

Features of exocrine pancreatic insufficiency in patients with non-alcoholic fatty liver disease in combination with type 2 diabetes and COVID-19

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ABSTRACT

Aim: The aim of the research was to study the features of pancreatic exocrine insufficiency (EPI) in patients with nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (DM) at COVID-19.

Materials and Methods: 72 patients with NAFLD and COVID-19 were examined. The patients have been divided into two groups: group 1 included 42 patients with NAFLD and insulin resistance (IR); group 2 consisted of 30 patients with NAFLD in the combination with type 2 DM. EPI was detected by ^{13}C-mixed triglyceride breath test (^{13}C-MTBT) in all the patients.

Results: The result of ^{13}C-MTBT indicates EPI in the examined subjects of the 2 group. A significant decrease in the maximum concentration of $^{13}CO_2$ between 150 and 210 min was also diagnosed in group 1 patients. research (up to 8.2 ± 0.9% – $p < 0.05$), however, the total concentration of $^{13}CO_2$ at the end of 360 min. the study reached only 27.7 ± 1.1% ($p < 0.05$).

Conclusions: Based on the results of laboratory-instrumental methods of research, patients with NAFLD and type 2 diabetes with COVID-19 were diagnosed with severe EPI. The results of ^{13}C-MTBT in NAFLD and IR with COVID-19 indicate a decrease in the functional reserves of the pancreas and the formation of its EPI.

KEY WORDS: nonalcoholic fatty liver disease, insulin resistance, type 2 diabetes mellitus, COVID-19, exocrine pancreatic insufficiency; ^{13}C-mixed triglyceride breath test

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INTRODUCTION

In December 2019, China reported an outbreak of pneumonia of unknown causes in Wuhan, the capital city of Hubei province. Using unbiased next-generation sequencing, an unknown betacoronavirus was discovered from lower respiratory tract samples of these patients. Human airway epithelial cells were used to isolate the virus that was named 2019–novel Coronavirus (2019–nCoV). Phylogenetically, the novel coronavirus was found to be more similar to two bat derived coronavirus strains (~88% similarity) than coronaviruses which infect humans including SARS (~79% similarity) and MERS (~50% similarity) [1]. The World Health Organization (WHO) used the term 2019 novel coronavirus to refer to a coronavirus that affected the lower respiratory tract of patients with pneumonia in Wuhan, China on 29 December 2019/ The WHO announced that the official name of the 2019 novel coronavirus is coronavirus disease (COVID-19) [2].

The most common clinical symptoms of the COVID-19 patients are fever, cough, shortness of breath, and other breathing difficulties in addition to other nonspecific symptoms including headache, dyspnea, fatigue, and muscle pain and digestive symptoms such as diarrhea and vomiting [3]. The gastrointestinal tract can be a potential site for virus replication and feces a source of transmission [4].

The leading hypothesis for the mechanism of transmission of SARS-CoV-2 is the aerosol route, which occurs through droplets released into the air from the respiratory tract. When a person comes into contact with the pathogen, the virus binds to angiotensin-converting enzyme 2 (ACE2) receptors in the lungs. The SARS-CoV-2 adhesion glycoprotein binds to the ACE2 receptor and ensures effective cellular entry, which leads to virus replication and spread throughout the body. The epithelium of the intestine (mainly the absorptive enterocytes of the ileum and colon) and oesophagus also highly express ACE2 receptors. In addition, glandular cells in the stomach and duodenum express ACE2, so SARS-CoV-2 can infect intestinal epithelial cells via ACE2 receptors. ACE2 receptors in the gastrointestinal tract play a regulatory role in amino acid homeostasis, the gut microbiome and innate immunity. Therefore, binding of SARS-CoV-2 to ACE2 receptors in the gastrointestinal tract may lead to gastrointestinal symptoms such as abdominal pain and diarrhoea [5].

Therefore, the study of the features of the combined pathology of the organs of the digestive system, including damage to the liver and pancreas in patients with COVID-19, is of interest to the medical community.

AIM

To study the features of pancreatic exocrine insufficiency (EPI) in patients with nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (DM) at COVID-19.

