CLINICAL STUDY

Evaluation of pancreatic exocrine functions in rheumatoid arthritis

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ABSTRACT

BACKGROUND: Rheumatoid arthritis (RA) is one of the most common chronic inflammatory diseases. It mainly involves the joints and also affects directly or indirectly nearly all organ systems. The question whether RA causes exocrine pancreatic disfunction remains unclear. The purpose of this study is to evaluate whether or not RA contributes to pancreatic exocrine insufficiency. This was done by ruling out seconder Sjögren's syndrome (SjS) by using Schirmer's test.

METHODS: A total of 60 patients (20 RA, 20 RA + SjS and 20 SjS) and 20 healthy volunteers were included in the study. Patients with RA who had not undergonethe Schirmer's test in the last 6 months and all healthy volunteers included in the study underwent the Schirmer's test at an outpatient clinic. Random fecal samples were taken from all participants and fecal pancreatic elastase was measured to evaluate pancreatic exocrine functions.

RESULTS: In the study, a statistically significant difference was found between the control group,SjS and RA+SjS groups. But there was no significant difference between the control group and RA group. In RA group, fecal elastase levels were statistically significantly higher compared to the SjS group. But there was no significant difference between RA+SjS and SjS groups.

CONCLUSION: Fecal elastase significantly decreased in SjS compared to the normal population while pancreatic exocrine functions are considered to be impaired in SjS. There are also impaired pancreatic exocrine functions in the secondary SjS associated with RA. Consequently, pancreatic exocrine dysfunction, which can be seen in patients with RA, may be thought to be caused by secondary SjS associated with RA *(Tab. 6, Fig. 1, Ref. 19)*. Text in PDF *www.elis.sk*.

KEY WORDS: rheumatoid arthritis, fecal elastase, pancreatic exocrine function, Sjögren's syndrome.

Introduction

Although it is defined as a joint disease, RA has systemic manifestations. Extraarticular findings of RA are seen in 18–40 % of patients and are associated with worsened prognosis (1). The disease affects directly or indirectly nearly all organ systems, while causing a wide range of health issues from cardiovascular and respiratory problems to infections, depression and gastrointestinal ulcers (2). In an autopsy study conducted by Belly et al., acute pancreatitis was found in 6 out of 60 RA patients while chronic pancreatitis was found in 15 of them (3). In another study, the incidence of acute pancreatitis in RA patients was found in 185.7 per 100,000 person-years and excess risk of 1.62 compared with non-RA patients (2). However, Michaud et al. found that there was no evidence of increased rate of pancreatitis in RA (4).

The main histological feature is the lymphocytic infiltration of the salivary and ocular glands. Xerophthalmia is a major finding. The signs may be seen in various systems other than exo-

crine glands, including skin, muscle, veins, joints, internal organs, blood and lymphatic system of 1/3 of the patients (5, 6). Afzelius and colleagues observed in their study that 25 % of the patients had morphological changes of the pancreas as evaluated by secretin-stimulated magnetic resonance cholangiopancreatography (MRCP), and two patients had chronic pancreatitis-like changes (7). In another study, the authors evaluated pancreatic functions by fecal elastase-1 test in 50 chronic polyarthritis cases. They found that two cases (4 %; 95% confidence interval, 1–14 %) had abnormally low fecal elastase level (8).

The main clinical finding of the exocrine pancreatic disorder is fat malabsorption. Patients suffer from weight loss, uncomfortable and bloating feeling in the abdomen. The diagnosis is based on clinical symptoms and assessment of direct and indirect tests (9). Indirect pancreatic function tests have lower sensitivity but higher applicability compared to direct tests. (10). The fecal elastase test is more sensitive and specifically reflects the pancreatic exocrine function, compared to other indirect tests although it does not achieve high specificity and sensitivity of direct function tests (11). Sensitivity and specificity of fecal elastase test were found to be 93 % when cut-off value is accepted as $< 200\ \mu g/g$ (12). The purpose of this study is to evaluate whether or not RA contributes to pancreatic exocrine insufficiency. This is done by ruling out secondary SjS by using Schirmer's test.

