Prevalence of Functional Gastrointestinal Disorders Among Patients with Rheumatoid Arthritis

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Abstract

Introduction and objective: Rheumatoid arthritis (RA) is a common autoimmune inflammatory disorder characterized by persistent joint affection mainly and extra-articular organ involvement as skin, heart and gastrointestinal (GI) systems. Functional GI manifestations are one of the most common extra-articular manifestations of RA as gastrointestinal reflux disease (GERD) and irritable bowel syndrome (IBS). Our study aimed to study the prevalence of GERD and IBS among RA patientsin a Rheumatology Outpatient Clinic in Sohag University Hospital and to assess the relationship of GERD and IBS to clinical factors (age, sex) and medications prescribed for RA.

Patients and methods: We evaluated the prevalence of GERD & IBS in patients with RA and controls using the FSSG questionnaire and Rome III criteria.

Results: Using FSSG scale, we found that the percentage of GERD among RA patients was much higher than control subjects (62% versus 38%; P<0.001). We found that the mean FSSG score for GERD among RA cases was significantly higher than that in control subjects (10.52±8.76 versus 7.96±8.50). As regards IBS, 43% of RA patients of our study were diagnosed as having IBS, compared to 33% of the control subjects. This difference was, however, non-significant (p>0.05).

Our study showed that 28% of RA patients were diagnosed as having both GERD and IBS, compared to only 13% of the control subjects. This difference was statistically significant (p=0.003). In Conclusion**,** the prevalence of GERD symptoms in RA patients is significantly higher than that in healthy controls. IBS is also frequent in RA patients (43%) compared to (33%) in healthy controls.IBS and GERD are two common disorders that frequently overlap in RApatients and healthy controls.

Keywords: gastroesophageal reflux disease, irritable bowel syndrome, rheumatoid arthritis.

Introduction

Rheumatoid arthritis (RA) is a common autoimmune inflammatory disorder characterized by persistent joint affection mainly and extra-articular organ involvement as skin, heart, lung, nervous and gastrointestinal (GI) systems[(1)]. Functional GI manifestations are one of the most common extra-articular manifestations of RA as gastrointestinal reflux disease (GERD) and irritable bowel syndrome(IBS)[(2)].

GERD is disorder that results from abnormal reflux of gastric contents into esophagus resulting in symptoms, heartburn, acid regurgitation are the most common or/ and mucosal damage detected by upper endoscopy[(3)]. Multiple simple methods and investigations have been developed to diagnose and score GERD symptoms. One of them is the F-scale[(4)].

IBS is a functional disease of lower gastrointestinal tract, characterized by the presence of abdominal pain and/ or discomfort accompanied by alteration in bowel habits in the absence of biochemical or structural pathology[5]. Rome working parties have elaborated detailed definitions of the syndrome[6]. One of them for IBS diagnosis is Rome III criteria[7].

Aim of the work:

This work aimed to study the prevalence of GERD and IBS among patients with RA in a Rheumatology Outpatient Clinic in Sohag University Hospital and to assess the relationship of GERD and IBS to clinical factors (age, sex) and medications prescribed for RA.

Patients:

Our study was conducted on 100 adult patients with a documented rheumatoid arthritis that were diagnosed according to ACR /AULAR 2010 classification criteria of rheumatoid arthritis (Table 1)[8], attending the Rheumatology Outpatient Clinic of Sohag University Hospital. A control group composed of 100 adult healthy individuals (34 male, 66 female; mean age 40 years), was also included. Patients and controls were matched for age and sex. Patients with known organic GI diseases such as peptic ulcer disease, liver cirrhosis were excluded from our study.

