Higher prevalence of gastrointestinal symptoms among patients with rheumatic disorders

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ABSTRACT

Introduction: Chronic disorders, such as rheumatic disorders, are associated with increased gastrointestinal (GI) complaints. Medications may be a contributory factor. This study assessed the prevalence of GI symptoms among patients followed-up in a rheumatology clinic.

Methods: Enquiries about GI, psychological and psychosomatic symptoms (headache, insomnia, anxiety, backache and depression) were made from patients. Non-related visitors served as the control group. The underlying disorders were rheumatoid arthritis (RA, 37 percent), systemic lupus erythromatosus (SLE, 23 percent) and others (40 percent).

Results: The symptom prevalence of the following complaints were: reduced appetite (10.2 percent), nausea (20.2 percent), vomiting (10.7 percent), dysphagia (7.3 percent), odynophagia (5.1 percent), early satiety (27.5 percent), heartburn (15.2 percent), dyspepsia (44.6 percent), abdominal bloating (20.8 percent) and irregular bowel habit (6.7 percent). There were no differences between the various rheumatic disorders (RA/SLE and RA/others) except for more heartburn in SLE compared to others (p-value is less than 0.05). There was no significant difference between non-steroidal anti-inflammatory drug (NSAID) users and non-users. Patients on medications with GI (disease modifying/steroid/NSAIDs) adverse effects, experienced a higher rate of early satiety (odds-ratio [OR] 3.5, 95 percent confidence interval [CI] 1.4-8.9) and dyspepsia (OR 2.1, 95 percent CI 1.2-4.3). Compared to the control group, patients had more GI symptoms (all p-values are less than 0.05) except for irregular bowel habits. Patients also experienced more anxiety (OR 2.1, 95 percent CI 1.1-2.4) and backache (OR 2.6, 95 percent CI 1.6-4.2), and had significantly higher symptom clustering (more than two symptoms) compared to the controls (p-value is less than 0.001).

Conclusion: GI symptoms are common among patients with rheumatic disorders. Medications alone do not account for the high prevalence, suggesting that the underlying conditions predispose to GI symptoms.

Keywords: dyspepsia, endoscopy, heartburn, rheumatoid arthritis, systemic lupus erythromatosus

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INTRODUCTION

Chronic disorders, such as rheumatic disorders, are associated with increased gastrointestinal (GI) symptoms.[1-4] This may be due to the underlying conditions. However, medications used for treatment of these rheumatic disorders, such as the non-steroidal anti-inflammatory drugs (NSAIDs), steroids and disease modifying drugs, have been associated with significant GI adverse events.[1,5-7] In addition, chronic disorders have been shown to be associated with significant impairment to quality of life and predisposition to depressive disorders.[8,9] Certain rheumatic disorders, such as systemic lupus erythromatosus (SLE) and rheumatoid arthritis (RA), are particularly associated with acute GI events, such as bowel ischaemia, ulceration, bleeding and perforation.[10,11] These may be life-threatening. However, adverse events associated with medications used for treating rheumatic disorders are more common. NSAIDs are well known to cause GI adverse events. Mortality likelihood aside, patients with rheumatic disorders usually experience more non-life threatening GI symptoms that can severely impair their quality of life instead.[12] This questionnaire study assesses the prevalence of GI symptoms, in patients with rheumatic disorders followed-up in a tertiary referral centre, and also to assess their relations to the medications prescribed for the treatment of their underlying conditions.

METHODS

Patients with various rheumatic disorders attending follow-up in the rheumatology clinic of a tertiary referral centre (Raja Isteri Pengiran Anak Saleha Hospital, Brunei

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Table I. Demographical features of patients and controls.