MATERIALS AND METHODS

The study and treatment of patients was carried out at the clinical base of the Department of Propedeutics of Internal Medicine, School of Medicine, State Higher Educational Institution "Uzhhorod National University". The study included 72 patients with NAFLD at the stage of outpatient follow-up after COVID-19. All patients included in the study had previously been hospitalized in the department for treating COVID-19 infected patients based on communal non-profit enterprise «The Transcarpathian Regional Clinical Hospital Named after A. Novak» of Transcarpathian Regional Council during the period between March 2021 and October 2023 and had a confirmed diagnosis of COVID-19 pneumonia (the positive polymerase chain reaction (PCR test) to SARS-CoV-2 RNA (the RdRP SARS-CoV-2 gene, the E SARS-CoV-2 gene) and did not require patients be connected to the artificial ventilator. The hospitalised patients were treated in accordance with the standards of medical care for patients with COVID-19, including antiviral therapy, glucocorticoids, anticoagulants, vitamin D3, zinc and antibiotic therapy.

Exclusion criteria for the study include patients with NAFLD and carbohydrate metabolism disorders with COVID-19. Criteria for inclusion from the study were acute respiratory infection with COVID-19 at the time of the examination, the presence of alcohol, autoimmune, viral (hepatitis B, C, D viruses) liver damage.

The patients with NAFLD have been divided into two groups depending on the presence of insulin resistance (IR) or type 2 DM, namely:

- group 1 included 42 patients with NAFLD and IR (among them there were 24 men (57.1 %), 18 women (42.9 %); the average age was 48.6 ± 6.3 years)
- group 2 consisted of 30 patients with NAFLD in the combination with type 2 diabetes mellitus (there were 18 men (60.0 %) among them, 12 women (40.0 %; the average age was 47.3 ± 5.8 years). The examined patients of 2 group were diagnosed with type 2 diabetes mellitus of mainly mild and moderate severity, which was characterized by the absence of hypoglycemic reactions, the level of glucose in the fasting blood up to 8.5 mmol/l, after eating - up to 10 mmol/l, HbA1c - did not exceed 7% .

The control group included 30 healthy individuals (there were 17 men (56.7 %), 13 women (43.3 %) with the average age 47.8 ± 5.8 years).

All research studies were performed with the consent of the patients (written consent), and the methodology was in line with the Helsinki Declaration of Human Rights of 1975 and its revision of 1983, the Council of Europe Convention on Human Rights and Biomedicine, and the legislation of Ukraine.

Patients underwent general clinical, anthropometric, instrumental and laboratory tests. To make a diagnosis, complaints and medical history were assessed.
Patients underwent an ultrasound examination of the abdominal cavity according to the generally accepted method. Standard general and biochemical tests based on blood serum were performed to determine the functional state of the liver (alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase, gamma-glutamyltransferase), indicators of lipid metabolism (total cholesterol, triglycerides, high-density lipoproteins, low-density lipoproteins, very-low-density lipoproteins, the atherogenic index was calculated), carbohydrate metabolism (glucose, insulin, glycated hemoglobin (HbA1c,%), calculated the insulin resistance index (HOMA-IR)). Also, the level of α-amylase in the blood serum of the patients was identified.

NAFLD was diagnosed in accordance with the EASL-EASD-EASO guidelines for the diagnosis and treatment of NAFLD [6]. The degree of liver damage was determined using the online calculators NAFLD fibrosis score (NFS), Fibrosis 4 calculator (FIB-4), as well as FibroTest and liver elastography results.

The diagnosis of type 2 diabetes was established in accordance with the recommendations of the IDF (2005) and criteria European Association for the Study of Diabetes (EASD) i *American Diabetes Association (ADA)* [7]. The severity of type 2 diabetes was assessed by the level of HbA1c.

All patients underwent coprological examination.

A ^{13}C -mixed triglyceride breath test was also carried out. The respiratory samples were analyzed with the infrared spectroscopy of IRIS (Izinta, Hungary). The diagnostic value of the ^{13}C -mixed triglyceride breath

Table 1. Distribution of the surveyed depending on BMI

Indicator	Examined		
	Control group (n=30)	Patients with NAFLD and COVID-19	
		I group (n=42)	II group (n=30)
Normal weight (BMI: 18.5 – 24.9)	76.7 %**	11.9 %	3.3 %
Overweight (BMI: 25.0 – 29.9)	23.3 %	54.8 %*++	20.0 %
Obese Class I (BMI: 30.0 – 34.9)	–	16.7 %	40.0 %++
Obese Class II (BMI: 35.0 – 39.9)	–	11.9 %	26.7 %+
Obese Class III (BMI: >40)	–	4.7 %	10.0 %

