https://doi.org/10.22416/1382-4376-2023-33-3-49-60
UDC 616.37-006.6+616.37-002]:616.008

Metabolic Risk Factors and Their Impact on Quality of Life in Patients with Pancreatic Cancer, Acute or Exacerbated Chronic Pancreatitis

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Aim: to evaluate metabolic risk factors and their impact on quality of life in patients with pancreatic cancer (PC) and in patients with acute or exacerbated chronic pancreatitis.
Materials and methods. Forty-five patients with PC (group 1) and 141 patients with acute pancreatitis or exacerbated chronic pancreatitis (group 2) in an observational multicenter clinical cross-sectional uncontrolled study were examined. Clinical, laboratory and instrumental examination of patients and assessment of risk factors (lipid profile, blood plasma glucose, obesity, arterial hypertension) were carried out in accordance with clinical recommendations. Patients completed the SF-36 questionnaire once to assess quality of life at hospital admission before treatment.
Results. In group 1, indicators of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) in blood serum (3.7 ± 0.2; 2.2 ± 0.2 and 0.8 ± 0.1 mmol/L) were lower than in group 2 (5.1 ± 0.1; 3.1 ± 0.1 and 1.2 ± 0.1 mmol/L; $p < 0.05$). Arterial hypertension was more common in group 1 (55.6 %) than in group 2 (34.8 %; $p = 0.013$). The presence of arterial hypertension increases the chance of having PC by 2.7 times ($p < 0.05$). Body mass index parameters, including obesity, as well as parameters of triglycerides, and fasting plasma glucose, did not differ between the groups. Logistic regression analysis revealed a direct relationship with PC HDL hypocholesterolemia (Exp B = 4.976; $p < 0.001$) and arterial hypertension (Exp B = 2.742; $p = 0.027$) and an inverse relationship — with hypercholesterolemia (Exp B = 0.204; $p = 0.002$). The chance of having PC was not associated with age, fasting plasma glucose ≥ 7.0 mmol/L, obesity. Quality of life indicators were higher in group 1 than in group 2 on four SF-36 scales: bodily pain (68.1 ± 5.1 and 36.8 ± 2.0; $p < 0.001$), general health (51.1 ± 2.5 and 38.0 ± 1.7 points; $p < 0.001$), social functioning (74.7 ± 3.0 and 64.5 ± 2.2 points; $p = 0.007$), role emotional functioning (28.2 ± 5.2 and 12.5 ± 3.1 points; $p = 0.007$) and in the general domain "physical component of health" (40.2 ± 1.0 and 33.6 ± 0.8 points; $p < 0.001$). In group 1 with HDL hypocholesterolemia compared with its absence, the indicators of role emotional functioning (22.2 ± 5.1 and 51.9 ± 13.7 points; $p = 0.020$) were lower, with arterial hypertension compared with its absence — role physical functioning (5.0 ± 4.0 and 25.5 ± 7.5 points; $p = 0.036$) and role emotional functioning (16.0 ± 5.1 and 43.3 ± 8.8 points; $p = 0.007$) were lower.
Conclusions. In patients with PC arterial hypertension was more common and the levels of total cholesterol, LDL-C and HDL-C were lower than in patients with acute or exacerbated chronic pancreatitis. The chance of having PC is directly associated with HDL hypocholesterolemia, with arterial hypertension, inversely — with hypercholesterolemia, and is not associated with age, fasting plasma glucose ≥ 7 mmol/L, or obesity. In patients with PC, quality of life indicators were higher on four SF-36 scales and on the general domain "physical component of health" than in the group with acute or exacerbated chronic pancreatitis. In patients with PC metabolic factors significantly worsened self-assessment of quality of life in terms of role functioning; in patients with acute or exacerbated chronic pancreatitis there was no such association.

Keywords: pancreatic cancer, acute pancreatitis, exacerbated chronic pancreatitis, serum lipids, plasma glucose, arterial hypertension, quality of life
Conflict of interest: the authors declare no conflict of interest.
Funding: the work was carried out under the State Assignment in the budgetary theme "Epidemiological monitoring of the population's health and the study of molecular genetics and molecular biological mechanisms of the development of common therapeutic diseases in Siberia to improve approaches to their diagnosis, prevention and treatment" No. AAAA-A17-117112850280-2.

For citation: Grigor'eva I.N., Efimova O.V., Tov N.L., Suvorova T.S., Nepomnyashchikh D.L. Metabolic Risk Factors and Their Impact on Quality of Life in Patients with Pancreatic Cancer, Acute or Exacerbated Chronic Pancreatitis. Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2023;33(3):49–60. https://doi. org/10.22416/1382-4376-2023-33-3-49-60

Метаболические факторы риска и их влияние на качество жизни у пациентов с раком поджелудочной железы и у пациентов с острым или обострением хронического панкреатита

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Цель исследования: оценить метаболические факторы риска и их влияние на качество жизни (КЖ) у пациентов с раком поджелудочной железы (РПЖ) и у пациентов с острым или обострением хронического панкреатита.

Материалы и методы. В рамках наблюдательного многоцентрового клинического кросс-секционного неконтролируемого исследования обследовано 45 пациентов с РПЖ (1-я группа) и 141 пациент с острым панкреатитом или обострением хронического панкреатита (2-я группа). Клиническое, лабораторное и инструментальное обследование пациентов и оценка факторов риска (липидный профиль, глюкоза плазмы крови, наличие ожирения, артериальной гипертензии) проведено в соответствии с клиническими рекомендациями. Пациенты однократно заполняли опросник SF-36 для оценки КЖ при поступлении до лечения.