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Methods

A total of 60 patients (20 RA, 20 RA + SjS and 20 SjS) and 20 healthy volunteers, who applied to our rheumatology outpatient clinic and met the criteria mentioned below were included in the study. Signed written consent was taken from the participants of the study, and the approval of the ethics committee of Başkent University was obtained. Inclusion criteria for RA patients: (i) patients younger than 60 years, (ii) duration of the disease > 1 year, (iii) detection of Schirmer's test result > 15 mm or ≤ 5 mm in the last 6 months. Inclusion criteria for SjS patients: (i) patients younger than 60 years, (ii) duration of the disease > 1 year. Inclusion criteria for control group: (i) patients younger than 60 years, (ii) Schirmer's test > 15 mm, (iii) volunteers without systemic disease. Excluded from the study were conditions that affect pancreatic exocrine functions and Schirmer's test results, namely chronic pancreatitis, pancreatic cancers, pancreatic resections, gastrointestinal surgeries, diabetes mellitus, cystic fibrosis, amyloidosis, gluten enteropathy, periampullary tumors, Zollinger Ellison syndrome, Crohn's disease, short bowel syndrome, antidepressant, anticholinergic, neuroleptic, clonidine, diuretic use, granulomatous diseases (sarcoidosis, tuberculosis, leprosy), therapeutic radiation, head and neck trauma and surgery, dehydration, and patients over 60 years of age (except patients with SjS who were diagnosed with biopsy). The patients involved in the study were questioned about the duration of the illness, accompanying diseases, and the drugs they use. Abdominal ultrasonography was performed to evaluate the pancreatic morphology of the patients. The Schirmer's test was carried out in patients with RA who had not undergone it in the last 6 months and all control patients included in the study at the outpatient clinic. A 5-mm wide Whatman filter paper No 41 was placed inside the lateral third of the lower eyelid without anesthesia. The amount of moisture within the paper was measured after 5 minutes. If the moisture was ????? mm or less, the eye was considered "dry" (secondary SjS); if it was more than 15 mm, the result of Shirmer's test was considered normal. According to the Schirmer's test results, patients were divided into 2 groups. Patients with RA who were diagnosed as having the Schirmer's test 5 mm or less were accepted as SjS associated with RA (Group RA + SjS).

Random fecal samples were taken from all participants and stored at −20 °C until elastase measurement. Fecal pancreatic elastase was measured with a commercially avaliable ELISA test (Pancreatic Elastase ELISA; Bioserv Diagnostic GmbH, Rostock Germany), according to the manufacturer's instructions. Serum CRP levels were measured simultaneously with the fecal sample.

Statistical analysis

Baseline characteristics and fecal elastase results for all subjects and groups were given as mean (± standard deviation), median (smallest-highest), or median (width between quarters) for appropriate variables after normal distribution tests of the data had been performed. The categorical variables are given as number (percentage). The Kruskal–Wallis variance analysis test was used for inferential statistics between the disease groups and control group, while Mann–Whitney-U test was used for the binary comparison of drug use. Pearson / Spearman correlation coefficients were given in the correlation analysis with variables affecting the fecal elastase level. Multiple regression analysis was performed to examine the relationship of fecal elastase levels between groups independently of age. The SPSS program (Version 17, IBM SPSS Statistics, IBM Corporation, NY, USA) was used for calculations. p values < 0.05 were considered statistically significant.

Results

The mean age of the patients included in the study was 49.2 ± 7.9 years in the RA group, 52.3 ± 6.6 years in the RA + SjS group, 51.0 ± 11.3 years in the SjS group, and 44.5 ± 9.8 years in the control group. There was a statistically significant difference between the mean ages of control group and RA group (Tab. 1). The duration of disease was 1.2 (0–5) years in SJS group, 6 (1–25) years in RA + SjS group and 7 (1–25) years in RA group.

When fecal elastase values were compared according to sex, mean fecal elastase level in males was 643.0 ± 134.4 μg/g and mean fecal elastase level in females was 666.1 ± 234.6 μg/g. It was observed that sex did not affect fecal elastase levels (p = 0.799) (Tab. 2). When fecal elastase levels were measured in all groups, the median fecal elastase was 750.5 μg/g in the control group, 628.5 μg/g in SjS group, 577.5 ug/g in RA + SjS group, and 802.5 μg/g in RA group. Statistically significant differences were found

Tab. 1. Evaluation of age and gender distribution by groups.