Note: the difference between the indicators of the control group and the examined patients is statistically significant: * – p<0.01; ** – p<0.001; the difference between indicators in patients of the I and II groups is significant: + - p<0.05; ++ - p<0.01.

test is that with the help of this test we determine the number of lipase, which is in the lumen of the duodenum, set the number of enzymes necessary for a particular patient to eliminate exocrine pancreatic insufficiency (EPI), and also allows to distinguish the pancreatic steatore from the intestinal. During the test, 13 respiratory samples received: the initial, before the test and after the test breakfast (100 g of white bread and butter (from 0.5 d / kg of body weight), with added a mixture of triglycerides (fatty acids labeled with non-radioactive carbon isotope - 13 ° C 42 mg / kg body weight) and another 12 samples for 10 hours (every 30 min each) [8].

Triglycerides containing various fatty acids are the main components of natural fats. The active pharmacological substance is 1,3-distearol-2- (1-13C) octanoil glycerol, labeled with a steady carbon isotope. It is metabolized in two stages. The first stage involves the cleavage of 1-13C caprylic acid at positions 1,3, which occurs mainly under the action of pancreatic lipase entering the lumen of the duodenum. he second stage involves the absorption of cleaveaprylic acid molecules and 2-(1-13 C) mono-octanoyl glycerol, which may be preceded by its cleavage to caprylic acid.. Upon entering the small intestine, caprylic acid is rapidly absorbed, binds to blood albumin, and is transported to the liver via the portal blood flow system or the lymphatic system in the general circulation as part of lipoproteins. The main channel of caprylic acid metabolism is mitochondrial beta-oxidation, which leads to the formation of bicarbonate ion containing carbon-13 (^{13}C) and replenishes the bicarbonate pool of the blood. This leads to an increase in the proportion of ^{13}C in the carbon dioxide (CO_2) of exhaled air. The percentage of 13C released depends on the activity of pancreatic lipase. In case of exocrine insufficiency, the amount of lipase produced decreases or is absent, which means that triglycerides are broken down less intensively and less $^{13}CO_2$ is released. Depending on the concentration of $^{13}CO_2$ in different samples, a curve is built, the nature of which reflects the presence and degree of pancreatic exocrine insufficiency. Pancreatic exocrine insufficiency accompanied by lipase deficiency was detected by analyzing the curve reflecting the concentration of $^{13}CO_2$ in breath samples (maximum concentration between 150 and 210 minutes of the study and total concentration after 360 minutes of the study). Normally, the maximum concentration of $^{13}CO_2$ between 150 and 210 minutes of the study is more than 8%, and the total concentration at 360 minutes of the study is 30-35% of 13CO2. In case of exocrine insufficiency of the pancreas, there is a decrease in the activity of intraduodenal pancreatic lipase with a maximum concentration between 150 and 210 minutes of the study of less than 8% $^{13}CO_2$ and a total concentration of $^{13}CO_2$ at the end of 360 minutes - less than 23% [8].

The data were analysed and processed using STATISTICA 10.0 (StatSoft Inc, USA) using parametric and non-parametric methods of evaluating the results.

RESULTS

In all examined patients with NAFLD and COVID-19 were determined BMI changes, especially increasing in weight (table 1).

As the data obtained, among the patients of group 1, the majority were overweight persons (54.8% 0 and the obesity class I (16.7%) - p <0.01, while in the group2 , there were more persons with obesity class I (40.0% - p <0.01) and obesity class II (26.7% - p <0.05).

According to the results, all patients with NAFLD and COVID-19 had complaints of digestive system (table 2)

Table 2. Clinical symptoms from the digestive organs in examined patients with NAFLD and COVID-19

Symptoms	Examined patients with NAFLD and COVID-19	
	I group (n=42)	II group (n=30)
Pain	42.9 %	60.0 % *
Periodicity		
Constant	28.6 %	80.0 %**
Periodic	71.4 %**	20.0 %
Localization		
- in the upper parts of the abdomen (left hypochondrium, epigastric area)	28.6 %	56.7 %**
- in the right hypochondrium	57.1 %**	16.7 %
- without clear localization, diffuse character	14.3 %	26.6 %*
Flatulence	52.4 %	80.0 %**
Defecation disorders:	61.9 %	73.3 %*
- diarrhea	30.8 %	72.7 %**
- constipation, which was later replaced by diarrhea	69.2 %**	27.3 %
- polyfaecalia	33.3 %	63.3 %**
Nausea	61.9 %**	26.7 %
Vomiting	19.0 %	23.3 %
Bitterness in the mouth	57.1 %**	20.0 %

Note: statistically significant difference between indicators in patients of the I and II groups: * – p<0.05; ** – p<0.01.