Результаты. В 1-й группе показатели общего холестерина (ОХС), холестерина липопротеидов низкой плотности (ХС ЛНП), холестерина липопротеидов высокой плотности (ХС ЛВП) в сыворотке крови (3,7 ± 0,2; 2,2 ± 0,2 и 0,8 ± 0,1 ммоль/л) были ниже, чем во 2-й группе (5,1 ± 0,1; 3,1 ± 0,1 и 1,2 ± 0,1 ммоль/л; $p < 0,05$). Артериальная гипертензия чаще встречалась в 1-й группе (55,6 %), чем во 2-й группе (34,8 %; $p = 0,013$). Наличие артериальной гипертензии повышает шанс наличия РПЖ в 2,7 раза ($p < 0,05$). Показатели индекса массы тела, в том числе частота ожирения, триглицеридов и глюкозы плазмы крови натощак не различались между группами. Логистический регрессионный анализ выявил прямую связь с РПЖ гипохолестеринемии ЛВП (Exp B = 4,976; $p < 0,001$) и артериальной гипертензии (Exp B = 2,742; $p = 0,027$) и обратную связь — гиперхолестеринемии (Exp B = 0,204; $p = 0,002$). Шанс наличия РПЖ не был ассоциирован с возрастом, уровнем глюкозы плазмы натощак ≥ 7,0 ммоль/л, ожирением. Показатели КЖ были выше в 1-й группе, чем во 2-й, по четырем шкалам SF-36: телесной боли (68,1 ± 5,1 и 36,8 ± 2,0; $p < 0,001$), общего состояния здоровья (51,1 ± 2,5 и 38,0 ± 1,7 балла; $p < 0,001$), социального функционирования (74,7 ± 3,0 и 64,5 ± 2,2 балла; $p = 0,007$), ролевого эмоционального функционирования (28,2 ± 5,2 и 12,5 ± 3,1 балла; $p = 0,007$) и по общему домену «физический компонент здоровья» (40,2 ± 1,0 и 33,6 ± 0,8 балла; $p < 0,001$). У пациентов в 1-й группе с гипохолестеринемией ЛВП по сравнению с ее отсутствием показатели ролевого эмоционального функционирования (22,2 ± 5,1 и 51,9 ± 13,7 балла; $p = 0,020$) были ниже, с артериальной гипертензией по сравнению с ее отсутствием — ролевое физическое функционирование (5,0 ± 4,0 и 25,5 ± 7,5 балла; $p = 0,036$) и ролевое эмоциональное функционирование (16,0 ± 5,1 и 43,3 ± 8,8 балла; $p = 0,007$) были ниже.

Выводы. У пациентов с РПЖ чаще встречалась артериальная гипертензия и были ниже уровни ОХС, ХС ЛНП и ХС ЛВП, чем у пациентов с острым или обострением хронического панкреатита. Шанс наличия РПЖ прямо ассоциирован с гипохолестеринемией ЛВП, с артериальной гипертензией, обратно — с гиперхолестеринемией и не связан с возрастом, глюкозой плазмы натощак ≥ 7 ммоль/л или с ожирением. У пациентов с РПЖ показатели КЖ были выше по четырем шкалам SF-36 и по общему домену «физический компонент здоровья», чем в группе с острым или обострением хронического панкреатита. У пациентов с РПЖ метаболические факторы значительно ухудшали самооценку КЖ по ролевому функционированию, у пациентов с острым или обострением хронического панкреатита такой ассоциации не было.

Ключевые слова: рак поджелудочной железы, острый панкреатит, обострение хронического панкреатита, липиды крови, глюкоза крови, артериальная гипертензия, качество жизни

Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Финансирование: работа выполнена по Государственному заданию в рамках бюджетной темы «Эпидемиологический мониторинг состояния здоровья населения и изучение молекулярно-генетических и молекулярно-биологических механизмов развития распространенных терапевтических заболеваний в Сибири для совершенствования подходов к их диагностике, профилактике и лечению» № АААА-А17-117112850280-2.

Для цитирования: Григорьева И.Н., Ефимова О.В., Тов Н.Л., Суворова Т.С., Непомнящих Д.Л. Метаболические факторы риска и их влияние на качество жизни у пациентов с раком поджелудочной железы и у пациентов с острым или обострением хронического панкреатита. Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2023;33(3):49–60. https://doi.org/10.22416/1382-4376-2023-33-3-49-60

Introduction

The incidence and number of deaths caused by tumors of the pancreas is gradually increasing and despite advances in the detection and treatment of pancreatic cancer (PC) only about 4 % of patients survive 5 years after diagnosis [1]. Metabolic risk factors for PC include alcohol, smoking, diet, high body mass index, diabetes mellitus, dyslipidemia, etc. [2]. In a systematic review (analysis of 88 independent studies), the overall summary relative risk of PC among patients with diabetes mellitus was 1.97 (95 % confidence interval (CI): 1.78–2.18) [1]. Hypothetical mechanisms of the association between diabetes mellitus and PC include hyperglycemia, chronic inflammation, hyperinsulinemia (insulin promotes not only cell growth, but also the proliferation of blood vessels in the pancreas), insulin resistance, and increased levels of circulating insulin-like growth factors [1]. A meta-analysis of 23 prospective studies, including 9504 cases, found an association between body mass index and PC: an increase in body mass index by 5 units increased the risk of PC by 1.10 times; increase in waist circumference by 10 cm – 1.11 times; an increase in "waist/hips" ratio by 0.1 units – 1.19 times [3]. Not only a negative association of a high body mass index with the risk of developing PC was noted, but a relationship was also found between an increase in mortality from PC and overweight and obesity; an increase in body mass index by 1 kg/m^2 increases the risk of mortality from PC by 10 % [4].