***Methods*:**

Before starting our study, the protocol was approved by faculty ethics committee. All participants signed written consents then the following were done. All cases and control groups were subjected to complete history taking, clinical examination. Also, all patients and control subjects were interviewed for GERD symptoms using FSSG questionnaire[4]and ROME III criteria[7]for diagnosis of IBS. F score includes 12 questions (Table 2) about GERD symptoms. All participants in our study answered these questions and frequency of GERD symptoms was be measured on the following scale: Never = 0; occasionally = 1; sometimes = 2; often= 3; and always = 4. If the patient scores more than 7 points, GERD is considered to be present. The presence or absence of GERD symptoms and the total FSSG score were studied inrelation to clinical factors such as age and sex.

IBS was diagnosed according to Rome III criteria[7] (Table 3). IBS is diagnosed by the presence of recurrent abdominal pain or discomfort at least 3 days per month in the 3 months associated with 2 or more of the following:

- ✓ Improved with defecation.
- ✓ Onset associated with a change in frequency of stool.
- ✓ Onset associated with a change in form (appearance) of stool.

Statistical analysis:

The frequency of GERD and IBS in patients with rheumatoid arthritis was compared with that of healthy controls. Quantitative data was represented by mean± standard deviation. Comparison between both means among groups was be done by student's t- test. Qualitative data was presented by numbers and percentages. Both univariate and multivariate logistic regression analyses were performed to determine the possible risk factors for GERD and IBS in these patients. P value less than 0.05 was be considered significant.

Results

The mean duration of RA was 8.73 years, with a relatively high standard deviation of over 6.8 years. This was reflected in the very wide range (from one year to 33 years). Treatment that was taken by RA patients include methotrexate, leflunomide, hydroxychloroquine, alexoquine, sulfasalazine, NSAIDs and steroids and our results show that there is non-significant relation between the use of NSAIDs and development of either GERD and/or IBS symptoms. Also, there is non-significant relation between the intake of steroids and development of either GERD and/or IBS symptoms. This may be simply explained by the fact that most of the RA patients received NSAIDs and steroids.

As regard GERD: Using FSSG scale, we found that the percentage of GERD among RA patients was much higher than control subjects (62% compared to 38%; respectively). The difference was highly significant (P<0.001). Also, the mean total FSSG score for GERD among RA cases was 10.52±8.76, with a median of 10, while the mean among control subjects was 7.96±8.50, with a median of 5.5. The difference between RA patients and controls was statistically significant (Table 4).

Our results show that the possible risk factors for GERD in our study included rheumatoid arthritis, older age, male sex, cigarette smoking, DM and high ESR. These factors were subjected to multivariate regression analysis and the results show that rheumatoid arthritis is an independent risk factor for the development of GERD (Table 5).

As regard IBS, Our results show that 43% of RA patients were diagnosed as having IBS, compared to 33% of the control subjects. This difference was, however, non-significant (p>0.05) (Table 6). Our results show that none of the factors in table 7 could be considered as possible risk factors for IBS.

We found that 28% of RA patients were diagnosed as having both GERD and IBS, compared to only 13% of the control subjects. This difference was statistically significant (p = 0.003).

Among RA patients: our results show that there is a positive association between GERD and IBS. The prevalence of IBS among GERD positive cases was 45.2%, compared to 39.5% among GERD negative cases. On the other hand, the prevalence of GERD among IBS positive cases was 65.1%, compared to 59.6% among IBS negative cases.

Among control subjects, we found also similar positive association between GERD and IBS. The prevalence of IBS among GERD positive cases was 34.2%, compared to 32.3% among GERD negative cases. On the other hand, the prevalence of GERD among IBS positive cases was 39.4%, compared to 37.3% among IBS negative cases.

Table (1): The 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria For RA Score[8]**.**

To be applied to patients: (1) who have ≥ 1 joint with definite synovitis, excluding the DIP joints, first MTP joints, and first CMC joints, and (2) in whom the synovitis cannot be explained by another disease.