Table 3. The results of laboratory research methods in the examined

Indicator	Control group (n=30)	Examined patients with NAFLD and COVID-19	
		group 1 (n=42)	group 2 (n=30)
Coprological research			
Steatorrhea (+)	-	71.4 %	90.0 %++
Amylorrhea (+)	-	52.4 %	60.0 %
Creatorrhoea, due to muscle fibers that preserved transverse striations (+)	-	42.9 %	53.3 %+
Soap	3.3 %	54.8 %	66.7 %**
Amylase in blood serum (normal range: 0 - 115 (U/L)	58.7 ± 3.2	98.7 ± 3.1*	112.4 ± 2.4**+

Note: statistically significant difference between the indicators of the control group and the examined patients: * – p < 0.05; ** – p < 0.01; statistically significant difference between indicators in patients of the I and II groups: + - p < 0.05; ++ - p < 0.01.

There is a difference between the recurrence of the pain symptom in the examined patients, namely: in patients of the group 2 (NAFLD in combination with type 2 diabetes and COVID-19), the pain was constant, less severe (in 80.0% of cases – p<0.01)), while in the patients of the 1st group, there was a repeated and recurrent character (in 71.4% of cases – p<0.01). In patients of the group 2 , the pain was more often localized in the left hypochondrium and epigastric area (in 56.7% of observations – p<0.01), while in patients of the group 1, it was more often in the right hypochondrium (in 57.1% of observations – p<0 ,01).

Flatulence was more often diagnosed in patients of the group 2 (in 80.0% of cases – p<0.01). Defecation disorders were detected in patients of the group 2 more often, which was manifested mainly by diarrhea (in 72.7% of patients) and polyfecality (63.3% of the examined) – p<0.01. In patients of the 1st group, constipation alternating with diarrhea was more often established (in 69.25 cases – p<0.01). – p<0.01

It should be noted that signs of biliary dyspepsia (nausea, bitterness in the mouth) were more often diagnosed in patients of the group 1 (in 61.9% and in 57.1% of the examined, respectively – p<0.01). The peculiarity of biliary dyspepsia in patients of the group 2 was that nausea in almost all patients was accompanied by vomiting, which did not bring relief to the patients.

All patients who were under our observation had a coprological examination and determination of the

Table 4. Results of 13C -mixed triglyceride breath test in the examined patients and the control group

Indicator	Control group (n=30)	Patients with NAFLD and COVID-19	
		I group (n=42)	II group (n=30)
The maximum concentration of $^{13}CO_2$ between 150 and 210 min. research	16.9 ± 0.8 %	8.2 ± 0.9 %*	6.1 ± 0.4 %**
Total concentration of $^{13}CO_2$ at the end of the study (360 min.)	34.1 ± 1.2 %	27.7 ± 1.1 %*	17.8 ± 0.9 %**+

Note: + – a statistically significant difference was found between the indicators of the control group and the examined patients: * – $p < 0.05$; ** – $p < 0.01$; statistically significant difference between indicators in patients of the I and II groups: + - $p < 0.05$.

level of amylase in blood serum. The level of amylase in the blood serum of the examined patients of both groups was statistically significantly different from the indicators of the control group, but at the same time it did not go beyond the reference values – Table 3.

According to the results of the coprological study, signs of exocrine insufficiency of the pancreas were found in patients with NAFLD and impaired carbohydrate metabolism (IR or type 2 diabetes) with COVID-19. More pronounced changes during the coprologic examination of the EPI were found in patients of the group 2, namely - in 90.0% of patients, steatorrhea due to fatty acids was detected, in 60.0% - amylorrhea (the presence of starch grains) and in 53.3% - creatorea due to muscle fibers , which preserved the transverse banding.

Changes in the secretory pancreatic function were also found in patients of the group 1, but less severe than in the group 2 of subjects. In patients of the group 2, a more severe increase in soap was also found during coprological examination, which indicates the dysfunction of the biliary system in patients with type 2 diabetes and indicates the biliary genesis of the lesion of the pancreas in these patients.

For a more accurate study of the EPI in patients with NAFLD and impaired carbohydrate metabolism in COVID-19, ^{13}C -mixed triglyceride breath test was performed - Table 4.