Demographic	Patients (%) (n = 178)	Controls (%) (n = 359)	p-value
Age (years)*	48.2 ± 14.08	48.3 ± 12.1	0.977
Gender (female: male)	137 (77.0) : 41 (23.0)	278 (77.4) : 81 (22.6)	0.902
Rheumatic conditions			
Rheumatoid arthritis (RA)	65 (36.5)		
Systemic lupus erythromatosis	41 (23.0)		
Others	72 (40.5)		
Psoriatic arthritis	16 (9.0)		
Osteoarthritis	15 (8.4)		
Gout	14 (7.9)		
Miscellaneous‡	27 (15.2)		
Comorbid conditions*	1.9 ± 1.1 (0–5)		
Diabetes mellitus	18 (10.1)	59 (16.4)	0.049
Hypertension	58 (32.6)	105 (29.2)	0.429
Hyperlipidaemia	16 (9.0)	49 (13.6)	0.119
Ischaemic heart disease	5 (2.8)	12 (3.3)	0.740
Medications*	4.8 ± 2.7 (0–12)	1.2 ± 1.8	< 0.001
NSAIDs	89 (50.0)		
Acid suppression/antacid	54 (30.3)		
Medications with GI adverse effects**	129 (72.5)		

NSAIDs: non-steroidal anti-inflammatory drugs
* Data is expressed as mean ± standard deviation (range)
** Include medications such as NSAIDs, aspirin, steroids and the various disease modifying drugs used for treatment (i.e. methotraxate, azathioprine, sulphasalazine, cyclophosphamide, cyclosporine, mycophenolate mefotil and hydroxychloroquine).
‡ Other rheumatic diseases such as fibromyalgia, frozen shoulders, chronic juvenile arthritis and anti-phospholipid syndrome.

Darussalam) were invited to participate in a questionnaire study. The purpose of the questionnaire study was explained to all patients. For patients who agreed to participate in the study (n = 178), verbal consent was obtained prior to the face-to-face interviews conducted in the rheumatology clinics (held on Tuesdays and Thursdays). Patients with recent illnesses or exacerbations of the rheumatic disorders within the last four weeks were excluded from the study.

The questionnaire evaluated general demographical data (age, gender, ethnicity, type and duration of rheumatic disorders and comorbid conditions), clinical GI symptoms (appetite, nausea, vomiting, dysphagia, odynophagia, early satiety, heartburn, dyspepsia, bloating, bowel habits and bleeding per rectum) experienced within the last twelve months, medications prescribed (particularly, acid suppression, antacid, NSAIDs and disease-modifying drugs such as methotrexate, sulphasalazine, azathioprine, cyclophosphamide, cyclosporine, mycophenolate mefotil and hydroxychloroquine), and use of supplemental medications (traditional remedies, over-the-counter medications including dietary supplements, use of complementary and alternative medications). Medications prescribed for these patients were counterchecked against their prescription cards. Enquires were also made regarding psychological and psychosomatic symptoms (headache, anxiety, insomnia, backache and depression). The questions were asked in three different languages (English, Malay and Chinese), depending on the ethnic backgrounds of the patients. These were done in the same format for all patients.

Due to the possibility of patients using various layman's terms to describe certain complaints, the presence of these complaints were ascertained by using the various terminologies for symptom description. Only the commonly-used terminologies were used, to avoid confusion and introducing error into the estimation. Types of complaints were also clarified by further description. The main complaints that have confusing terminologies are dyspepsia and heartburn. The other GI complaints have quite specific terminologies in the various languages. Dyspepsia can be described by at least four, and heartburn by at least three, commonly-used terminologies. These were used in the questionnaire. Dyspepsia is defined as any abdominal discomfort centred in the epigastrium that can be related to fasting, postprandial changes or no association. Ulcer-like and dysmotility-like complaints were grouped together as dyspepsia. Heartburn is considered present when patients complained of retrosternal burning feeling with or without regurgitation or sour taste in the mouth. Other complaints were enquired using standard terminology in the questionnaire. Similarly, various terminologies in the different languages that are commonly used in the local setting to describe anxiety disorders, insomnia and depression were used. Terminologies to describe headache and backache are specific. Symptom clustering was considered when there were more than two symptoms experienced within any

Table II. Comparison of GI symptoms among NSAIDs users and non-users in patients with rheumatic disorders.

