ANATOL J FAMILY MED

Original Article

The Anatolian Journal of Family Medicine

DOI: 10.14744/anatoljfm.2020.25349
Anatol J Family Med 2020;3(3):229–233

Effects of Pancreatin therapy on Gastrointestinal Symptoms in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Objectives: Gastrointestinal symptoms (GIS) are more common in individuals with type 2 diabetes mellitus (DM) in comparison to normal population. This study aimed to evaluate the effects of the pancreatin therapy on the GIS in patients with type 2 DM.

Methods: This study included patients with type 2 DM admitted to the Gastroenterology Department between February to July 2017. Age, HbA1c, level of C-peptide, triglyceride, antidiabetic treatments, fecal elastase levels were evaluated in the files of all patients. The GIS of the patients, who were considered to suffer from the exocrine pancreatic insufficiency, including abdominal pain, bloating, constipation and diarrhea were evaluated before and after the 25000 IU pancreatin therapy.

Results: The study included 35 patients with type 2 DM, the mean age was 59.1±7.6 years, and 24 (68.6%) of the patients were female. The exocrine pancreatic insufficiency was detected in 1 (2.9%) of the patients. Prior to the pancreatin therapy, 33 (94.3%) of the patients were determined to have abdominal pain, 34 (97.1%) had bloating, 33 (94.3%) had constipation and 32 (91.4%) had diarrhea. After the therapy, 29 (82.9%) of the patients were found to have abdominal pain, 31 (88.6%) had bloating, 31 (88.6%) had constipation and 29 (82.9%) had diarrhea. GIS including abdominal pain, bloating, constipation and diarrhea were decreased after pancreatin treatment (p=0.015, p<0.001, p=0.001 and p=0.024, respectively).

Conclusion: GIS in patients with type 2 DM can be treated with pancreatic enzyme replacement therapy.

Keywords: Abdominal pain, constipation, diarrhea, exocrine pancreatic insufficiency

Please cite this article as:
Dabak R, Şimşek EE, Tüzün S, Öner C, Tamer İ, Orbay E, et al. Effects of Pancreatintherapy on Gastrointestinal Symptoms in Patients with Type 2 Diabetes Mellitus. Anatol J Family Med 2020;3(3):229–233.

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Received Date: 16.06.2020
Accepted Date: 10.09.2020
Published online: 04.11.2020

INTRODUCTION

Gastrointestinal symptoms (GIS) are more common in patients with type 2 diabetes mellitus (DM) in comparison to normal population and the etiopathogenesis is not completely known.[1] Nausea, vomiting, abdominal pain, bloating, diarrhea and constipation are the most common GIS in patients with type 2 DM. Abdominal pain frequency is found to vary between 8% and 20%, bloating between 10% and 40%, diarrhea between 35% and 41%, and constipation between 28% and 33%.[1] Gastroparesis, exocrine pancreatic insufficiency (EPI) and some anti-diabetic drugs are among the causes of the GIS in the patients with DM.[1] Observed as delayed gastric emptying, gastroparesis is especially more common in female patients with

type 2 DM who have poor glycemic control.[1] Moreover, the frequency of EPI increases in patients with DM compared to the healthy population. A study determined that 1/3 of the patients with DM had the EPI.[2-4] There are few studies on the possibility of the pancreatin therapy being beneficial for patients with DM who have the EPI. Even though a study on individuals with type 1 DM who had EPI determined that the pancreatin therapy did not reduce abdominal pain and bloating problems, it was observed that the therapy might reduce diarrhea, mild and moderate pain problems.[5] Another significant cause of GIS in patients with DM is some particular antidiabetic drugs such as metformin.[1] Metformin has some kind of side effects in 30% of the patients with DM, and 5% of the patients could not tolerate the metformin therapy.[6, 7] This study aimed to evaluate the effects of pancreatin therapy on the GIS in the patients with type 2 DM independently of the fecal elastase levels.

METHOD

This retrospective study included patients with type 2 DM admitted to the Gastroenterology Department of Kartal Dr. Lutfi Kırdar City Hospital between February to July 2017. The patients were older than 50 years, had type 2 DM for more than 5 years and had one of the GIS such as abdominal pain, bloating, diarrhea or constipation. The files of all patients were examined retrospectively.

Age, HbA1c level, C-peptide, triglyceride and antidiabetic treatments were evaluated. EPI was diagnosed by measuring the fecal elastase (Pancreatic Elastase, ELISA kit, Eagle Biosciences Inc., Nashua, New Hampshire, USA) levels in stools, and the patients with the fecal elastase level of <200 µg were considered to suffer from EPI.[4] Accepting 200 µg as the cut-off value, the fecal elastase level's specificity was determined to be 93%; its accuracy was 63% for mild EPI and 100% for moderate and severe EPI.[4] In addition, the patients whose fecal elastase level was 200 µg and above were considered to have EPI according to the characteristics of their stools and the history of the disease. The 25000 IU pancreatin tablets were given three times a day for 4 weeks. GIS such as abdominal pain, bloating, constipation and diarrhea were evaluated retrospectively before and after treatment. The patients were asked to score the severity of each gastrointestinal system problem from 0 to 5.