The analysis of the ^{13}C -mixed triglyceride breath test data indicates a severe EPI in the examined patients of the group 2. Patients of the group 2 showed a significant decrease in the maximum concentration of $^{13}CO_2$ between 150 and 210 min. research, as well as the total concentration of $^{13}CO_2$ at the end of 360 min. research - $p<0.01$. A significant decrease in the maximum concentration of $^{13}CO_2$ between 150 and 210 min was also diagnosed in group I patients. research (up to 8.2 ± 0.9% – $p < 0.05$), however, the total concentration of $^{13}CO_2$ at the end of 360 min. study decreased to only 27.7 ± 1.1% - $p < 0.05$. Therefore, according to the results of highly informative ^{13}C -mixed triglyceride breath test, EPI was detected in patients with NAFLD and type 2 diabetes, and also a violation of exocrine insufficiency of pancreas was established in patients with NAFLD and IR in case of COVID-19.

DISCUSSION

The proportion of diabetics among COVID-19-positive patients varies according to the regions in the world. For example, in Italy as many as 36% of those seriously ill, having a positive result from a COVID-19 test, were burdened with diabetes, and in the United States, this same phenomenon was noted in as many as 58% of patients. The vast majority of infected patients present a mild form of COVID-19, but some develop a severe form of infection that can be fatal [9]. Type 2 diabetes is associated with low-grade chronic inflammation induced by the excessive visceral adipose tissue. This inflammatory condition affects the homeostatic glucose regulation and peripheral insulin sensitivity. Chronic hyperglycemia and inflammation can determine an abnormal and ineffective immune response [10]. Diabetic patients with COVID-19 are at higher risk of being in an excessively hypercoagulable state and uncontrolled inflammation responses, which may contribute to a poorer outcome [11].

Damage to the pancreas can lead to loss of blood glucose control. The β-cells of the pancreas in type 2 diabetes are depleted over time as a result of compensatory insulin secretion in insulin resistance. The negative impact of hyperglycaemia on the secretory function of the islets of Langerhans is increasingly discussed [12].

During the SARS-CoV-2 pandemic, patients with reduced pancreatic function are at high risk of contracting the virus. High blood glucose levels in patients with and without diabetes mellitus have been shown to increase the risk of mortality in COVID-19, and hyperglycaemia impairs the immune response and negatively affects the excessive cytokine response, and thus has a strong pro-inflammatory effect [12].

ACE2 receptors, which are also present in the pancreas, are targeted by SARS-CoV-2 in the body, which can lead to acute failure of both the islets of Langerhans and exocrine cells. This can lead to an uncontrolled hyperglycaemic state, especially in patients with diabetes mellitus. Consequently, hyperglycaemia leads to a more severe course of COVID-19 and viral infection complicated by secondary infections. In patients with diabetes, the coexistence of other risk factors (atherosclerosis, hypertension, obesity) should also be taken into account, which leads to a worse prognosis and course of COVID-19 [13, 14].

The impact of coronavirus on exocrine pancreatic function is not fully understood, and the available literature cannot clearly answer whether tissue damage leading to acute pancreatitis is a consequence of direct SARS-CoV-2 infection or a syndrome of systemic multiorgan dysfunction with elevated amylase and lipase levels. A study by Liu et al. involving 121 patients with COVID-19 with an average age of 57 years and variable course of infection found that amylase and lipase levels were higher than normal in 1-2% of patients with moderate COVID-19 and 17% of patients with severe COVID-19. This confirms the hypothesis that the SARS-CoV-2 virus has a destructive effect on both the endocrine and exocrine parts of the pancreas [13, 15, 16].

As indicated by the data obtained by us, patients with NAFLD, regardless of the form of impaired carbohydrate metabolism (either type 2 diabetes or IR) with COVID-19, were diagnosed with clinical and laboratory-instrumental signs of EPI. At the same time, exocrine pancreatic insufficiency in these patients has a number of features, namely, in patients with type 2 diabetes, it is clinically manifested by diarrhea and polyfecaly, while in patients with NAFLD and IR, signs of biliary dyspepsia (nausea, bitterness in the mouth) are more often diagnosed. The data of the coprological study indicate a severe EPI, and the results of 13C -mixed triglyceride breath test confirm the depletion of the functional reserves of the pancreas in patients with NAFLD and type 2 DM with COVID-19.

