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Pancreatic exocrine disfunction in children with type 1 diabetes mellitus

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Summary

The aim of the present study was to evaluate exocrine pancreatic function in children with type 1 diabetes mellitus during the course of the disease.

Fecal elastase varied between 24.4 and 169.6 μg /g (median 134.5 μg /g) in children with type 1 DM and concomitant PEI. Number of children with diarrhea was not significantly different between children with low pancreatic elastase levels and those with normal levels (43.0% versus 35.5%, p=0.359). The remainder of the children with type 1 DM had fecal elastase-1 levels between 201.4 and 810.5 μg /g stool (median 650.7 μg /g). Differences between the type 1 DM patients without PEI and the comparison group were not significant (p=0.112).

Median daily fecal fat excretion in type 1 DM patients with PEI was 8.31 g/day (min-max 7.81–9.21 g/day), which was significantly higher than in type 1 DM children without PEI (3.87 g/day; min-max 2.97–6.33 g/day; p= 0.0003). There was no significant difference in daily fecal fat excretion between children with type 1 DM without signs of PEI and children in the control group (2.91 g/d; min-max: 2.31–5.74 g/d; p= 0.091).

The results of this study demonstrate PEI in children with long-standing type 1 DM.

Fecal elastase-1 concentration significantly correlates with duodenal exocrine elastase output. Fecal elastase-1 levels have a good correlation with fecal fat excretion, which was measured by employing the acid steatocrit test.

EDN: GSQTZI

Keywords: pancreas, pancreatic exocrine insufficiency, diabetes mellitus, children

Conflict of interest. Authors declare no conflict of interest.

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Экзокринная дисфункция поджелудочной железы у детей с сахарным диабетом 1 типа

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Резюме

Целью настоящего исследования явилась оценка экзокринной функции поджелудочной железы у детей с сахарным диабетом (СД) 1 типа в динамике течения заболевания.

Уровень фекальной эластазы варьировал от 24,4 до 169,6 мкг/г (медиана 134,5 мкг/г) у детей с СД 1 типа и сопутствующей экзокринной недостаточностью (ЭН). Количество детей с диареей достоверно не различалось между детьми с низким уровнем панкреатической эластазы и детьми с нормальным уровнем (43,0% против 35,5%, p=0,359). У остальных детей с СД 1 типа уровень фекальной эластазы-1 находился в пределах от 201,4 до 810,5 мкг/г стула (медиана 650,7 мкг/г). Различия между больными СД 1 типа без ЭН и группой сравнения были недостоверны (p=0,112).

Медиана суточной фекальной экскреции жира у больных СД 1 типа с ЭН составила 8,31 г/сут (min-max 7,81–9,21 г/сут), что достоверно выше, чем у детей с СД 1 типа без ЭН (3,87 г/сут; min-max 2,97–6,33 г/сут; p= 0,0003). Достоверной разницы в суточной экскреции жира с калом между детьми с СД 1 типа без признаков ЭН и детьми контрольной группы не было (2,91 г/сут; min-max: 2,31–5,74 г/сут; p=0,091).

Результаты настоящего исследования демонстрируют ЭН у детей с длительно текущим СД 1-го типа.

Концентрация эластазы-1 в кале достоверно коррелирует с уровнем экзокринной эластазы двенадцатиперстной кишки. Уровень фекальной эластазы-1 имеет сильную корреляцию с экскрецией жира с калом, который измеряли с помощью кислотного стеатокритного теста.

Ключевые слова: поджелудочная железа, экзокринная недостаточность, сахарный диабет, дети