Recognized metabolic risk factors for acute pancreatitis are obesity, dyslipidemia, and diabetes mellitus [5–12]. Several meta-analyses have shown that obesity, as one of the most important negative prognostic factors of acute pancreatitis, increases the risk of development, correlates with the severity, development of local and systemic complications of the disease [5–7]. In a meta-analysis by D. Dobszai et al. (2019) showed that in the presence of an increased body mass index > 25 kg/m^2 compared with a normal body mass index, the risk of developing severe acute pancreatitis increases three times (odds ratio (OR) = 2.87; 95 % CI: 1.90–4.35; $p < 0.011$) [7]. In studies of the role of dyslipidemia in the development of acute pancreatitis [8–11], serum levels of apolipoprotein A-I and high-density lipoprotein (HDL) cholesterol were negatively correlated with poor clinical outcomes of acute pancreatitis [8]; another study showed that both low (< 90 mg/dL) and high (> 150 mg/dL) levels of low-density lipoprotein (LDL) cholesterol, low levels of HDL (< 30 mg/dL) were independently associated with increased risk of developing severe acute pancreatitis, but not associated with high (> 150 mg/dL) serum triglyceride levels [9]. The risk of developing acute pancreatitis increases with a triglyceride level of more than 10 mmol/L [10], however, other authors have shown that acute pancreatitis can also occur at a triglyceride level of 177 mg/dL [11]. Type 2 diabetes mellitus, as a generally recognized risk factor for the development of acute pancreatitis, is associated with an increased incidence of its complications (OR = 1.553; 95 % CI: 1.266–1.904; $p < 0.001$) and mortality [12].

Dyslipidemia and diabetes mellitus are also considered as metabolic risk factors for chronic pancreatitis. Hyperlipidemia and hypertriglyceridemia are etiological factors of chronic pancreatitis according to the classifications of V.T. Ivashkin et al. (1990), TIGAR-O (1994) and M-ANNHEIM (2007), however, the role of lipid metabolism disorders in the development of certain etiological forms (alcoholic, biliary) of chronic pancreatitis remains poorly understood [13]. The prevalence of diabetes mellitus in patients with chronic pancreatitis – about 30–40 % – increases in the presence of other factors: alcohol abuse, a long history of chronic pancreatitis, pancreatic surgery [14]. The development of diabetes mellitus secondary to chronic pancreatitis ("pancreatogenic" or "pancreatogenous" diabetes mellitus) is associated with negative clinical outcomes in the course of the chronic pancreatitis: the frequency of exacerbations, the duration of relapses, and the number of days of disability increase.

In recent years, there has been a significant increase in interest in the study of quality of life (QoL), which is an integral characteristic of the physical, mental, emotional and social functioning of the patient, based on his subjective perception in various diseases. In gastroenterology, the most common questionnaires for assessing QoL are the specific GSRS questionnaire (Gastrointestinal Symptom Rating Scale) and the nonspecific SF-36 questionnaire (Short Form-36; Medical Outcomes Study Short Form-36 Health Survey) [15]. In addition, special questionnaires are being actively developed, for example, the European Organization for Research and Treatment of Cancer developed a special questionnaire (1999) designed to assess the QoL of patients with PC (QLQ PAN 26) [16]. However, the SF-36 questionnaire has a number of advantages – assessment of QoL in any disease, an integrated approach in determining not only physical, but also social and psychological disorders. As the most widely used questionnaire in the world, this questionnaire provides an opportunity to compare patients' QoL indicators in a wide range of tasks, both in population and clinical studies.

The risk factors affecting the QoL in patients with acute pancreatitis include the severity of the disease, the amount of damage to the pancreas and the according surgery, the period after acute destructive pancreatitis, and the presence of relapses of the disease [17]. Factors affecting QoL in chronic pancreatitis include obligatory diet, the need for constant medication, recurrence of pain, anxiety and depression, the presence of a threat of complications, and with their development – a decrease in the

patient's ability to daily activities, financial costs of treatment [18].

This work is devoted to the assessment of QoL in patients with PC, acute pancreatitis and exacerbated chronic pancreatitis with and without concomitant metabolic factors, which will expand our understanding of the contribution of these factors to the QoL of patients with pancreatic diseases.

Aim of the study: to evaluate metabolic risk factors and their impact on QoL in patients with PC and in patients with acute or exacerbated chronic pancreatitis.

Materials and methods

The observational multicenter clinical cross-sectional uncontrolled study included 186 patients with pancreatic diseases: group 1 — 45 patients with PC, group 2 — 141 patients with acute pancreatitis or exacerbated chronic pancreatitis as a comparison group (a group of patients with inflammatory diseases of the pancreas). Clinical, laboratory and instrumental examination of patients to verify the diagnosis and assess risk factors (lipid profile, blood glucose, obesity, arterial hypertension) was carried out in accordance with clinical recommendations. Patients completed the SF-36 QoL questionnaire once on admission to the hospital, prior to surgical treatment in case of PC. The Russian version of the SF-36 questionnaire was validated by us earlier.

Ethical review

The study was performed in accordance with Good Clinical Practice and the principles of the Helsinki Declaration of World Medical Association. The study protocol was approved by the ethics committees of the Research Institute of Therapy and Preventive Medicine — Branch of the Federal Research Center Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences (protocol No. 38 dated September 23, 2014), the State Budgetary Healthcare Institution of the Novosibirsk Region "City Clinical Hospital No. 7" (No. 1 of 31.03.2014), the State Budgetary Institution of Healthcare of the Novosibirsk Region "State Novosibirsk Regional Clinical Hospital" (No. 1 of 01.29.2014). Each patient received detailed information about the study, about the possible use of their data in scientific purposes and signed a voluntary informed consent to participate in the study. All patients remained anonymous during subsequent data analysis.