Gastrointestinal symptoms	No. users (%) (n = 89)	No. non-users (%) (n = 89)	p-value
Reduced appetite	8 (9.1)	10 (11.2)	0.619
Nausea	21 (23.9)	15 (16.9)	0.247
Vomiting	12 (13.6)	7 (7.9)	0.215
Dysphagia	7 (8.0)	6 (6.7)	0.757
Odynophagia	6 (6.8)	3 (3.4)	0.297
Early satiety	27 (30.7)	22 (24.7)	0.375
Heartburn	12 (13.6)	15 (16.9)	0.552
Dyspepsia	45 (51.1)	33 (37.5)	0.069
Abdominal bloating	18 (20.5)	19 (21.3)	0.884
Irregular bowel habit	6 (6.8)	6 (6.8)	0.984
Abnormal stool	20 (22.7)	22 (24.7)	0.755
Loose stool	1 (1.1)	3 (3.4)	0.317
Hard stool	14 (15.9)	12 (13.5)	0.648
Bleeding per rectum	14 (15.9)	10 (11.4)	0.380

given time period.

A similar questionnaire was used to interview visitors (control subjects) to the various medical wards by a single investigator (VHC). Explanations of the study were given, and verbal consent was also obtained prior to the interviews. Recruitment of control subjects occurred on most days during the study period. Controls were randomly selected from this pool (approximately 2:1 ratio) based on their age (about 2–3 years younger or older than patients) and gender to match the rheumatic patients who had just been interviewed. In total, there were 359 controls randomly selected for the study. Controls that were not randomly selected were excluded from the study. Enquiries into previous upper GI endoscopy were also made and the results of the endoscopy were obtained from case note reviews. Records of indications, findings of endoscopy and *Helicobacter pylori (H. pylori)* status were retrieved from case notes. Data was coded and entered into the Statistical Package for Social Sciences version 10.0 (SPSS Inc, Chicago, IL, USA) for analysis. The Student *t*-test, Fischer's exact test and χ^2 test were used, where appropriate, for statistical analysis. Continuous data is presented as mean and standard deviation. The measure of association is quoted as odds-ratio (OR) with a 95% confidence interval (CI). Level of significance is taken at $p < 0.05$ (two-tailed).

RESULTS

The patients' demographics and comparisons to the controls are shown in Table I. There was no significant difference between the controls and patients, except for higher incidence of diabetes mellitus (DM) and smaller amount of medications used by the controls. 50 (28.1%) patients had previously undergone upper GI endoscopy. The main indications for endoscopy were dyspepsia, evaluation of anaemia and acute GI bleed. The overall prevalence of *H. pylori* infection was 35%. The findings were gastritis/duodenitis (n = 24, 48.0%), oesophagitis (n = 2, 4.0%), peptic ulcer disease (n = 7, 14.0%) and normal (n = 17, 34.0%). Of the seven patients with ulcer disease, four patients were on NSAIDs and six were already on acid suppressions therapy. Two patients presented with bleeding, one of whom did not have dyspepsia. Overall, three patients did not have any dyspepsia symptoms. Self-medication was reported in 37.6% (n = 67) of the patients. This was mostly done with food supplements, traditional remedies and over-the-counter analgesics.

Difficulty in bowel evacuation was reported by 41 (23.0%) patients, 20 (11.2%) of whom experienced pain during bowel evacuation. Manual evacuations of stool were reported by eight patients (4.5%). There were no differences between the various rheumatic conditions (RA/SLE and RA/others), except for heartburn which was significantly more common in SLE patients compared to the "Others" group ($p < 0.05$, OR 3.5, 95% CI 1.2–10.6). Similarly, there was no difference in the prevalence of psychological and psychosomatic symptoms among the various groups of rheumatic conditions.

89 (50%) patients were using NSAIDs intermittently. There was no significant difference between users and non-users of NSAIDs, except for a prevalence of dyspepsia in NSAIDs users ($p = 0.069$, OR 1.7, 95% CI 1.0–3.2). Significantly more patients without dyspepsia were using gastro-protection medications (Table II). 129 (72.5%) patients were using medications associated with GI adverse effects. Users experienced significantly higher rates of early satiety ($p < 0.05$, OR 3.5, 95% CI 1.4–8.9) and dyspepsia ($p < 0.05$, OR 2.1, 95% CI 1.2–4.3). Patients on these medications had decreased passage of loose stool ($p < 0.05$, OR 0.12, 95% CI 0.1–1.2). The comparisons are

Table III. Impacts of the overall medication use (inclusive of NSAIDs) and GI symptoms among patients with rheumatic disorders.