Criteria	Score
A. Joint involvement:	
1 large joint	0
2 - 10 large joints[a]	1
1 - 3 small joints (with or without involvement of large joints)	2
4 - 10 small joints[b] (with or without involvement of large joints)	3
> 10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification):	
Negative RF and negative anti-CCP antibodies	0
Low-positive RF or low-positive anti-CCP antibodies[c]	2
High-positive RF or high-positive anti-CCP antibodies[d]	3
C. Acute phase reactants:	
Normal CRP level and normal ESR	0
Abnormal CRP level or abnormal ESR	1
D. Duration of symptoms:	
< 6 weeks	0
≥ 6 weeks	1

ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; RA, rheumatoid arthritis; DIP, distal interphalangeal; MTP, metatarsophalangeal; CMC, carpometacarpal; MCP, metacarpophalangeal; PIP, proximal interphalangeal; IP, interphalangeal; RF, rheumatoid factor; anti-CCP, anti–cyclic citrullinated protein; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

[a] Large joints = shoulders, elbows, hips, knees, ankles.

[b] Small joints = MCPs, PIPs, second - fifth MTPs, thumb IPs, wrists.

[c] Low-positive is ≤ 3 times the upper limit of normal.

[d] High-positive is > 3 times the upper limit of normal.

Table 2: FSSG Questionnaire .

Question	Never	Occasionally	Sometimes	Often	Always
Q1: Do you get heartburn?	0	1	2	3	4
Q2: Does your stomach feel bloated?	0	1	2	3	4
Q3: Does your stomach ever feel heavy after meals?	0	1	2	3	4
Q4: Do you sometimes subconsciously rub your chest with your hand?	0	1	2	3	4
Q5: Do you ever feel sick after meals?	0	1	2		4
Q6: Do you get heartburn after meals?	0	1	2	3	4
Q7: Do you have an unusual (e.g., burning) sensation in your throat?	0	1	2	3	4
Q8: Do you feel full while eating meals?	0	1	2	3	4
Q9: Do some things get stuck when you swallow?	0	1	2	3	4
Q10: Do you get bitter liquid (acid) coming up into your throat?	0	1	2	3	4
Q11: Do you burp a lot?	0	1	2	3	4
Q12:Do you get heartburn if you bend over?	0	1	2	3	4

Table 3: Rome III criteria.

Questions
Q: Do you have abdominal pain or discomfort?
Q: Its duration?
Q: Improved or not by defecation?
Q: Associated with any change in frequency or form of stool?

Table 4: The mean results of individual questions of the FSSG score between RA patients and controls.

	RA	Control	Mann Whitney	P value
Q1. Heart burn	1.73±1.37	1.07±1.37	8673	**<0.001 (HS)**
Q2. Feel bloated	1.01±1.28	0.82±1.17	9653	0.279 (NS)
Q3. Heavy after meal	1.18±1.29	1.07±1.37	9717	0.383 (NS)
Q4. Rub your chest with hand	0.78±1.14	0.88±1.20	9838	0.556 (NS)
Q5. Feel sick after meal	0.61±1.02	0.48±0.93	9782	0.413 (NS)
Q6. Heart burn after meal	1.66±1.36	1.23±1.42	9136	**0.019 (S)**
Q7. Unusual sensation in the throat	0.63±1.06	0.40±0.92	9437	0.055 (NS)
Q8. Fullness during meal	0.35±0.74	0.23±0.61	9729	0.241 (NS)
Q9. Things get stuck during swallowing	0.60±1.02	0.38±0.91	9351	**0.022 (S)**
Q10. Liquid bitter	0.75±1.07	0.68±1.05	9846	0.560 (NS)
Q11. Burb a lot	0.55±1.03	0.40±0.97	9582	0.121 (NS)
Q12. Heart burn when leaning forward	0.67±1.18	0.32±0.78	9215	**0.008 (S)**
Total FSSG score	10.52±8.76	7.96±8.50	9075	**0.017 (S)**

In this table, Mann Whitney test in stead of Student t test as the data were non parametric (SD is higher than half of the mean).