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Introduction

Diabetes mellitus (DM) is a group of metabolic disorders caused by abnormal insulin secretion and chronic hyperglycemia. The 8th edition (2017) of the IDF Diabetes Atlas reported that the number of young people (<20 years old) living with type 1 DM worldwide was estimated to be 1,106,500 million (this is 1 billion as appears to be too high) [1]. Insulin-dependent, type 1 DM is caused by autoimmunedestruction of insulin-producing β-cells of pancreatic islets and subsequent absolute insulin deficiency [2]. The pancreas is a multifunctional gland composed of three structurally and functionally associated groups of cells: endocrine, exocrine acinar and exocrine ductal. Seventy-five percent of islet tissue is closely associated with pancreatic ductal cells reflecting functional interaction between the exocrine and endocrine pancreatic element. Balance within this complex system is maintained by insulin and pancreatic polypeptide secreted by acinar cells, which regulate exocrine pancreatic secretion [3]. When insulin secretion decreases due to endocrine cells autoimmune

destruction, the resulting disturbance in hormonal equilibrium leads to a predominance of glucagon and somatostatin effects, including suppression of lipase and chymotrypsin secretion and atrophic changes in the acinar tissue of the exocrine pancreas [4]. With long-term uncontrolled disease, diabetic microangiopathy can disturb perfusion and cause ischemia of the pancreas leading to pancreatic tissue fibrosis and atrophy [5]. With marked exocrine pancreas involvement, there is a progressive maldigestion of nutrients, including fat malabsorption [6]. Pancreatic steatorrhea is caused by disruptions of the normal process in which pancreatic enzymes are either inactivated or are otherwise unavailable (e.g., blockage of the pancreatic duct, or resection or destruction of the glandular pancreas) [7]. Pathological mechanisms determining the development of pancreatic exocrine insufficiency (PEI) in type 1 DM are not fully elucidated, although circulating auto-antibodies against exocrine pancreatic enzymes are reported to mediate exocrine pancreas dysfunction [8, 9]. In an experimental model of DM an important mechanism of PEI is associated with an imbalance in the system of elastases and their inhibitors (eg. α2-macroglobulin) [10]. Elastase deficiency in children and adolescents with insulin-dependent DM has been reported previously [11, 12]. We have found only two publications about PEI in diabetic children and adolescents [11, 12]. There is an evidence of lower elastase-1 levels in stools in patients with DM duration more than 15 years [13]. Pancreatic elastase-1 is a carboxyendopeptidase with a molecular weight of 26, which catalyzes the hydrolysis of elastin and accounts for roughly 6% of all secreted exocrine pancreas enzymes. Fecal elastase-1 (FE-1) measurement is currently considered the best non-invasive test for determining PEI [13, 14]. Pancreatic elastase-1(PE-1) can be directly measured in stool samples, because the enzyme is not affected by bacterial degradation or pancreatic enzyme supplementation [14]. The test is accurate in pediatric practice, demonstrating 100% sensitivity and 96% specificity. One caveat is that the concentration is measured such that in the presence of watery diarrhea false positive results may occur [15]. According to the data of some authors, this test emphasizes lower sensitivity and specificity in mild/moderate PEI cases. The sensitivity of the FE-1 test was found to be 41.7%, whereas the specificity was 49.2%. The positive predictive value of the FE-1 test was only 14%. Although elastase can be used as a first step in diagnosis [16]. Steatorrhea is considered present when the fecal elastase-1 level is less than 200 μg/g stool [17]. This study also used the steatocrit which is a direct assessment of the proportion of stool that is fat. The aim of the present study was to evaluate exocrine pancreatic function in children with type 1 diabetes mellitus during the course of the disease.

Methods

Patients with type 1 DM were recruited to participate in the study. The control group was comprised of 89 children (11.9 ± 1.7 years, male/female: 33:56) who had no gastrointestinal disorder or DM. All diabetic children were recruited in the Outpatient Department of the Children's Republican Hospital in Ufa, Russia. Healthy children for control group were recruited in accordance with the National program of total medical pediatric observation. As shown in Table 1, there were no differences in gender (p=0.775) and age (p=0.07) between two study groups. Written informed consent was obtained from all children or their parents who were enrolled into the study. The study protocol was reviewed and approved by the Ethics Committee of the hospital.