The patients with any known gastrointestinal disease, a history of gastrointestinal surgery, alcohol addiction, type 1 DM, chronic renal failure, chronic liver disease or without scoring of GIS in the file were excluded from the study. Moreover, patients receiving GLP-1 agonists or alpha glucosidase inhibitors which could typically cause GIS were excluded.[1]

The data were analyzed using the SPSS 15.0 software. Frequency, percentage, mean, standard deviation, median, minimum and maximum values were used as descriptive statistics. Continuous variables with normal distribution were evaluated with the Pearson correlation test; continuous variables without normal distribution were evaluated with the Spearman correlation analysis and the Wilcoxon test. In all analysis results, $p<0.05$ was considered significant.

RESULTS

The study included 35 patients with type 2 DM and 24 (68.6%) of the patients were female. Table 1 summarizes the characteristics of the patient group.

Before the pancreatin therapy, 33 (94.3%) of the patients were determined to have abdominal pain, 34 (97.1%) had bloating problems, 33 (94.3%) had constipation problems and 32 (91.4%) had diarrhea problems. After the therapy, 29 (82.9%) of the patients were determined to have abdominal pain, 31 (88.6%) had bloating problems, 31 (88.6%) had constipation problems and 29 (82.9%) had diarrhea problems. The severity of the GIS before and after the pancreatin therapy is summarized in Table 2.

Mean fecal elastase level of the patients was 444.7±91.1 µg, and EPI was detected in 1 (2.9%) patient. There was a relationship between fecal elastase levels and age, but there was no significant relationship between HbA1c, C-peptide and triglyceride levels ($r=-0.342$, $p=0.045$; $p>0.05$, respectively).

Evaluating the antidiabetic treatments used by the patients, 27 (77.1%) of them used metformin, 5 (14.3%) used gliclazide, 15 (42.9%) used DPP-4 inhibitors, 2 (5.7%) used pioglitazone, 5 (14.3%) was on basal insulin, 10 (28.6%)

Table 1. Age, duration of type 2 diabetes mellitus and metabolic parameters of the patients

	n (%)	Mean±SS
Age (years)	35 (100.0)	59.1±7.6
Duration of diabetes mellitus (years)	17 (48.6)	9.9±3.9
HbA1c (%)	35 (100.0)	8.1±1.9
C-peptide (µg/L)	32 (91.4)	2.2±0.9
	n (%)	**Median (min-max)**
Triglyceride (mg/dl)	35 (100.0)	181.0 (64.0 - 623.0)

Some variables are missing.

Table 2. Severity of the gastrointestinal symptoms before and after the pancreatin therapy

	Before treatment	After treatment	p
Abdominal pain (n=35)	2.0 (0.0-4.0)	1.0 (0.0-5.0)	0.015
Bloating (n=35)	4.0 (0.0-5.0)	2.0 (0.0-5.0)	<0.001
Constipation (n=35)	3.0 (0.0-5.0)	2.0 (0.0-5.0)	0.001
Diarrhea (n=35)	1.0 (0.0-5.0)	1.0 (0.0-4.0)	0.024

Wilcoxon test.

were using an insulin mixture, and 6 (17.1%) were on intensive insulin. The severity of the patients' GIS before and after the pancreatin therapy in relation to metformin usage is summarized in Table 3.

DISCUSSION

It is hypothesized that the GIS may reduce with the pancreatin therapy because EPI is more common in patients with DM in comparison to healthy population.[3, 5, 8] The study aimed to evaluate the effects of the pancreatin therapy on the gastrointestinal symptoms in patients with type 2 DM. We found that the severity of the GIS might be reduced with pancreatin therapy.

EPI is not always symptomatic and there is not enough studies demonstrating the benefits of enzyme replacement therapy on the patients with DM who have EPI but no symptoms.[9] There are not enough studies on whether pancreatin therapy is beneficial for patients with DM with EPI.[5] A study determined a decline in the stool consistency, bloating and abdominal pain problems with the pancreatin therapy in patients with type 1 DM who had EPI.[5] In addition to this, the same study found an improvement in the symptoms such as mild or moderate pain and diarrhea attributed to EPI with the use of pancreatic enzyme therapy.[5] Our study showed a significant decrease in the severity of the GIS of the patients with type 2 DM such as abdominal pain, bloating, constipation and diarrhea.

