diagnosed at stage IV and clinical group IV (Fig. 2).

A similar situation in the diagnostics of PC is observed in other countries, as this type of cancer is characterized by latent aggressive progression and patients do not have specific symptoms of the disease in the early stages. However, scientists suggest improving the diagnostics of PC by informing the population about the need to screen for cancer of this localization for persons whose close

relatives (1 person or more) have had ovarian cancer at any age or breast cancer before the age of 50 years, or if two relatives have had cancer of the pancreas, ovaries, breast, or prostate. These people are advised to have genetic counseling to identify possible germinal mutations of the BRCA1, 2 genes, because in 10 % of cases, PC is genetically conditioned [19].

Patients involved in the study sought help for the first time in the late stages. Such their late visit makes it impossible to use radical surgery intervention. Most patients received palliative care, which, of course, will affect their survival.

Treatment of patients with diabetes included various combinations of antidiabetic pills and insulin (Table 2).

Table 2

Therapy of patients with type 2 DM involved in the study

Therapy type	Daily doses	Number of patients of group II	Prevalence, (%)	Number of patients of group IV	Prevalence, (%)
Metformin	1000 mg	1	7.7	2	25.0
	2000 mg	2	15.4	0	
Glimepiride	4mg	0	0	2	25.0
Glimepiride / Metformin	2mg/1000mg	1	7.7	0	0
	4mg/1000mg	0	0	1	12.5
	4mg/2000mg	1	7.7	0	0
	6mg/2000mg	2	15.4	0	0
Insulin	34—44 IU	0	0	3	37.5
	58 IU	1	7.7	0	0
Metformin/ insulin	1000mg /36—38 IU	2	15.4	0	0
	2000mg /40—54 IU	3	23.0	0	0

Note. 1. % — in relation to the number of patients in the group.

Table 3

Level of insulin, IGF-1 and HbA1c in patients with type 2 DM and PC ($x \pm SD$)

Parameters	Group I, control n = 10	Group II, patients with type 2 DM n = 13	Group III, patients with PC n = 11	Group IV, patients with type 2 DM+PC n = 8
HbA1c, %	— #	7.68 \pm 1.66 ^a	— #	8.20 \pm 0.73 ^a
Insulin, μ U/ml	7.9 \pm 2.1 ^a	20.1 \pm 7.1 ^b	8.7 \pm 3.8 ^a	11.2 \pm 9.9 ^a
IGF-1, ng/ml	143.6 \pm 22.5 ^a	190.0 \pm 27.28 ^b	205.5 \pm 61.2 ^b	167.2 \pm 31.7 ^a

Note. Different letters indicate values, which reliably differed one from another within one line of table according to the results of comparison using Bonferroni correction; # HbA1c for patients without diabetes was not determined.

It should be noted that three of eight patients in group IV (37.5%) were treated by insulin monotherapy with duration of diabetes up to 3 years.

Laboratory studies of patients revealed a state of hyperinsulinemia only in patients of group II with type 2 DM (Table 3).

The level of insulin in group II was significantly higher compared to the control group ($P = 0.0001$), group III ($P = 0.0002$) and group IV ($P = 0.04$), which confirms the insulin resistance status in patients with type 2 diabetes (Table 3). Significant hyperinsulinemia ($P > 0.05$) was not found in non-diabetic patients with PC and in combination with DM (Table 3).

The obtained results in group IV confirm that non-obese patients with PC that emerged from the recently diagnosed type 2 diabetes do not have firm hyperinsulinemia, which contradicts the data on the main role of hyperinsulinemia in the development of PC. These patients are likely to have another secondary type of diabetes, T3cDM, described by Yun Feng Cui and Dana K Andersen in 2012 and characterize the parenchymal insufficiency of the gland. This type of diabetes reflects endocrine dysfunction in PC caused by cellular damage by the proliferative process. T3cDM occurs in other diseases of the pancreas: pancreatitis, cystic fibrosis, haemosiderosis, benign and malignant diseases and, by definition of the American Diabetes Association (2011), is characterized by a deficiency of all glucose regulating hormones of the pancreas [20].

There are no clear diagnostic criteria for T3cDM, but its clinical characteristics may be: no diabetes in a family history, age over 65 years, weight loss more than 2 kilograms in a short time or normal BMI, cases of PC in family history.

Laboratory signs of T3cDM may be: moderate hyperglycaemia, hypoglycaemia predisposition, increased

peripheral insulin sensitivity, decreased hepatic insulin sensitivity, decreased insulin, glucagon, glucagon-like peptide-1 (GLP) and reduced level of pancreatic polypeptide (PP) after meals. PP deficiency is of paramount importance for the diagnosis of this type of diabetes, as it reflects the parenchymal damage of the pancreas. In 30 % of patients with PC, T3cDM is diagnosed [20].

On the other hand, the absence of hyperinsulinemia can be explained by the late stage of the disease (in most patients it is the fourth stage, clinical group IV), which is characterized by total organ damage, hormonal and enzymatic deficiency.