All study participants underwent clinical blood analysis and urinalysis, including tests for glucosuria and acetonuria, and glycated hemoglobin measurement. Other tests included: determination of exocrine pancreatic enzyme activities (amylase, lipase), lipid profile levels of aminotransferases, bilirubin, total protein, gamma-glutamyl transpeptidase and alkaline phosphatase. Measurement of fecal elastase-1 levels (ELISA-test with monoclonal antibodies, "Bioserv diagnostics", Germany) was performed as a single random determination [18]. Criteria used for the stratification of exocrine pancreatic function were: normal >200 μg elastase-1/g stool; mild/moderate PEI; 100–200 μg elastase-1/g stool; and severe < 100 μg elastase-1/g stool [15]. To assess fecal fat excretion the steatocrit test was used [19]. A 500 mg sample of blended stool was diluted 1:3 times (by weight) with double distilled water in a 12 ml test tube. It was then mixed well by vortex action and homogenized for 2 minutes. 500 pl of homogenized stool was pipetted into a 3 ml test tube into which 100 ml of 5M HCIO 4 was added and then vortexed for a minute. The pH was confirmed to be <1. This stool acid mixture was aspirated into a 75 IJI capillary tube and one end of the tube was sealed with wax. This tube was then centrifuged at 13,000 rpm for 15 minutes. This resulted in the separation of the fatty layer from the solid layer. Using a focusing magnifier and scale, the fatty layer and the solid layer were measured. Feces samples were collected during 24 hours in accordance with authors recommendations [19]. Test was performed twice: initially to detect PEI and subsequently to evaluate the efficacy of treatment and determine the severity of PEI. With a value of <7 g fat excretion/day taken as the normal standard of daily excretion of fecal fat [20]. In all study subjects, liver, pancreas and biliary tract examination by abdominal ultrasound was performed, including measurements of the diameter of both the common bile duct and exocrine pancreatic ducts including duct of Wirsung. If chronic pancreatitis was suspected, magnetic resonance cholangiopancreatography was performed [21].

Statistical analysis was used to assess if the data is significantly deviated from the normal distribution by using the Shapiro-Wilk normality test. For normal distributions, parametric statistics, the unpaired Student's t-test was employed. For variables without a normal distribution, differences between groups were assessed using the Mann-Whitney U test. Differences were considered statistically significant at $p < 0.05$. Categorical variables were summarized using proportions and compared using the Fisher's exact test, where appropriate.

Results

Glycated hemoglobin (HbAlc) level did not exceed 7.5% (optimal compensation) in 21 (22%) children. Twenty-five children (26%) had HbAlc values between 7.5 and 9% (suboptimal compensation). In 51 (52%) children, the level exceeded 9% (decompensation with a high risk of complications development). Disease duration varied from one to 14 years (mean 5.9 + 2.2 years). PEI (fecal elastase-1 of < 200 μg/g feces) was diagnosed in 21 patients with type 1 DM (21.6%) versus none of 89 children in the control group (P =0,000001). Fecal elastase varied between 24.4 and 169.6 μg /g (median 134.5 μg /g) in children with type 1 DM and concomitant PEI. All children with reduced fecal elastase levels had a history of DM of more than 10 years. Number of children with diarrhea was not significantly different between children with low pancreatic elastase levels and those with normal levels (43.0% versus 35.5%, p=0.359). The remainder of the children with type 1 DM had fecal elastase-1 levels between 201.4 and 810.5 μg /g stool (median 650.7 μg /g). Differences between the type 1 DM patients without PEI and the comparison group were not significant (p=0.112). The average fasting level of serum amylase (31.7 ± 2.3 U/L) and serum lipase (27.3 ± 1.3 U/L) in children with type 1 DM corresponded to age-related norms [22, 24]. But they were significantly higher than values in the control group: amylase 28.9 ± 1.7 U/L (p=0.0003) and lipase levels were 21.3 ± 2.3 U/L (p=0.0001). Median values for both lipase and amylase in patients with PEI were lower than those in diabetic children with normal fecal elastase-1 levels (Table 2).

Median daily fecal fat excretion in type 1 DM patients with PEI was 8.31 g/day (min-max 7.81–9.21 g/day), which was significantly higher than in type 1 DM children without PEI (3.87 g/day; min-max 2.97–6.33 g/day; p= 0.0003). There was no significant difference in daily fecal fat excretion between children with type 1 DM without signs of PEI and children in the control group (2.91 g/d; min-max: 2.31–5.74 g/d; p= 0.091).