The EPI is more common in the patients with type 1 and type 2 DM than in healthy individuals however, its frequency varies.[2-4] Recent studies determined that the EPI's frequency was between 6% and 56.7% in the patients with type 1 DM, and the frequency was between 5% and 35% in the patients with type 2 DM.[2, 10] A meta-analysis found that the frequency of EPI varied between 6% and 57% in the patients with type 1 DM, and it varied between 5% and 36% in the patients with type 2 DM.[3] A large community-based study determined the EPI's frequency as 11.9% in the patients with DM.[8] Our study showed EPI in 2.9% of the patients. The result that our study determined a lower frequency of EPI compared to the literature could be attributed to small size of the study group. Also, when 200 µg was accepted as the cut-off value of the fecal elastase test used in the diagnosis of EPI due to being non-invasive and cheap, its accuracy being at a low level such as 63% for especially mild EPI diagnosis may be another reason.[4, 5, 8, 11]

The relationship between the fecal elastase level and glucose metabolism is controversial.[8, 9, 12, 13] Although some studies found a negative relationship between the HbA1c and the fecal elastase level in patients with type 1 and type 2 DM, some studies found no relationship.[2, 8, 9, 12, 14] A study on individuals with type 2 DM in Turkey determined no relationship between the fecal elastase level and glycemic control.[4] A study on individuals with type 1 and type 2 DM found a relationship between poor glycemic control and low fecal elastase levels.[8] There was no relationship between the fecal elastase level and the HbA1c in our study.

Although a study on individuals with type 1 and type 2 DM found no relationship between the fecal elastase level and age, it found a positive relationship between the fecal elas-

Table 3. Severity of gastrointestinal symptoms before and after the pancreatin therapy in relation to metformin use

	Patients Using Metformin (n=27)			Patients Not Using Metformin (n=8)		
	Before treatment	After treatment	p	Before treatment	After treatment	p
Abdominal pain	2.0 (0.0-4.0)	1.0 (0.0-4.0)	0.031	2.0 (1.0-4.0)	1.5 (0.0-5.0)	0257
Bloating	4.0 (0.0-5.0)	2.0 (0.0-5.0)	<0.001	4.0 (3.0-5.0)	2.5 (1.0-4.0)	0.026
Constipation	3.0 (0.0-5.0)	2.0 (0.0-5.0)	0.008	3.0 (3.0-4.0)	2.0 (0.0-4.0)	0.040
Diarrhea	1.0 (0.0-4.0)	1.0 (0.0-4.0)	0.038	1.0 (0.0-5.0)	1.0 (0.0-4.0)	0.285

Wilcoxon test.

tase level and C-peptide level.[14] Another study on individuals with type 1 DM determined a positive relationship between the fecal elastase level and C-peptide level.[13] While a study on healthy elderly individuals found a negative relationship between the fecal elastase level and age, other studies found no relationship between the fecal elastase level and age.[11, 15, 16] A study found a negative relationship between age and the fecal elastase level, and the fecal elastase level was found significantly low in individuals aged 70 and above compared to younger individuals.[11] While our study determined a relationship between the fecal elastase level and age, it could not determine a significant relationship between the fecal elastase level and C-peptide level. A study found a positive relationship between the fecal elastase level and postprandial triglyceride level in individuals with type 2 DM who were the control group.[17] Our study did not determine a significant relationship between the fecal elastase level and the fasting triglyceride level. The reason for this might be the fact that our study evaluated the fasting triglyceride level unlike the other study.

Metformin is the most frequently used oral antidiabetic agent in the treatment of DM and it is one of the first-choice drugs in guidelines of diabetic treatments.[7] However, one of the most common side effects of metformin is GIS.[6] Our study found a decrease in all GIS of patients on metformin after the pancreatin therapy. Also, while a decrease was found in abdominal pain, bloating and constipation of patients not using metformin, the decrease was found significant for only bloating and constipation problems, and it was thought the reason for this might be the overlapping of predominant irritable bowel syndrome and EPI.

One of the limitations of our study was the small study size. Another limitation was the inclusion of patients with type 2 DM receiving metformine therapy. Metformin is the most commonly used oral antidiabetic drug group in treating type 2 DM; and for a significant proportion of the patients, the metformin therapy causes GIS similar to those caused by the EPI.[6, 7]

Gastrointestinal symptoms are frequently observed in individuals with type 2 DM due to various reasons such as gastroparesis and EPI.[5-8, 18] Tests evaluating pancreatic deficiency should be kept in mind for individuals with DM who have GIS not responding to therapeutic treatments, and they should be scanned for EPI.[3] Our study determined that the severity of GIS in the patients with DM, whose fecal elastase level was not low enough for the diagnosis of EPI but who had GIS, might decline with pancreatin therapy.

Disclosures

Acknowledgements: We thank Prof. Dr. Cem Kalaycı, MD for his contribution during the planning of the study.

Disclosure of interest: The authors declare that they have no competing interest.

Funding source: This work was supported by the Turkish Foundation of Family Medicine [Grant numbers: 0013, Grant date: 2016].

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Ethics Committee Approval: The study was approved by the Ethics Committee of Kartal Dr. Lutfi Kirdar Training and Research Hospital (Date of Approval: 01.31.2017, Decision No: 2017/514/100/7).

Authorship Contributions: Concept – R.D., O.U.B.; Design – R.D.; Supervision – R.D., O.U.B.; Materials – R.D., E.O.; Data collection &/or processing – S.T., C.Ö., E.O., İ.T.; Analysis and/or interpretation – R.D., S.T., İ.T., E.E.Ş.; Literature search – R.D., S.T., E.E.Ş., C.Ö.; Writing – R.D., S.T., E.O.; Critical review – R.D., O.U.B.

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