Table 5: Multivariate regression analysis for the possible risk factors of GERD.

Item	Odd's ratio	CI of odd's	P value
RA	2.431	1.272-4.648	**0.007 (S)**
Age	1.019	0.997-1.041	0.097 (NS)
Male sex	1.725	0.803-3.705	0.162 (NS)
Cigarette smoking	2.255	0.720-7.061	0.163 (NS)
DM	3.482	0.675-17.962	0.136 (NS)
ESR	1.009	0.997-1.021	0.155 (NS)

Table 6: Prevalence of IBS among the study groups.

			Group		Total
			RA	Control	
IBS or not	Not IBS	Number	57	67	124
		%	57.0%	67.0%	62.0%
	IBS	Number	43	33	76
		%	43.0%	33.0%	38.0%
Total		Number	100	100	200
		%	100.0%	100.0%	100.0%

Chi square = 2.122, p value = 0.145 (NS)

Table 7:Univariate regression analysis for the possible risk factors of IBS.

Item	Odd's ratio	CI of odd's	P value
RA	1.532	0.862-2.722	0.146 (NS)
Age	1.001	0.982-1.021	0.887 (NS)
Male sex	1.714	0.889-3.306	0.109 (NS)
Rural residence	1.097	0.592-2.035	0.768 (NS)
Cigarette smoking	1.854	0.697-4.930	0.216 (NS)
Goza smoking	1.728	0.645-4.630	0.276 (NS)
Hypertension	1.056	0.397-2.812	0.913 (NS)
DM	1.678	0.431-6.531	0.455 (NS)
Duration of RA	1.024	0.966-1.085	0.430 (NS)
Methotrexate	2.576	0.703-9.447	0.153 (NS)
Leflunomide	1.686	0.479-5.942	0.416 (NS)
Hydroxychloroquine	0.658	0.294-1.477	0.311 (NS)
Sulfasalazine	0.529	0.180-1.557	0.247 (NS)
Steroid	1.625	0.654-4.039	0.296 (NS)
NSAIDs	2.333	0.234-23.246	0.470 (NS)
ESR	1.001	0.991-1.011	0.893 (NS)
GERD	1.089	0.615-1.927	0.771 (NS)

Discussion

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease affecting about 1% of the adult population and associated with progressive deterioration of joint function[9]**.** Upper GI disorders are recognized as one of the major comorbidities in RA leading to a significant increase in the risk of mortality[10]**.**

The gastro esophageal reflux disease and irritable bowel syndrome are among the functional disorders previously described in patients with RA in USA[2]**.**

In the current study, the percentage of GERD among RA patients was much higher than control subjects (62% compared to 38%; respectively).This frequency is much higher than that reported by**Nampei et al[11]** in RA patients (29.5 %).

Our results show that the mean FSSG score for GERD among RA cases was significantly higher than control subjects (10.52±8.76 versus 7.96±8.50). **Nampei et al[11]**reported that the mean FSSG score for RA cases was 5.6. **Chong and Wang[10]**reported thatheartburn was significantly more frequent in patients with different rheumatic disorders than the general population in **Singapore.**In agree with our study, **Miura et al[12]**found that the frequency of GERD symptoms using FSSG score was significantly higher in RA patients compared to that in the general Japanese population (24.5 % versus 11.5%).

The mechanism of GERD symptoms in RA patients is unclear. A well known histological disorder in GI system in RA should be amyloidosis that is a deposit within GI mucosa causing dysfunction of GI tract. This condition is rather well known in lower GI tract, but can also be observed in upper GI tract in RA[13] and significantly associated with reflux esophagitis in chronic renal failure patients[14]**.**Univariate analysis of the possible risk factors of GERD in RA patients showed that RA, older age, being male sex, cigarette smoking, DM and high ESR were significantly associated with the development of GERD.