Inclusion criteria for the study: being diagnosed with PC or acute pancreatitis or exacerbated chronic pancreatitis, age of 25–70 years. Criteria for exclusion from the study: age younger than 25 and older than 70 years, severe comorbidities. Acceptable comorbidities included: non-erosive reflux disease, gastric ulcer, duodenal ulcer without exacerbation, non-atrophic gastritis, postcholecystectomy syndrome, functional disorder of the sphincter of Oddi in exacerbated chronic pancreatitis, cholelithiasis, type 2 diabetes mellitus, arterial hypertension (AH). The study was conducted from 2014 to 2019. To verify the diagnosis, general clinical, laboratory, instrumental and morphological methods of examining the pancreas were used. The diagnosis of acute pancreatitis was established according to the clinical guidelines of the Russian Society of Surgeons (2020). The diagnosis of chronic pancreatitis was established on the basis of the Recommendations of the Russian Gastroenterological Association [13]. The diagnosis of PC was suspected on the basis of the data of instrumental methods of research, verified by a pathoanatomical study of the removed tumor preparation of the pancreas (including using immunohistochemical methods).

Plasma glucose, blood serum total cholesterol, HDL cholesterol, triglycerides were determined according to standard methods; LDL cholesterol, very low-density lipoprotein (VLDL) cholesterol were calculated using standard formulas. Hypercholesterolemia was defined as total serum cholesterol > 5.0 and/or serum LDL cholesterol > 3.0 mmol/L; hypertriglyceridemia — the level of fasting triglycerides > 1.7 mmol/L; hyperlipidemia — the level of total cholesterol > 5.0 and/or the level of LDL cholesterol > 3.0 mmol/L and/or the level of fasting triglycerides > 1.7 mmol/L; dyslipidemia — hyperlipidemia and/or HDL hypocholesterolemia [19]. Depending on the level of fasting plasma glucose, patients of groups 1 and 2 were divided into three subgroups: fasting plasma glucose < 6.1 mmol/L; fasting plasma glucose ≥ 6.1 < 7.0 mmol/L; fasting plasma glucose ≥ 7.0 mmol/L. According to the values of the body mass index, patients of groups 1 and 2 were divided into subgroups: deficient (body mass index < 18.5 kg/m^2), normal body weight (body mass index — 18.5–24.9 kg/m^2), overweight (body mass index — 25.0–29.9 kg/m^2), obesity (body mass index ≥ 30 kg/m^2). AH was diagnosed at systolic blood pressure levels ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg [20] and in persons with normal blood pressure while taking antihypertensive drugs during the last two weeks prior to this examination.

To assess the QoL of patients in groups 1 and 2, the SF-36 questionnaire was used, containing 36 questions, which are combined into eight scales: physical functioning, role physical functioning, bodily pain, general health, vitality, social functioning, role emotional functioning, mental health; the first four scales characterize the physical component of health, the last four — the mental component of health. The indices of each scale are evaluated in points from 0 to 100; higher scores on the SF-36 questionnaire correspond to a higher level of QoL. According to the SF-36 questionnaire, the QoL in all patients was assessed during the previous four weeks before the examination [15].

Group 1 (the main one) of patients with PC included 41 patients with pancreatic adenocarcinoma and 4 patients with neuroendocrine PC (n = 45; mean age — 58.5 ± 1.1 years; 48.9 % of men and 51.1 % of women; 57.8 % of patients with stages I–II and 42.2 % of patients with stages III–IV of the disease). Group 2 included 44 (31.2 %) patients with acute pancreatitis and 97 (68.8 %) with exacerbated chronic pancreatitis (n = 141; mean age — 53.5 ± 0.9 years (p < 0.05 with compared with patients with PC); 32.6 % of men and 67.4 % of women; according to etiology: 24.1 % — alcoholic, 73.1 % — biliary, 2.8 % — idiopathic pancreatitis).

Statistical analysis

Statistical data processing was performed using the SPSS software package (v. 13.0). Count data analyzed using the chi-square test, and measurement data are expressed as $M \pm m$ and analyzed using Student's t-test. Differences were considered statistically significant at $p < 0.05$. For a comparative assessment of the mean values of quantitative data one-way analysis ANOVA was used. Standardization of the mean values of quantitative data was carried out in multiple covariance analysis. The analysis of the relationships of the main features was carried out using logistic regression analysis.

Results

Comparative analysis of blood serum lipids, fasting plasma glucose, body mass index between the two groups of patients was carried out in multiple analysis of covariance (Table 1). Total serum cholesterol levels were lower in group 1 (3.7 ± 0.2 mmol/L) than in group 2 (5.1 ± 0.1 mmol/L; $p < 0.001$). The average level of triglycerides and VLDL cholesterol practically did not differ between group 1 (1.6 ± 0.1 and 0.7 ± 0.1 mmol/L) and group 2 (1.8 ± 0.1 and 0.8 ± 0.1 mmol/L; $p > 0.05$ in both cases). Serum HDL cholesterol levels were lower in patients of group 1 (0.8 ± 0.1 mmol/L) than in group 2 (1.2 ± 0.1 mmol/L; $p < 0.001$). The average level of LDL-C in blood serum was significantly lower among patients of group 1 (2.2 ± 0.2 mmol/L; $p < 0.001$) than in group 2 (3.1 ± 0.1 mmol/L; $p < 0.001$). The average fasting plasma glucose level practically did not differ between group 1 (6.7 ± 0.1 mmol/L) and group 2 (6.6 ± 0.1 mmol/L; $p > 0.05$), as did the average level body mass index (25.9 ± 0.7 and 25.6 ± 0.5 kg/m^2 in groups 1 and 2, respectively).