Gastrointestinal symptoms	No. users (%) (n = 129)	No. non-users (%) (n = 49)	p-value
Reduced appetite	12 (9.3)	6 (12.5)	0.531
Nausea	29 (22.5)	7 (14.5)	0.246
Vomiting	16 (12.4)	3 (6.3)	0.240
Dysphagia	11 (8.5)	2 (4.2)	0.323
Odynophagia	8 (6.2)	1 (2.1)	0.268
Early satiety	43 (33.3)	6 (12.5)	0.006
Heartburn	22 (17.1)	5 (12.4)	0.275
Dyspepsia	63 (48.8)	15 (31.3)	0.033
Abdominal bloating	26 (20.2)	11 (22.9)	0.688
Irregular bowel habit	11 (8.5)	1 (2.1)	0.130
Abnormal stool	30 (23.3)	12 (25.0)	0.808
Loose stool	1 (0.8)	3 (6.3)	0.029
Hard stool	20 (15.5)	6 (12.5)	0.616
Bleeding per rectum	20 (15.5)	4 (8.5)	0.232

Includes all medications prescribed to patients that are known to cause adverse gastrointestinal effects (e.g. NSAIDs, steroid and disease-modifying drugs).

Table IV. Comparisons between patients with rheumatic conditions and controls.

	No. patients (%) (n = 178)	No. controls (%) (n = 359)	OR	95% CI	p-value
Gastrointestinal symptoms					
Reduced appetite	18 (10.2)	5 (1.4)	7.9	2.9–21.8	< 0.05
Nausea	36 (20.2)	36 (10.1)	2.3	1.4–3.7	< 0.05
Vomiting	19 (10.7)	4 (1.1)	10.6	3.6–31.7	< 0.05
Dysphagia	13 (7.3)	1 (0.3)	28.2	3.7–217	< 0.05
Odynophagia	9 (5.1)	3 (0.8)	6.3	1.7–23.6	< 0.05
Early satiety	49 (27.5)	43 (12.0)	2.8	1.8–4.4	< 0.05
Heartburn	27 (15.2)	34 (9.5)	1.7	1.0–2.9	0.05
Dyspepsia	79 (44.6)	73 (20.3)	3.1	2.1–4.7	< 0.05
Abdominal bloating	37 (20.8)	42 (11.7)	2.0	1.2–3.2	< 0.05
Irregular bowel habit	12 (6.7)	12 (3.3)	2.1	0.9–4.8	0.07
Abnormal stool	42 (23.6)	47 (13.1)	2.1	1.3–3.3	< 0.05
Loose stool	16 (9.0)	28 (7.8)	1.2	0.6–2.2	ns
Hard stool	38 (21.3)	35 (9.7)	2.5	1.5–4.1	< 0.05
Bleeding per rectum	25 (14.0)	22 (6.1)	2.5	1.4–4.6	< 0.05
Psychological and psychosomatic symptoms					
Headache	70 (39.3)	138 (38.4)	1.0	0.6–1.7	ns
Insomnia	36 (20.2)	51 (14.2)	1.5	0.8–2.8	ns
Anxiety	28 (15.7)	29 (8.1)	2.1	1.1–4.2	< 0.05
Backache	74 (41.6)	78 (21.7)	2.6	1.6–4.2	< 0.05
Depression	8 (4.5)	6 (1.7)	2.8	0.8–10.0	ns

shown in Table III.

Patients experienced significantly more GI symptoms compared to controls, except for irregular bowel habits. This was marginally non-significant. In addition, they experienced more psychological and psychosomatic symptoms of anxiety ($p < 0.05$, OR 2.1, 95% CI 1.1–4.2) and backache ($p < 0.05$, OR 2.6, 95% CI 1.6–4.2). However, there were no differences in headache, insomnia and depression. The comparison is shown in Table IV. At least 79.9% of patients experienced at least one GI symptom compared to controls (40.1%, $p < 0.001$). Similarly, symptom clustering was more common in patients with rheumatic disorders (29.9% vs. 10.3%, $p < 0.001$).