Table 1. Demographic characheristics of patients with type 1 diabetes mellitus and patients from control group

Note: *- results were calculated using Mann-Whitney t-test
**- results were calculated using Fisher`s exact test

	Diabetes patients (n=97)	Control group) n=89)	P-values
Age, years	12.9 ± 1.3	11.9 ± 1.7	P=0.07*
Male/female gender	39/58	33/56	P=0.775**

Table 2. Changes in serum pancreatic amylase and lipase in diabetic patients with and without exocrine pancreatic insufficiency

Note: *- Results were calculated as a median, minimum – maximum values.

Variables (normal range)	DM1 patients with exocrine pancreatic insufficiency* (n=21)	DM1 patients without exocrine pancreatic insufficiency* (n=76)	P-values, Mann-Whitney U-test
Serum pancreatic amylase (22–80 U/L)	7.31 (mix-max: 4.11–12.5)	27.3 (min-max: 13.4–48.2)	0.00002
Serum lipase (5–39 U/L)	5.17 (min-max: 3.12–11.3)	24.6 (min-max: 13.7–47.3)	0.000002

Discussion

The results of this study demonstrate PEI in children with long-standing type 1 DM. The information about prevalence of exocrine pancreatic disturbance among DM patients is contradictory [6]. Among adults, with DM, PEI is reported to occur in up to 80% of subjects [4, 20]. Pediatricians from Germany reported PEI in 35% of children with type 1 DM [18]. Conversely, Sierra et al. [24] described a lower (4.2%) frequency of PEI in type 1 DM children. In both studies levels of fecal elastase were used as criteria of PEI. However, Laass et al. [18] demonstrated cut-off point as 200 mg/g stool, but Sierra et al. [24] showed the borderline index as 100 mg/g stool which might be the reason for the different results. Regardless of initial localization of pathological process (endocrine or exocrine structures), close anatomical and physiological interrelation of pancreatic cells converts any type of pancreatic disturbance into an integrated pathological process [3, 5, 6]. Exocrine atrophy and the lack of insulin are closely associated [4, 6, 25]. The volume of patients in DM patients was significantly less than that of healthy subjects. Moreover, morphometric study demonstrated severe acinar atrophy due to a reduction in size of acinar cells in type 1 DM adult patients [25]. Insulin modulates acinar cholecystokinin receptors, inducing pancreatic regeneration and potentiating secretagogue action on the exocrine pancreas [5, 26]. The hyperglycemia has significantly reduced basal and cholecystokininstimulated pancreatic secretion with the pattern of a delayed response [27]. Occurrence of PEI is also believed to be associated with autoimmune mechanisms. Up to three-quarters of type 1 DM patients produce antibodies against pancreatic bile salt-dependent lipase [8]. The presence of alpha-2A amylase autoantibodies among patients with DM1 has been reported too [9]. Taken together, these different pathogenic mechanisms contribute to the occurrence of PEI the resulting maldigestion of fat [6]. Semakula et al. [28] reported increased lipase/amylase levels in

10% of patients with type 1 DM and these enzyme activities were associated with higher titers of islet cell autoantibodies. Level of lipase/amylase was decreased in 18% of patients. The authors suggest that high levels of pancreatic enzymes may due acute acinar cell destruction, whereas decrease of the enzymes levels may be associated with reduction of function of peri-insular cells.

We think that elevated concentrations of amylase/lipase in diabetic children (at comparison with the children without type 1 DM), probably, are not specific markers of rapid-onset diabetes, because they may result from severe ketoacidosis and metabolic derangements [27, 29]. Serum pancreatic enzyme fluctuations are common in children with diabetic ketoacidosis, but not associated with clinical symptomatology development (including abdominal pain etc.) [30]. The leading European pancreatologists also emphasize the possible role of diabetic acidosis in the development of PEI in diabetic patients [6]. Low fasting activities of amylase/lipase in our children with exocrine pancreatic dysfunction and type 1 DM for sure reflect deficiency of pancreatic secretion in this group of patients. Decreased pancreatic amylase secretion has been demonstrated in animal models of DM [31] and in clinical surveys [32]. It has been hypothesized that insulin deficiency and subsequent decreases in pancreatic amylase output results in decreased absorption of carbohydrates from digested starch. This may be one of the mechanisms of hyperglycemia compensation [26].