However, multivariate logistic regression analysis of these factors revealed that only RA is independently associated with GERD. **Myasoedova et al[2],** compared the prevalence of GIdisorders in RA versus non-RA subjects using bowel disease questionnairefound that no significant difference in the prevalence of GERD in RA patients than non-RA subjects. The discrepancy between this study and our results might have been resulted from the difference of the questionnaire used to evaluate the GERD symptoms.

As regard IBS in our study, 43% of RA patients were diagnosed as having IBS, compared to 33% of the control subjects. This difference was, however, statistically non-significant. In the current study, three of IBS symptoms included in Rome III criteria were significantly more frequent in RA patients than the control group. These symptoms are abdominal pain and discomfort, change in frequency of bowel habits and loose stools.

The link between IBS and RA was discussed in previous studies. Firstly, IBS may be of an autoimmune origin. That is supported by the presence of the antibodies against GnRH that were common in patients with IBS, but not in organic diseases, compared with healthy controls[15]**.** So IBS must be more common in RA patients and this is against to results our study that may be due to small number of the cases of the study. **Myasoedova et al[2]**using Bowel Disease Questionnaire found that

abdominal pain/discomfort was significantly more common in RA patients.Also, there is study published in **the Journal of Rheumatology** followed people with RA and people without RA for about 10 years found that 50% greater chance of having a lower GI problem in RA patients compared to people who didn't have RA.

As mentioned in HealtyCentral, the fact that these two conditions (RA & IBS) might be connected is significant[16]**.** In our study, no possible risk factors for IBS were found by univariate regression analysis.

In our study, 28% of RA patients were diagnosed as having both GERD and IBS, compared to only 11% of the control subjects. This difference was statistically significant. Among RA patients, our results show that there is a positive association between GERD and IBS as mentioned previously.These findings confirm previous studies reporting the prevalence of IBS among GERD positive patients ranging from 19% to 71%[17-21]. This differences in the prevalence among these studies could be due to different criteria for diagnosis of IBS and/or GERD. On the other hand, previous studies demonstrated that patients with IBS frequently report GERD-related symptoms in a frequency ranging from 32.9% to 43.1%[17, 22]**.**

Conclusion

The prevalence of GERD symptoms in RA patients is significantly higher than that in healthy controls. Rheumatoid arthritis is an independent risk factor for the development of GERD. IBS is also frequent in RA patients (43%) compared to (33%) in healthy controls. IBS and GERD are two common disorders that frequently overlap in RApatients and healthy controls.

Recommendation:

Upper endoscopy and biopsy may be included for comparison between two results (by questionnaire & by biopsy) and trial to identify the underlying aetiology of the gastrointestinal manifestations of RA aiming to management and prevention of this aetiology to improve the quality of life for RA patients and decreasing up to prevention of morbidity and mortality.

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الملخص العربي

معدل انتشار اضطرابات الجهاز الهضمي الوظيفيه بين المرضي الذين يعانون من الروماتويد المفصليي المزمن
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الروماتويد المفصلي المزمن هومرض المناعة الذاتية المزمن الذي يتميز بالتهاب المفاصل المستمرالذي يؤدي إلى تلف المفاصل وفقدان وظائفها الرئيسية ،كما يمتد الي اجهزه اخري بالجسم ،بمافي ذلك الجلد والعين والقلب والرئة والكلى والجهازالعصبي والجهازالهضمي. ومن المسلم به ان امراض الحزء العلوي من الجهازالهضمي هي احد اهم الاسباب المؤديه لزياده مخاطر الوفاه ف الروماتويد المفصلي المزمن.و يعد مرض الارتجاع المعدي المريئ ومتلازمه القولون العصبي من بين الاضطرابات الوظيفية التي سبق وصفها في هولاء المرضي.