In multivariate regression analysis (Table 2) with dependent variables (presence/absence of PC) and independent variables (age, body mass index, total cholesterol, triglycerides, serum HDL-C and fasting plasma glucose), an increase in serum HDL-C by 1 mmol/L significantly reduced the chance of having PC (Exp B = 0.024; 95 % CI: 0.005–0.126; $p < 0.001$).

A comparative analysis of the frequency of metabolic factors was carried out using the χ^2 test (Table 3). The frequency of obesity practically did not differ between patients of group 1 (20.0 %) and group 2 (21.3 %). Deficient, normal weight and overweight occurred in 0.0, 44.4 and 35.6 % of patients in group 1 and in 5.7, 41.8 and 31.2 % of patients in group 2, respectively ($p > 0.05$ in all cases).

Table 1. Clinical and biochemical parameters in patients of groups 1 and 2 *(M ± m)*
Таблица 1. Клинико-биохимические показатели у пациентов 1-й и 2-й групп *(M ± m)*

Parameter Показатель	Group 1 1-я группа (n = 45)	Group 2 2-я группа (n = 141)	p
Body mass index, kg/m^2 Индекс массы тела, кг/м^2	25.9 ± 0.7	25.6 ± 0.5	0.685
Fasting plasma glucose, mmol/L Глюкоза плазмы натощак, ммоль/л	6.7 ± 0.2	6.6 ± 0.2	0.719
Total cholesterol, mmol/L Общий ХС, ммоль/л	3.7 ± 0.2	5.1 ± 0.1	< 0.001
Triglycerides, mmol/L Триглицериды, ммоль/л	1.6 ± 0.1	1.8 ± 0.1	0.111
High density lipoprotein cholesterol, mmol/L ХС липопротеинов высокой плотности, ммоль/л	0.8 ± 0.1	1.2 ± 0.1	< 0.001
Very low density lipoprotein cholesterol, mmol/L ХС липопротеинов очень низкой плотности, ммоль/л	0.7 ± 0.1	0.8 ± 0.1	0.112
Low density lipoprotein cholesterol, mmol/L ХС липопротеинов низкой плотности, ммоль/л	2.2 ± 0.2	3.1 ± 0.1	< 0.001

Note: standardization of average values of clinical and biochemical parameters by age was carried out using Generalized Estimating Equations in the module of the multidimensional general linear model (General Linear Model).

Примечание: стандартизацию средних значений клинико-биохимических показателей по возрасту осуществляли с помощью обобщенных оценивающих уравнений (Generalized Estimating Equations) в модуле многомерной общей линейной модели (General Linear Model).

However, the incidence of obesity in history (one year before the present examination) in patients of group 1 was 2.5 times higher than in group 2 (55.6 and 22.0 %, respectively; $\chi^2 = 18.3$; $p < 0.001$.

In patients of group 1, hypercholesterolemia occurred 3.4 times less frequently (15.6 and 53.2 %; $\chi^2 = 19.6$; $p < 0.001$), and HDL hypocholesterolemia, on the contrary, 2.4 times more often (80.0 and 33.2 %; $\chi^2 = 30.1$; $p < 0.001$) than in group 2. The frequency of hypertriglyceridemia practically did not differ between the two groups of patients: 35.6 % — in group 1 and 46.8 % — in group 2 ($p > 0.05$). Fasting plasma glucose < 6.1 mmol/L (corresponding to normoglycemia) occurred in less than half of the patients in group 1 (48.9 %) and group 2 (47.5 %; $p > 0.05$). Fasting plasma glucose frequency ≥ 6.1 < 7.0 mmol/L (corresponding to prediabetes) did not differ in groups 1 and 2 (17.8 and 12.8 %; $p > 0.05$). Fasting plasma glucose ≥ 7.0 mmol/L (corresponding to diabetes mellitus) occurred in 33.3 % of patients in group 1 and in 39.7 % of patients in group 2 ($p > 0.05$). AH was more common in patients of group 1 (55.6 %) than in group 2 (34.8 %; $\chi^2 = 6.2$; $p = 0.013$).

In multivariate regression analysis with dependent variables (presence/absence of PC) and independent variables (age, obesity, fasting plasma glucose ≥ 7.0 mmol/L, hypercholesterolemia, HDL hypocholesterolemia, AH) HDL hypocholesterolemia (Exp B = 4.976; 95 % CI: 2.040–12.134; $p < 0.001$) and AH (Exp B = 2.742; 95 % CI: 1.124–6.689; $p = 0.027$) increased, while hypercholesterolemia (Exp B = 0.204; 95 % CI: 0.075–0.558; $p = 0.002$), on the contrary, reduced the chance of having PC (Table 4). In our study, the chance of having PC

Table 2. Associations of clinical and biochemical parameters with the chance of having pancreatic cancer
Таблица 2. Ассоциации клинико-биохимических показателей с шансом наличия рака поджелудочной железы

Indicator Показатели	Exp B	95 % CI 95% ДИ	*p*
Age Возраст	1.043	0.007–1.092	0.069
Fasting plasma glucose Глюкоза плазмы натощак	1.001	0.747–1.341	0.994
Total cholesterol Общий ХС	0.729	0.497–1.070	0.106
High density lipoprotein cholesterol ХС липопротеинов высокой плотности	0.024	0.005–0.126	0.024
Body mass index Индекс массы тела	1.050	0.959–1.151	< 001

Note: multivariate analysis of relationships of the main features was carried out using logistic regression analysis (Enter method). Exp B (exponent B) reflects the risk ratio, shows how many times the risk of an outcome changes if the predictor value changes by one.
Примечание: многомерный анализ связей главных признаков проводился с помощью логистического регрессионного анализа (метод Enter). Exp B (экспонента B) отражает отношение рисков, показывает, во сколько раз изменяется риск возникновения исхода, если значение предиктора изменяется на единицу.