In our study fecal elastase-1 test was used as a measure of exocrine pancreas function [33, 34], because of high accuracy of the test in children [15] and adults [35]. Fecal elastase-1 concentration significantly correlates with duodenal exocrine elastase output [14]. In addition to fecal elastase-1 measurement for the diagnosis of PEI in type 1 DM patients, the test also provides an indirect assessment of pancreatic islet' β-cellresidual secretion and an indication of disease duration [13, 36]. Animal studies demonstrate that an imbalance in elastase and its inhibitors are involved in the development of PEI in DM [10]. Fecal elastase-1 levels have a good correlation with fecal fat excretion, which was measured by employing the acid steatocrit test [34]. The steatocrit test used, due to its simple performance and noninvasiveness, is used in pediatric practice to monitor dietary fat malabsorption [37]. The present study has important limitation: there was a relatively small sample size. To ensure generalizability, the findings should be replicated in other pediatric centers outside of the European continent.

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References | Литература

1. International Diabetes Federation, IDF Diabetes Atlas, International Diabetes Federation, Brussels, Belgium, 8th edition, 2017. Available at: http://www.diabetesatlas.org. Access 05.05.2022.
2. Simmons K. M., Michels A. W. Type 1 diabetes: A predictable disease. *World J Diabetes*. 2015;6(3):380–390. doi:10.4239/wjd.v6.i3.380.
3. Andren-Sandberg A., Hardt P. D. Second Giessen International Workshop on Interactions of Exocrine and Endocrine Pancreatic Diseases. Castle of Rauischholzhausen of the Justus-Liebig-university, Giessen (Rauischholzhausen), Germany. March 7–8, 2008. *JOP*. 2008 Jul 10;9(4):541–75. PMID: 18648151.
4. Keller J., Layer P. Human pancreatic exocrine response to nutrients in health and disease. *Gut*. 2005 Jul;54 Suppl 6 (Suppl 6): vi1–28. doi: 10.1136/gut.2005.065946.
5. Czakó L., Hegyi P., Rakonczay Z. Jr, Wittmann T., Otsuki M. Interactions between the endocrine and exocrine pancreas and their clinical relevance. *Pancreatology*. 2009;9(4):351–9. doi: 10.1159/000181169.
6. Vujasinovic M., Tepes B., Makuc J., at al. Pancreatic exocrine insufficiency, diabetes mellitus and serum nutritional markers after acute pancreatitis. *World J Gastroenterol*. 2014 Dec 28;20(48):18432–8. doi: 10.3748/wjg.v20.i48.18432.
7. Trang T., Chan J., Graham D. Y. Pancreatic enzyme replacement therapy for pancreatic exocrine insufficiency in the 21(st) century. *World J Gastroenterol*. 2014 Sep 7;-20(33):11467–85. doi: 10.3748/wjg.v20.i33.11467.
8. Panicot L., Mas E., Thivolet C., Lombardo D. Circulating antibodies against an exocrine pancreatic enzyme in type 1 diabetes. *Diabetes*. 1999 Dec;48(12):2316–23. doi: 10.2337/diabetes.48.12.2316.
9. Endo T., Takizawa S., Tanaka S., Takahashi M., Fujii H., Kamisawa T., Kobayashi T. Amylase alpha-2A autoantibodies: novel marker of autoimmune pancreatitis and fulminant type 1 diabetes. *Diabetes*. 2009 Mar;58(3):732–7. doi: 10.2337/db08–0493.
10. Borysiuk M. V., Dosenko V. Ie., Byts' Iu. V. Stan elastolitychnoï systemy pidshlunkovoï zalozy pry modeliuvanni tsukrovoho diabetu [Elastolytic system of the pancreas in modelling diabetes mellitus]. *Fiziol Zh*. (1994). 2002;48(5):17–21. Ukrainian. PMID: 12449609.
11. Sato M., Yamamoto K., Mayama H., Yamashiro Y. Exocrine pancreatic function in diabetic children. *J Pediatr Gastroenterol Nutr*. 1984 Jun;3(3):415–20. doi: 10.1097/00005176–198406000–00019.
12. Lorini R., Cortona L., Scotta M. S., Melzi d'Eril G.V., Severi F. Exocrine pancreatic function in children and adolescents with insulin-dependent diabetes mellitus. *Diabetes Res Clin Pract*. 1990 Mar;8(3):263–7. doi: 10.1016/0168–8227(90)90125-d.
13. Cavalot F., Bonomo K., Perna P., et al. Pancreatic elastase-1 in stools, a marker of exocrine pancreas function, correlates with both residual beta-cell secretion and metabolic control in type 1 diabetic subjects. *Diabetes Care*. 2004 Aug;27(8):2052–4. doi: 10.2337/diacare.27.8.2052.