Groups	Age mean±SD	Gender M/F
Control	44.5±9.8[c]	3/17
SjS	51.0±11.3	1/19
RA+SjS	52.3±6.6[c]	3/17
RA	49.2±7.9	0/20
p	0.044[a]	0.126

SD: Standart Deviation, M: Male, F: Female, a: One-Way ANOVA, b: Chi-square test, c: The difference between the control group and the RA+SjS group was statistically significant (p=0.039)

Tab. 2. Evaluation of fecal elastase levels according to gender.

Variables	Fecal Elastase (μg/g) mean±SD	p
Gender		
Male (n=7)	643.0±134.4	
Female (n=73)	666.1±234.6	0.799

SD: Standard Deviation

Tab. 3. Evaluation of fecal elastase levels according to the groups.

Groups	Fecal Elastase (μg/g) median (WBQ)
Control (n:20)	750.5 (88.5)[b,c]
SjS (n:20)	628.5 (402.0)[b,d]
RA+SjS (n:20)	577.5 (371.5)[c]
RA (n:20)	802.5 (433.7)[d]
p [a]	0.034

WBQ: Width Between Quartiles, a: Kruskal Wallis test, b: The difference between the control group and the SjS group was statistically significant (p = 0.006), c: The difference between the control group and the RA+SjS group was statistically significant (p = 0.037), d: The difference between the SjS group and the RA group was statistically significant (p = 0.013)

Tab. 4. Examination of the effects of SjS, RA + SjS and RA groups according to the control group on the fecal elastase level when the age correction was performed.

Variables	Regression Coefficient (B)	p	95% Confidence Interval (B)	
			Lower Limit	Upper Limit
SjS	−0.378	0.006	−0.646	−0.109
RA+SjS	−0.261	0.059	−0.533	0.011
RA	−0.088	0.511	−0.352	0.177
Age	−0.003	0.558	−0.013	0.007

Tab. 5. Correlation coefficient and significance levels between age, duration of disease and CRP, fecal elastase.

Variables	R	p
Age	−0.146	0.195
Duration of disease	0.093	0.479
CRP	−0.167	0.139

Tab. 6. Evaluation of fecal elastase levels according to drugs.

Variables	Fecal Elastase (µg/g) Mean±ss	p
NSAID		0.542
positive (n=38)	617.7±238.3	
negative (n=22)	658.1±259.0	
CORTICOSTEROIDS		0.112
positive (n=43)	600.9±237.3	
negative (n=17)	712.5±252.1	
PPI		0.948
positive (n=33)	634.4±217.2	
negative (n=27)	630.3±279.0	
HCQ		0.266
positive (n=16)	582.4±183.0	
negative (n=44)	650.8±263.1	
MTX		0.674
positive (n=36)	621.6±233.6	
negative (n=24)	649.0±264.8	
SLZ		0.145
positive (n=46)	607.0±232.1	
negative (n=14)	716.4±274.6	
LEFLUNOMID		0.964
positive (n=54)	633.0±253.2	
negative (n=6)	628.2±164.5	

NSAID: Nonsteroid anti-inflammatory drugs, PPI: Proton pump inhibitors, HCQ: Hydroxychloroquine, MTX: Methotrexate, SLZ: Sulfasalazine

between the control group and SjS group (p = 0.006) as well as between the control group and RA + SjS group (p = 0.037). In the RA group, fecal elastase levels were statistically higher than in SjS group (p = 0.013). The difference between RA + SjS and RA groups was not statistically significant (p = 0.07) (Tab. 3).

When adjusted for age, it was observed that the level of fecal elastase in the SjS group was lower compared to the control group (p = 0.006). When adjusted for age, the level of fecal elastase in the RA+SjS group was not statistically significant (p = 0.059). The similarity between the control group and RA group was also observed when age-adjusted correction was made (p = 0.558) (Tab. 4).

There was no significant correlation between age and fecal elastase levels in our study (r = −0.146; p = 0.195). There was no significant correlation between disease duration and fecal elastase level (r = 0.093; p = 0.479). There was no significant correlation

between CRP and fecal elastase levels (r = −0.167; p = 0.139). The results are given in Table 5.