Table 3. Frequency of metabolic risk factors in patients of groups 1 and 2, %
Таблица 3. Частота метаболических факторов риска у пациентов 1-й и 2-й групп, %

Indicator Фактор риска	Group 1 1-я группа (*n* = 45)	Group 2 2-я группа (*n* = 141)	*p*
Obesity Ожирение	20.0	21.3	0.855
Fasting plasma glucose ≥ 7.0 mmol/L Глюкоза плазмы натощак ≥ 7,0 ммоль/л	33.3	39.7	0.443
Hypercholesterolemia Гиперхолестеринемия	15.6	53.2	< 0.001
Hypertriglyceridemia Гипертриглицеридемия	35.6	46.8	0.186
High density lipoprotein hypocholesterolemia Гипохолестеринемия липопротеинов высокой плотности	80.0	33.3	< 0.001
Arterial hypertension Артериальная гипертензия	55.6	34.8	0.013

Note: the comparison of the frequencies of qualitative features was carried out using the χ^2 test.
Примечание: сравнение частот качественных признаков проводилось с помощью критерия χ^2.

was not associated with age (Exp B = 1.040; 95 % CI: 0.996–1.087; $p = 0.077$), with fasting plasma glucose ≥ 7.0 mmol/L (Exp B = 0.740; 95 % CI: 0.313–1.746; $p = 0.491$), obesity (Exp B = 0.737; 95 % CI: 0.255–2.132; $p = 0.574$).

A comparative analysis of QoL indicators in patients of groups 1 and 2 is presented in Table 5. In patients of group 1, according to the scale of bodily pain (low scores on this scale indicate that pain significantly limits the patient's activity), the average score was 1.9 times higher (68.1 ± 5.1 and 36.8 ± 2.0 points; $p < 0.001$) than in group 2, which means that in patients of group 1, bodily pain had a lesser effect on the ability to engage in daily activities than in the group 2. Patients of group 1 had higher average indicators on the scale of general health (the patient's assessment of their state of health at the moment and the prospects for treatment; the lower the score on this scale, the lower the assessment of the state of health) than in group 2: 51.1 ± 2.5 and 38.0 ± 1.7 points ($p < 0.001$).

Higher average indicators of social functioning (low values indicate a significant limitation of social contacts, a decrease in the level of communication due to a deterioration in physical and emotional state) were determined in patients of group 1 compared with group 2: 74.7 ± 3.0 and 64.5 ± 2.2 points ($p = 0.007$). The average indicators of role emotional functioning (low values on this scale are interpreted as a limitation in the performance of daily work due to a deterioration in the emotional state) were low in both groups, however, in group 2 (12.5 ± 3.1 points), these values were in 2,3 times lower than in group 1 (28.2 ± 5.2 points; $p = 0.007$). The average number of points on the mental health scale (low values indicate the presence of depressive, anxious experiences, mental distress) did not differ between patients of group 1 (55.7 ± 1.3 points) and group 2 (55.1 ± 1.9 points; $p > 0.05$). The overall indicator "Physical component of health" was higher in patients of group 1 (40.2 ± 1.0 points) than in group 2 (33.6 ± 0.8 points; $p < 0.001$), the overall indicator "Psychological component of health" practically did not differ between groups 1 and 2 (37.7 ± 0.9 and 35.4 ± 0.7 points, respectively; $p > 0.05$).

Patients of group 1 with HDL hypocholesterolemia had lower values of role emotional functioning than patients of group 1 without HDL hypocholesterolemia (22.2 ± 5.1 and 51.9 ± 13.7 points; $p = 0.020$). In patients of group 1 with concomitant AH, worsening of indicators on the scales of role physical functioning (5.0 ± 4.0 and 25.5 ± 7.5 points; $p = 0.036$) and role emotional functioning (16.0 ± 5.1 and 43.3 ± 8.8 points; $p = 0.007$) compared with patients of group 1 without AH. In patients in group 2, the average indicators of all QoL scales practically did not differ in the presence/absence of metabolic factors (hyperglycemia ≥ 7.0 mmol/L, obesity, AH, hypercholesterolemia, HDL hypocholesterolemia), ($p > 0.05$ in all cases).

Discussion

In our study, according to the results of multiple covariance analysis in patients of group 1, compared with group 2, the lowest levels of total cholesterol, HDL-C, LDL-C in blood serum were revealed; the chance of having PC was directly associated with HDL hypocholesterolemia, and inversely — with hypercholesterolemia. According to a meta-analysis (2015), neither in Europe nor in Asia the level of total cholesterol and serum triglycerides was associated with PC [21]. In their work G.C. Kabat et al. (2018) found an inverse relationship between serum HDL-C and PC [22]. Our results are consistent with existing evidence of a significant inverse relationship between baseline serum HDL-C levels and cancer incidence: for every 10 mg/dL increase in HDL-C, there is a 36 % reduction in cancer risk (95 % CI: 24–47; $p < 0.001$), independent of age, BMI, gender, tobacco smoking and the presence of diabetes mellitus [23].