مرض الارتجاع المعدي المريئي هو الحاله التي تنتج عن ارتجاع محتويات المعدة للمرئ مما يسبب بعض الأعراض والمضاعفات. بينما متلازمة القولون العصبي هي اضطراب وظيفي للجزء السفلي من الجهازالهضمي ،الذي يظهر علي صوره ألام في البطن يصاحبه تغير بوظيفة القولون بشرط عدم وجود اي مرض عضوي.

الهدف الرئيسي لدراستنا هو دراسة معدل انتشارمرض الارتجاع المعدي المريئي و متلازمه القولون العصبي بين المرضى الذين يعانون من مرض الروماتويد المفصلي المزمن في العياده الخارجية لأمراض الروماتيزم في مستشفى سوهاج الجامعي.وقد اجريت الدراسة على 100 مريض بالغ من المرضي الذين يعانون من مرض الروماتويد المفصلي المزمن والمترددين علي العيادة الخارجيه لامراض الروماتيزم بمستشفي سوهاج الجامعي . وكانت هناك فالدراسه ايضا مجموعة ظابطه تتكون من100شخص صحيح بالغ متوافق فالعمر والجنس. وقد وقع جميع المشاركين موافقه خطيه مستنيره وطلب منهم الرد علي استبيان مقياس التردد لتقييم أعراض ارتجاع المريء ومعايير روما III لتشخيص القولون العصبي من خلال مقابلات شخصيه وجها لوجه.

وفقا لاستجابة المشاركين وردهم علي الاستبيان. اوضحت دراستنا التالي: تم تشخيص مرض الارتجاع المعدي المريئي في 62 مريض من مرضي الروماتويد المفصلي المزمن و في 38 شخص من الضوابط وقد تبين ان نسبه مرض الارتجاع المعدي المريئي في مرضي الروماتوي المفصلي المزمن اعلي من نسبته في الضوابط .ايضا تم تشخيص متلازمه القولون العصبي في 43 مريض من مرضي الروماتويد المفصلي المزمن و في 33 شخص من الضوابط وقد تبين ان متلازمة القولون العصبي في مرضي الروماتوي المفصلي المزمن اعلي من نسبته في الضوابط. وقد وجد ايضا ان ل 28٪ من مرضى الروماتوي المفصلي المزمن تم تشخيص وجود كل من ارتجاع المريء والقولون العصبي، بالمقارنة مع 13٪ فقط في الضوابط. وهذا يعني ان مرض الارتجاع المعدي المريئي ومتلازمه القولون العصبي قد يكونا مظهرين من مظاهر عمليه فسيولوجيه مرضيه كامنه والتي قد تؤثر علي اجزاء مختلفه من الجهاز الهضمي. وتشير دراسات متعددة أن مرض الارتجاع المعدي المريئي ومتلازمه القولون العصبي هما اضطرابات قد تتداخل في كثير من الأحيان.

الاستنتاج :

- ✓ مرض الارتجاع المعدي المريئي ومتلازمه القولون العصبي هما اضطرابات قد تتداخل في كثير من الأحيان.
- ✓ معدل انتشار اعراض مرض الارتجاع المعدي المريئي مرتفع في مرضي الروماتويد المفصلي المزمن بينما معدل انتشار متلازمه القولون العصبي في مرضي الروماتويد المفصلي المزمن لايختلف عن معدل انتشاره في مجموعه الضوابط.

التوصية:

- ✓ يمكننا ان نستخدم المنظار العلوي و اخد خزعة للمقارنة بين النتائج بواسطة استبيان والنتائج عن طريق اخذ خزعة والمحاوله لتحديد المسببات

المرضية محاوله لتحسين نمط الحياة لمرضى الروماتويد المفصلي المزمن وخفض معدلات الاصابه بالامراض والوفاة لديهم.

المرضية الكامنة وراء اضطرابات الجهاز الهضمي المصاحبه لمرضي الروماتويد المفصلي المزمن بهدف الوقاية وتجنب هذه المسببات