14. Dominici R., Franzini C. Fecal elastase-1 as a test for pancreatic function: a review. *Clin Chem Lab Med*. 2002 Apr;40(4):325–32. doi: 10.1515/CCLM.2002.051.
15. Soldan W., Henker J., Sprössig C. Sensitivity and specificity of quantitative determination of pancreatic elastase 1 in feces of children. *J Pediatr Gastroenterol Nutr*. 1997 Jan;24(1):53–5. doi: 10.1097/00005176–199701000–00013.
16. Wali P. D., Loveridge-Lenza B., He Z., Horvath K. Comparison of fecal elastase-1 and pancreatic function testing in children. *J Pediatr Gastroenterol Nutr*. 2012 Feb;54(2):277–80. doi: 10.1097/MPG.0b013e31820b0227.
17. Cavalot F., Bonomo K., Fiora E., Bacillo E., Salacone P., Chirio M., Gaia E., Trovati M. Does pancreatic elastase-1 in stools predict steatorrhea in type 1 diabetes? *Diabetes Care*. 2006 Mar;29(3):719–21. doi: 10.2337/diacare.29.03.06.dc05–1389.
18. Laass M. W., Henker J., Thamm K., Neumeister V., Kuhlisch E. Exocrine pancreatic insufficiency and its consequences on physical development and metabolism in children and adolescents with type 1 diabetes mellitus. *Eur J Pediatr*. 2004 Nov;163(11):681–2. doi: 10.1007/s00431–004–1501–2.
19. Bijoor A. R., Geetha S., Venkatesh T. Faecal fat content in healthy adults by the 'acid steatocrit method'. *Indian J Clin Biochem*. 2004 Jul;19(2):20–2. doi: 10.1007/BF02894252.
20. Hardt P. D., Hauenschild A., Jaeger C., Teichmann J., Bretzel R. G., Kloer H. U.; S2453112/S2453113 Study Group. High prevalence of steatorrhea in 101 diabetic patients likely to suffer from exocrine pancreatic insufficiency according to low fecal elastase 1 concentrations: a prospective multicenter study. *Dig Dis Sci*. 2003 Sep;48(9):1688–92. doi: 10.1023/a:1025422423435.
21. Bilgin M., Balci N. C., Momtahen A. J., Bilgin Y., Klör H. U., Rau W. S. MRI and MRCP findings of the pancreas in patients with diabetes mellitus: compared analysis with pancreatic exocrine function determined by fecal elastase 1. *J Clin Gastroenterol*. 2009 Feb;43(2):165–70. doi: 10.1097/MCG.0b013e3181587912.
22. Moss D. W., Henderson A. R. Clinical enzymology. In: Burtis C. A., Ashwood E. R., eds. Tietz textbook of clinical chemistry. 3 rd ed. Philadelphia: WB Saunders Company; 1999, pp. 689–698.
23. Moss D. W., Henderson A. R. Clinical enzymology. In: Burtis C. A., Ashwood E. R., eds. Tietz textbook of clinical chemistry. 3 rd ed. Philadelphia: WB Saunders Company; 1999, pp. 698–704.
24. Sierra C., Blasco J., Lopez-Siguero J., del Pino A., Garcia M., Vicioso I. Pancreatic fecal elastase in children with type 1 diabetes. *J Pediatr Gastroenterol Nutr*. 2004; 39 (Suppl. 1): 370. doi: 10.1097/00005176–200406001–00947.
25. Löhr M., Klöppel G. Residual insulin positivity and pancreatic atrophy in relation to duration of chronic type 1 (insulin-dependent) diabetes mellitus and microangiopathy. *Diabetologia*. 1987 Oct;30(10):757–62. doi: 10.1007/BF00275740.