In multivariate regression analysis, we showed that the presence of AH increases the chance of having PC by 2.7 times ($p < 0.05$). When reviewing the literature, we did not find data on the effect of AH on the risks of PC, however, there is evidence that AH is the most common comorbidity in patients with malignant neoplasms (37 %), but the prevalence of AH before chemotherapy is similar to that in the population in general (29 %) [24]. In addition, we previously described the negative impact of concomitant AH on clinical and biochemical parameters in patients with acute or exacerbated chronic pancreatitis: in comparison with the absence of AH in the presence of concomitant AH, patients with acute pancreatitis showed higher levels of fasting plasma glucose, serum triglycerides, the frequency of hypertriglyceridemia, in patients with chronic pancreatitis — fasting plasma glucose, the frequency of obesity [25].

There are data in the literature on the negative impact of AH on the state of the pancreas. Stimulation of the renin-angiotensin system is associated with systemic and local vasoconstriction, and in particular pancreatic vessels; restriction of blood flow to the pancreas leads to hypoperfusion and ischemia and, as a result, to an increase in the secretion of nitric oxide and reactive oxygen species, which reduce the lifespan of acinocytes and insulin-producing β-cells [26]. R. Liu et al. (2014) found a local islet of angiotensin-generating system in the exocrine part of the pancreas, which plays an important role in the physiological regulation of insulin secretion [27]. Angiotensin-converting enzyme (ACE) is able to locally produce angiotensin-II. ACE hyperactivity leads to a cascade of events involved in the development of pancreatitis, including an increase in the inflammatory response and oxidative stress. ACE2 cleaves angiotensin-II to angiotensin-(1–7), which has many effects (vasodilating, antifibrotic,

Table 4. Associations of metabolic factors with the chance of having pancreatic cancer
Таблица 4. Ассоциации метаболических факторов с шансом наличия рака поджелудочной железы

Indicator Показатели	Exp B	95 % CI 95% ДИ	*p*
Age Возраст	1.040	0.996–1.087	0.077
Fasting plasma glucose ≥ 7.0 mmol/L Глюкоза плазмы натощак ≥ 7,0 ммоль/л	0.740	0.313–1.746	0.491
Hypercholesterolemia Гиперхолестеринемия	0.204	0.075–0.558	0.002
HDL hypocholesterolemia Гипохолестеринемия ЛВП	4.976	2.040–12.134	< 0.001
Obesity Ожирение	0.737	0.255–2.132	0.574
Arterial hypertension Артериальная гипертензия	2.742	1.124–6.689	< 0.001

Note: multivariate analysis of relationships of the main features was carried out using logistic regression analysis (Enter method). Exp B (exponent B) reflects the risk ratio, shows how many times the risk of an outcome changes if the predictor value changes by one.
Примечание: многомерный анализ связей главных признаков проводился с помощью логистического регрессионного анализа (метод Enter). Exp B (экспонента B) отражает отношение рисков, показывает, во сколько раз изменяется риск возникновения исхода, если значение предиктора изменяется на единицу.

Table 5. Quality of life indicators in patients with pancreatic cancer and acute/chronic pancreatitis, points
Таблица 5. Показатели качества жизни у пациентов раком поджелудочной железы и острым/хроническим панкреатитом, баллы

Indicator Показатели	Group 1 1-я группа (*n* = 45)	Group 2 2-я группа (*n* = 141)	*p*
Physical functioning Физическое функционирование	61.0 ± 3.5	52.7 ± 2.8	0.084
Role physical functioning Ролевое физическое функционирование	12.8 ± 4.2	8.6 ± 2.6	0.385
Bodily pain Телесная боль	68.1 ± 5.1	36.8 ± 2.0	< 0.001
General health Общее здоровье	51.1 ± 2.5	38.0 ± 1.7	< 0.001
Vitality Жизненная активность	44.3 ± 1.5	46.7 ± 1.1	0.229
Social functioning Социальное функционирование	74.7 ± 3.0	64.5 ± 2.2	0.007
Role emotional functioning Ролевое эмоциональное функционирование	28.2 ± 5.2	12.5 ± 3.1	0.007
Mental health Психическое здоровье	55.1 ± 1.9	55.7 ± 1.3	0.772
Summary score “Physical component of health” Общий показатель «Физический компонент здоровья»	40.2 ± 1.0	33.6 ± 0.8	< 0.001
Summary score “Psychological component of health” Общий показатель «Психологический компонент здоровья»	37.7 ± 0.9	35.4 ± 0.7	0.056

Note: the assessment of the average values of quality of life indicators was carried out using ANOVA analysis of variance; results are presented as mean ± error of mean *(M ± m)*.
Примечание: оценка средних значений показатели качества жизни проводилась с помощью дисперсионного анализа ANOVA; результаты представлены как среднее арифметическое ± ошибка среднего арифметического *(M ± m)*.

antithrombotic, increasing insulin sensitivity), antagonistic to angiotensin-II [28]. Thus, ACE2 may play an important counter-regulatory role for the renin-angiotensin system, protecting tissues from angiotensin-II-mediated damage. An imbalance in the ACE2/ACE ratio plays an important role in the pathogenesis of severe acute pancreatitis, in which the ratio of ACE2 expression to ACE expression in the pancreas is significantly reduced and corresponds to the severity of the disease [27].

The definition of QoL is an additional tool in the clinic that has the structural independence of the domains ("Physical component of health" and "Mental component of health"), which improves the reliability of algorithms for calculating the total and discrete (on separate scales) assessment of the state of health in order to identify which particular domain of health needs correction.