Increased level of IGF-1 was revealed in group III of patients with PC compared with the control group ($P = 0.004$), which proves its important role in carcinogenesis, and in patients of group II with type 2 diabetes ($P = 0.04$) (Table 3). The increased level of IGF-1 in the patients of second group may be explained by increased bioavailability of this growth factor through the influence of hyperinsulinemia. In group IV, IGF-1 level can be explained by a decrease in the synthesis of this growth factor in liver of patients with cancer on the late stages of disease.

The level of HbA1c in patients of groups II and IV, was determined 8 % and 8.20 %, respectively and did not differ significantly between the groups ($P > 0.05$) (Table 3).

Regarding the analysis of the effects of antidiabetic drugs on insulin and IGF-1 indices, more patients need to conduct it. Of the 8 patients, two received sulphonylurea derivatives, three were on insulin monotherapy. The types of therapy used indirectly confirm the insulin deficiency status of the examined patients for such a relatively short period of diabetes.

Thus, the obtained results do not confirm the effect of hyperinsulinemia, increased IGF-1 and obesity on the development of PC in the study patients, which

may be explained by the presence of T3cDM. In this case, diabetes can be considered as an early sign of PC. However, the definitive answer needs to be supplemented, as clear T3cDM diagnostic criteria have not yet been developed.

Therefore, both hypotheses about diabetes as a marker of PC and as a risk factor are correct and have the right to exist.

Both types of diabetes (type 2 and T3cDM) require confirmation and differentiation. Early diagnostics of PC will have a positive effect on patient survival. A family predisposition of patients with diabetes is an indication for their genetic counseling for the diagnosis of genetically-induced forms of cancer. There is also a need to develop diagnostic criteria for T3cDM and to complement the algorithm of examination for patients with type 2 diabetes with regard to screening for pathogenetically-related cancers.

CONCLUSIONS

In the examined patients with pancreatic cancer that occurred on the background of type 2 diabetes mellitus, obesity, hyperinsulinemia and elevated IGF-1 levels were not revealed, which leads us to suggestion that they have secondary diabetes (T3cDM). Type 2 diabetes first diagnosed in patients without obesity and without hyperinsulinemia should be differentiated from T3cDM. Patients with newly diagnosed type 2 diabetes are advised to screen for pancreatic cancer, since diabetes can be both a marker and a risk factor for cancer of this localization.

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SUMMARY

Type 2 diabetes mellitus: a marker or a risk factor for pancreatic cancer?

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Introduction. Pancreatic cancer (PC) is characterized by asymptomatic, aggressive course, high mortality and low patients survival. Patients with diabetes mellitus (DM) have an increased risk of PC, but there are two views of diabetes: as a risk factor or as a PC marker.

The aim of the study was to investigate the role of pathogenetic factors of type 2 diabetes in the development of PC.

Materials and methods. The study included 42 participants that were divided into groups: I — healthy (control group) (n = 10), II — patients with type 2 diabetes mellitus (n = 13), III — non-diabetic patients with PC (n = 11), IV — patients with a combination of PC and type 2 diabetes (n = 8). DM compensation was determined by the level of glycosylated haemoglobin (HbA1c) and ion-exchange chromatography. The levels of insulin and insulin-like growth factor-1 (IGF-1) were determined by immune-enzymatic methods.

Results and discussion. Significant hyperinsulinemia was revealed only in patients of group II with type 2 diabetes compared with the control group (P = 0.0001), group III (P = 0.0002) and group IV (P = 0.04). Increased level of IGF-1 compared to the control group was detected in patients of group II with type 2 DM (P = 0.04) and in patients of group III with PC (P = 0.004). PC was diagnosed in non-obese patients of group IV with an average duration of diabetes up to 3 years. In patients of groups II and IV, the level of HbA1c was determined 7.68 % and 8.20 %, respectively and did not differ significantly between the groups (P > 0.05).

Conclusions. In the examined patients with pancreatic cancer that occurred on the background of type 2 diabetes mellitus, obesity, hyperinsulinemia and

elevated IGF-1 levels were not revealed, which leads us to suggestion that they have secondary diabetes (T3cDM). Type 2 diabetes, first detected in patients without obesity and without hyperinsulinemia, should be differentiated from T3cDM. Patients with newly diagnosed type 2 diabetes are advised to screen for pancreatic cancer, since diabetes can be both a marker and a risk factor of cancer of this localization.

Key words: diabetes mellitus; pancreatic cancer; insulin; insulin-like growth factor-1 (IGF-1).

РЕЗЮМЕ

Цукровий діабет 2 типу — маркер чи фактор ризику раку підшлункової залози?

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Вступ. Рак підшлункової залози (РПЗ) характеризується безсимптомним, агресивним перебігом, високою смертністю та низькою виживаністю пацієнтів. Доведено, що хворі на цукровий діабет (ЦД) мають підвищений ризик розвитку РПЗ. Проте існує два погляди на ЦД — як фактор ризику чи як маркер РПЗ.