At the same time, it should be noted that patients with NAFLD and IR with COVID-19 have signs of the formation of exocrine insufficiency of the pancreas, and the results of 13C -mixed triglyceride breath test with high accuracy confirm the compromise of not only the endocrine part, but also the exocrine part of the pancreas in these patients, which requires timely correction in order to prevent its EPI

CONCLUSIONS

1. Patients with NAFLD and impaired carbohydrate metabolism with COVID-19 have signs of intestinal and biliary dyspepsia. At the same time, the patients of the group 1 have clinically more pronounced signs of biliary dyspepsia, while the patients of the group 2 have clinical manifestations of EPI.
2. Based on the results of laboratory-instrumental methods of research, patients with NAFLD and type 2 diabetes with COVID-19 were diagnosed with severe EPI
3. The results of ^{13}C -mixed triglyceride breath test in NAFLD and IR with COVID-19 indicate a decrease in the functional reserves of the pancreas and the formation of its EPI.

REFERENCES

1. Dhar Chowdhury S, Oommen AM. Epidemiology of COVID-19. Journal of Digestive Endoscopy. 2020;11(1):3–7.
2. Adhikari S, Meng S, Wu YJ et al. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. Infect Dis Poverty. 2020;9(1):29. doi: 10.1186/s40249-020-00646-x. DOI
3. Halaji M, Heiat M, Faraji N, Ranjbar R. Epidemiology of COVID-19: An updated review.. J Res Med Sci. 2021;26:82. doi: 10.4103/jrms.JRMS_506_20. DOI
4. Gurung S, Karki S, Pathak BD et al. Gastrointestinal symptoms among COVID-19 patients presenting to a primary health care center of Nepal: A cross-sectional study. Health Sci Rep. 2023;6(9):e1568. doi: 10.1002/hsr2.1568. DOI
5. Groff A, Kavanaugh M, Ramgobin D et al. Gastrointestinal Manifestations of COVID-19: A Review of What We Know. Ochsner J. 2021;21(2):177-180. doi: 10.31486/toj.20.0086. DOI
6. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO) EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Obes Facts. 2016;9(2):65-90. doi: 10.1159/000443344. DOI
7. American Diabetes Association Professional Practice Committee; 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2022. Diabetes Care. 2022;45(1):S17-S38. doi: 10.2337/dc22-S002. DOI
8. Dangelo G, Di Rienzo TA , Scaldaferri F et al. Tricks for interpreting and making a good report on hydrogen and 13C breath tests. Eur Rev Med Pharmacol Sci. 2013;17(2):90-8.
9. Gęca T, Wojtowicz K, Guzik P, Góra T. Increased Risk of COVID-19 in Patients with Diabetes Mellitus-Current Challenges in Pathophysiology, Treatment and Prevention. Int J Environ Res Public Health. 2022;19(11):6555. doi: 10.3390/ijerph19116555. DOI
10. Iacobellis G. COVID-19 and diabetes: Can DPP4 inhibition play a role? Diabetes Res Clin Pract. 2020;162:108125. doi: 10.1016/j.diabres.2020.108125. DOI

11. Guo W, Li M, Dong Y et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020;36(7):e3319. doi: 10.1002/dmrr.3319. DOI
12. Abramczyk U, Nowaczyński M, Słomczyński A et al. Consequences of COVID-19 for the Pancreas. Int J Mol Sci. 2022;23(2):864. doi: 10.3390/ijms23020864. DOI
13. Liu F, Long X, Zhang B et al. ACE2 Expression in Pancreas May Cause Pancreatic Damage After SARS-CoV-2 Infection. Clin Gastroenterol Hepatol. 2020;18(9):2128-2130.e2. doi: 10.1016/j.cgh.2020.04.040. DOI
14. Apicella M, Campopiano MC, Mantuano M et al. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. Lancet Diabetes Endocrinol. 2020;8(9):782-792. doi: 10.1016/S2213-8587(20)30238-2. DOI
15. de-Madaria E, Capurso G. COVID-19 and acute pancreatitis: examining the causality. Nat Rev Gastroenterol Hepatol. 2021;18(1):3-4. doi: 10.1038/s41575-020-00389-y. DOI
16. Zippi M, Fiorino S, Occhigrossi G, Hong W. Hypertransaminasemia in the course of infection with SARS-CoV-2: Incidence and pathogenetic hypothesis. World J Clin Cases. 2020;8(8):1385-1390. doi: 10.12998/wjcc.v8.i8.1385. DOI

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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