Discussion

RA is one of the most common chronic inflammatory diseases. Although the disease mainly involves the joints, it also causes extra-articular manifestations (13). SjS is a chronic inflammatory autoimmune disease that predominantly involves exocrine glands. It can occur in conjunction with other autoimmune disorders and RA is the most common connective tissue disease associated with SjS (14).

Studies investigating pancreatic exocrine dysfunction have been performed on patients with SjS mostly in rheumatology. In a study conducted by Sumii T. et al., pancreatic exocrine functions (reduction in bicarbonate secretion) were investigated by performing a secretin stimulation test in patients with SjS (15). In this study, it was concluded that the decrease in bicarbonate secretion was characteristic. In another study conducted by Candellli and his colleagues, pancreatic exocrine functions were assessed by fecal chymotrypsin test and it was found that in patients with SjS, exocrine functions were statistically significantly lower than in the control group. It was also found that this was parallel to Schirmer test results (16). In this study, in the group of patients with SjS, the mean elastase level was 562.50 µg/g, and there was a statistically significant difference compared to control group. This result has been evaluated as SjS that affects pancreatic exocrine functions.

In the literature, there are also studies on pancreas functions and relationship with disease duration in SjS. In a study, PABA test, serum immunoreactivity trypsin levels and fecal fat measurement tests were performed in primary and secondary SjS and it was found that pancreatic dysfunction is more severe in long-term disease (17). In another study, serum immunoreactive trypsin levels were found to be higher in primary SJS compared to secondary SjS, and the disorder was more frequent in cases with disease duration over 10 years. However, there was no clinical pancreatitis in any of pancreatic exocrine dysfunction cases. (18). In our study, no
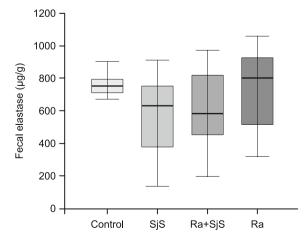

Fig. 1. Fecal elastase levels according to the groups.

statistically significant relationship was found between the duration of disease and pancreatic functions (p = 0.479). There was no clinical pancreatitis in our patients either.

There are also studies in the literature investigating the effect of RA on pancreatic exocrine functions. In a study conducted by Gobelet et al, pancreatic exocrine functions were investigated by PABA test which was abnormal in 37.5 % of SjS and 35 % of RA, with no abnormalities in the control group (19). In our study, no statistically significant difference was found between the control group and RA group in which the secondary SjS was excluded (p = 0.776).

In our study, mean fecal elastase levels of patients were 666.1 ± 234.6 µg/g in women and 643.0 ± 134.4 µg/g in men. There was no statistical difference in mean fecal elastase levels between women and men (p = 0.799). There was no statistically significant correlation between fecal elastase and age (p=0.195) either. There was no statistically significant relationship between pancreatic exocrine function and drugs used by the patients, e.g. methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, corticosteroids, proton pump inhibitors, nonsteroidal antiinflammatory drugs. There was no significant association between pancreatic exocrine functions and CRP levels in our study.

The best cut-off value for fecal elastase level was determined to be 200 µg/g. The fecal elastase results of 2 (2.5 %) of the patients in our study were found to be below 200 µg/g. It is known that fecal elastase is a sensitive test for detecting moderate and severe pancreatic insufficiency. Therefore, it can be assumed that other patients might have slightly exogenous pancreatic exocrine dysfunction or that fecal elastase 1 levels might have a different cut-off value for autoimmune diseases. Controlled studies involving a larger number of patients with long-term follow-up are necessary to be able to conclude in this decision.

In our study, fecal elastase levels in SjS and RA+SjS groups were statistically significantly lower than those of the control group. Fecal elastase levels in the RA group and control group were similar. In accordance with literature, these results have also shown that pancreatic exocrine functions were impaired in SjS. Pancreatic exocrine function was also impaired in the secondary SjS associated with RA. But there was no pancreatic exocrine dysfunction in patients with RA without concommitant secondary SjS. These results suggest that impaired pancreatic exocrine function in RA patients may be caused by secondary SjS associated with RA. However, for better understanding of the pancreatic exocrine dysfunctions seen in RA, long-term and controlled studies involving a larger number of patients are necessary.

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