Мета роботи — вивчити роль патогенетичних факторів цукрового діабету 2 типу у розвитку раку підшлункової залози.

Матеріали та методи. У дослідження залучено 42 пацієнти, яких розподілили на групи: I група (контрольна) — здорові особи ($n = 10$), II група — хворі на ЦД 2 типу ($n = 13$), III група — пацієнти з РПЗ без ЦД 2 типу ($n = 11$), IV група — хворі з поєднанням РПЗ і ЦД 2 типу ($n = 8$). Для оцінки стану компенсації ЦД визначали рівень глікозильованого гемоглобіну (HbA1c) методом іоно-обмінної хроматографії. Для визначення рівня інсуліну та інсуліноподібного фактора росту-1 (IGF-1) використовували метод імуноферментного аналізу.

Результати та обговорення. Достовірну гіперінсулінемію виявлено тільки у пацієнтів з ЦД 2 типу II групи порівняно з групою контролю ($p = 0,0001$), з III групою ($p = 0,0002$) і IV групою ($p = 0,04$). Підвищений рівень IGF-1 порівняно з контрольною групою мали хворі з ЦД 2 типу II групи ($p = 0,04$) і пацієнти з РПЗ III групи ($p = 0,004$). Рак ПЗ діагностований у пацієнтів без ожиріння IV групи із середньою тривалістю ЦД до 3 років. У пацієнтів II і IV груп рівень HbA1c становив 7,68 % та 8,20 % відповідно, тобто достовірної різниці показників між групами не було ($p > 0,05$).

Висновки. В обстежених нами пацієнтів із РПЗ, який розвинувся на тлі ЦД 2 типу, не виявлено ожиріння, гіперінсулінемії, підвищеного рівня IGF-1. Це дає підстави припустити можливу наявність у них вторинного діабету (T3cDM). Вперше виявлений ЦД 2 типу у хворих без ожиріння та гіперінсулінемії слід диференціювати з T3cDM. Пацієнтам із вперше виявленим ЦД 2 типу рекомендовано проводити скринінг на РПЗ, оскільки діабет може бути і маркером, і фактором ризику розвитку цього виду онкологічних захворювань.

Ключові слова: цукровий діабет 2 типу, рак підшлункової залози, інсулін, інсуліноподібний фактор росту-1 (IGF-1).

РЕЗЮМЕ

Сахарный диабет 2 типа — маркер или фактор риска рака поджелудочной железы?

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Вступление. Рак поджелудочной железы (РПЖ) характеризуется бессимптомным, агрессивным течением, высокой смертностью и низкой выживаемостью пациентов. Доказано, что больные сахарным диабетом (СД) имеют повышенный риск РПЖ. Однако существует два взгляда на СД — как фактор риска или как маркер РПЖ.

Цель работы — изучить роль патогенетических факторов сахарного диабета 2 типа в развитии рака поджелудочной железы.

Материалы и методы. В исследование были включены 42 пациента, которые были разделены на группы: I группа (контрольная) — здоровые добровольцы ($n = 10$), II группа — больные СД 2 типа ($n = 13$), III группа — пациенты с РПЖ без СД 2 типа ($n = 11$), IV группа — больные с сочетанием РПЖ и СД 2 типа ($n = 8$). Для оценки состояния компенсации СД определяли уровень гликозилированного гемоглобина (HbA1c) методом ионно-обменной хроматографии. Для определения уровня инсулина и инсулиноподобного фактора роста-1 (IGF-1) использовали метод иммуноферментного анализа.

Результаты и обсуждение. Достоверная гиперинсулинемия была выявлена только у больных с СД 2 типа II группы по сравнению с группой контроля ($p = 0,0001$), с III группой ($p = 0,0002$) и IV группой ($p = 0,04$). Повышенный уровень IGF-1 по сравнению с контрольной группой обнаружен у больных

с СД 2 типа II группы ($p = 0,04$) и у пациентов с РПЖ III группы ($p = 0,004$). РПЖ диагностирован у пациентов без ожирения IV группы со средней продолжительностью СД до 3 лет. У пациентов II и IV групп уровень HbA1c был 7,68 % и 8,20 % соответственно, и разница показателей между группами не была достоверной ($p > 0,05$).

Выводы. У обследованных нами пациентов с РПЖ, развившимся на фоне СД 2 типа, не выявлено ожирения, гиперинсулинемии, повышенного уровня IGF-1. Это дает основание предположить возможное

наличие у этих пациентов вторичного диабета (ТЗсDM). Впервые диагностированный СД 2 типа у пациентов без ожирения и гиперинсулинемии следует дифференцировать с ТЗсDM. Пациентам с впервые выявленным СД 2 типа рекомендуется проводить скрининг на РПЖ, поскольку диабет может быть и маркером, и фактором риска развития данного вида онкологического заболевания.

Ключевые слова: сахарный диабет 2 типа, рак поджелудочной железы, инсулин, инсулиноподобный фактор роста-1 (IGF-1).

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