26. Gröger G., Layer P. Exocrine pancreatic function in diabetes mellitus. *Eur J Gastroenterol Hepatol*. 1995 Aug;7(8):740–6. PMID: 7496861.
27. Lam W. F., Masclee A. A., de Boer S. Y., Souverijn J. H., Lamers C. B. Effect of acute hyperglycemia on basal and cholecystokinin stimulated exocrine pancreatic secretion in humans. *Life Sci*. 1997;60(24):2183–90. doi: 10.1016/s0024–3205(97)00233–6.
28. Semakula C., Vandewalle C. L., Van Schravendijk C. F., et al. Abnormal circulating pancreatic enzyme activities in more than twenty-five percent of recent-onset insulin-dependent diabetic patients: association of hyperlipasemia with high-titer islet cell antibodies. *Belgian Diabetes Registry. Pancreas*. 1996 May;12(4):321–33. doi: 10.1097/00006676–199605000–00001.
29. Zhang C., Zhou Z. G., Zhang D. M., Yang X. L., Zhou M., Lin J., Huang G., Wang J. P. [Clinical and immunological characteristics in rapid-onset type 1 diabetes with hyperamylasemia]. *Zhonghua Yi Xue Za Zhi*. 2005 Apr 13;85(14):967–71. Chinese. PMID: 16061004.
30. Quiros J. A., Marcin J. P., Kuppermann N., Nasrollahzadeh F., Rewers A., DiCarlo J., Neely E. K., Glaser N. Elevated serum amylase and lipase in pediatric diabetic ketoacidosis. *Pediatr Crit Care Med*. 2008 Jul;9(4):418–22. doi: 10.1097/PCC.0b013e318172e99b.
31. Patel R., Shervington A., Pariente J. A., Martinez-Burgos M.A., Salido G. M., Adeghate E., Singh J. Mechanism of exocrine pancreatic insufficiency in streptozotocin-induced type 1 diabetes mellitus. *Ann N Y Acad Sci*. 2006 Nov;1084:71–88. doi: 10.1196/annals.1372.038.
32. Aughsteen A. A., Abu-Umair M.S., Mahmoud S. A. Biochemical analysis of serum pancreatic amylase and lipase enzymes in patients with type 1 and type 2 diabetes mellitus. *Saudi Med J*. 2005 Jan;26(1):73–7. PMID: 15756357.
33. Lüth S., Teyssen S., Forssmann K., Kölbel C., Krummenauer F., Singer M. V. Fecal elastase-1 determination: 'gold standard' of indirect pancreatic function tests? *Scand J Gastroenterol*. 2001 Oct;36(10):1092–9. doi: 10.1080/003655201750422729.
34. Girish B. N., Rajesh G., Vaidyanathan K., Balakrishnan V. Fecal elastase1 and acid steatocrit estimation in chronic pancreatitis. *Indian J Gastroenterol*. 2009 Dec;28(6):201–5. doi: 10.1007/s12664–009–0079-z.
35. Domínguez-Muñoz J.E., D Hardt P., Lerch M. M., Löhr M. J. Potential for Screening for Pancreatic Exocrine Insufficiency Using the Fecal Elastase-1 Test. *Dig Dis Sci*. 2017 May;62(5):1119–1130. doi: 10.1007/s10620–017–4524-z.
36. Icks A., Haastert B., Giani G., Rathmann W. Low fecal elastase-1 in type I diabetes mellitus. *Z Gastroenterol*. 2001 Oct;39(10):823–30. doi: 10.1055/s-2001–17867.
37. Colombo C., Maiavacca R., Ronchi M., Consalvo E., Amoretti M., Giunta A. The steatocrit: a simple method for monitoring fat malabsorption in patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr*. 1987 Nov-Dec;6(6):926–30. PMID: 3681578.