When studying the quality of life in the group of patients with PC and in the group of patients with acute pancreatitis or exacerbated chronic pancreatitis, we obtained data on low scores on the scale of role physical functioning (shows the extent to which health limits life activity), role emotional functioning in both groups, which indicates the presence of restrictions in the performance of daily work ("the person did less work than they wanted"), associated with a deterioration in the physical and emotional state in patients with PC and with acute pancreatitis or exacerbated chronic pancreatitis. We found that bodily pain in patients with PC had a lesser impact on the ability to carry out daily activities than in patients with acute pancreatitis or exacerbated of chronic pancreatitis, and the summary score "Physical component of health" was significantly higher in the group of patients with PC than in the group of patients with acute pancreatitis or exacerbated chronic pancreatitis, which may be due to the "cunning" nature of PC and its untimely diagnosis, which is associated with the peculiarities of the clinical picture of PC (long-term latent course, late manifestation of the disease, similarity with the clinic of chronic pancreatitis, low information content of generally accepted research methods in the early stages of the disease) [29] and the presence of topographic and anatomical features that create conditions for rapid distant metastasis already in the early stages of cancer, as well as low sensitivity to chemoradiotherapy [30].

R. Shisler et al. (2018) believe that factors affecting QoL, such as pain, fatigue, emotional and social functioning, must be controlled after cancer diagnosis [31]. The results of the QoL study are used to make decisions in terms of selecting interventions that will improve all aspects of health-related QoL. For example, pain is one of the main factors that reduce QoL. But pain relief does not always lead to an improvement in QoL on the scales of role functioning and mental health [32]. Among cancer patients satisfied with pain medications, compared with patients with uncontrolled pain, QoL was better on all scales of the SF-36 questionnaire, except for role physical functioning, role emotional functioning, and mental health [33]. In patients with PC, after neurolytic blockade of the celiac plexus for the purpose of analgesia, QoL did not improve on the scales of role emotional functioning and general health [34]. On the contrary, physical exercises increased the QoL on the scale of role physical functioning in cancer patients [35].

In the group of patients with PC, the presence of AH and HDL hypocholesterolemia was accompanied by a deterioration in the scales of the role of physical and emotional functioning; in the group of patients with acute pancreatitis or with exacerbated chronic pancreatitis, no influence of metabolic risk factors on QoL was detected, which can be explained by the peculiarities of the clinical picture of these diseases when low-symptomatic PC brings to the fore the manifestations of other diseases, and in acute pancreatitis or exacerbated chronic pancreatitis, a vivid clinical picture has a more significant effect on the assessment of well-being than concomitant obesity, dyslipidemia, diabetes mellitus, AH. The fact of a negative association of HDL hypocholesterolemia and AH with QoL indicators suggests that the correction of these factors may lead to an improvement in QoL in PC patients.

Limitations

This study has some limitation. Since this study used a cross-sectional design, the causal relationship between risk factors and PC, acute or chronic pancreatitis should be interpreted in these circumstances. We performed a continuum of patient enrollments and a standardized assessment of risk factors and clinical findings to minimize observer bias and improve the generalizability of results.

The undoubted advantage of our work is the use of such a common instrument for assessing the quality of life as the SF-36 questionnaire, which is validated, reliable and widely used throughout the world over the past 25 years in patients with pancreatic pathology. Thus, the SF-36 questionnaire is used as an effective method for assessing the quality of medical care for patients with PC, which helps in choosing the modality of treatment for these patients [36]. It seems to us appropriate to use a combination of symptom-specific tools and global QoL tools to more fully reflect the condition and opinion of patients. In particular, the obtained data on the negative impact of AH on QoL in patients with PC suggest the advisability of timely diagnosis and treatment of AH in them, as well as the correction of other modifiable risk factors.

The order of the Ministry of Health of the Russian Federation of January 15, 2020 No. 8 "On approval of the Strategy for the formation of a healthy lifestyle of the population, prevention and control of non-communicable diseases for the period up to 2025" mentions "a significant decrease in the QoL … among the population of the Russian Federation" [37]. The SF-36 questionnaire is a very suitable tool for analyzing the cost-effectiveness of the use of certain activities in the evaluation of medical technologies, interventions or other products aimed at improving health at the lowest material cost. The Russian Federation is located in

both the European and Asian parts of the continent, and it has been proven that the widely used SF-36 questionnaire has been proven to be suitable for European and Asian populations [16, 38] and it can be used both in clinical practice, and in the healthcare organization.

Conclusions

1. In patients with PC, the indicators of total cholesterol, LDL-C and HDL-C in blood serum were lower, and AH was more common than in patients with acute or exacerbated chronic pancreatitis; the frequency and severity of other metabolic factors did not differ between groups.

2. There was a direct relationship between the chance of having PC and HDL hypocholesterolemia and AH, an inverse relationship with hypercholesterolemia, and the absence of such a relationship with age, fasting plasma glucose ≥ 7 mmol/L or obesity.

3. Patients with PC had higher QoL than patients with acute or exacerbated chronic pancreatitis on four scales and on the general domain "physical component of health" SF-36, but patients with PC with HDL hypocholesterolemia had lower indicators of QoL on the scale of role emotional functioning, patients with PC with AH had lower QOL on the scales of role physical and emotional functioning, and there was no such association in patients with acute or exacerbated chronic pancreatitis.

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Submitted: 30.08.2022 Accepted: 23.01.2023 Published: 30.06.2023
Поступила: 30.08.2022 Принята: 23.01.2023 Опубликована: 30.06.2023

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