DISCUSSION

Our results showed that GI symptoms are significantly more common in patients with rheumatic disorders compared to the general population, specifically visitors to the various medical wards in our local setting. This

is despite our controls having a significantly higher prevalence of DM. However, they were taking fewer medications. This is in agreement with many reports showing higher prevalence of GI symptoms in patients with rheumatic disorders.[1,13-15] Dyspepsia is particularly common in our patients. Almost half of the patients experienced dyspepsia at some point within the last 12 months. This is also reflected by the high usage of acid suppression medication and antacid among our patients. Similarly, other GI symptoms were also common. It is also important to know that multiple symptoms or symptom clustering are also very common. At least 29% of all patients had symptom clustering and almost 80% had at least one symptom. This is important as management may need to overlap, particularly if symptoms were both upper and lower GI in aetiology. This may have a significant impact on the quality of life of these patients.[12]

Studies have shown that prevalences of psychosomatic and psychological complaints are high among patients with chronic disorders other than rheumatic diseases.[2,16-18] The current study showed that our patients experienced significantly more anxiety and backache. Symptoms of backache in this group of patients may be a reflection of their underlying rheumatic disorders and not an indication of underlying psychosomatic disorders. Nevertheless, our patients did report higher prevalence of the other psychosomatic complaints, although these did not reach statistical significance. The discrepancy of our findings may be explained by the cultural background and health-seeking behaviour of our patients. These will require further studies to assess these possible connections.

There were no significant differences between the various rheumatic disorders, indicating that as a group, they were all predisposed to GI complaints. Although there are no direct comparisons of prevalence of GI symptoms among the various rheumatic disorders, published literature showed that these patients have a higher prevalence compared to the general population.[1,3,13-15] This knowledge is important as these patients are likely to require long-term therapy and compliance may be an issue. Like other chronic disorders, patients with rheumatic disorders have a reduced quality of life.[8,9] This may reduce patients' compliance with management. Therefore, timely management of even minor GI symptoms is important and can improve patients' quality of life, in addition to improving compliance with treatment. High prevalence of self-medication, as in our patients (37.5%), is also a reflection of the problem with chronic medical disorders. Patients with chronic disorders have been shown to be more likely to use complementary or alternative medication.[19,20] Self-medication may cause underlying GI symptoms and there is potential for adverse drug interactions.

Medications used to manage rheumatic disorders are well known to be associated with adverse GI symptoms.[1,5-7,21] These can range from minor to life-threatening events, such as ulceration, bleeding and perforations. Use of NSAIDs has been commonly associated with increased GI symptoms, particularly dyspepsia. Long-term users of NSAIDs have been shown in endoscopic studies to develop endoscopic mucosal injury in 50%–75%, with a five- to 15-fold increase in risk of developing gastroduodenal ulcerations (10%–37%) compared to the general healthy population.[22-24] It must be noted that the presence of mucosal injuries do not necessarily indicate presence of symptoms. Up to 58% of patients on long-term NSAIDs, without dyspepsia, experience a life-threatening complication as the first manifestation of GI adverse events.[25] 49% of our NSAIDs users did not experience any dyspepsia. In agreement with a previous study,[2] our study did not show significant differences between NSAIDs users and non-users, although there were numerical differences in the GI symptom prevalence.

There are a few possible reasons that may account for our findings. First, the overall number of patients was small. Second, a large proportion of our patients were using acid suppression or antacid as co-prescriptions and these may reduce the symptoms felt. Third, use of NSAIDs is known to have analgesic effects, and thus patients' dyspepsia may actually be masked. There are numerous reports of first presentations of NSAIDs users to be complicated ulcer diseases without many symptoms prior to presentations. Finally, use of the NSAIDS for most patients was mainly with intermittent courses. Unfortunately, in our study, we did not enquire on the duration and frequency of NSAIDs use. Four of our seven patients who developed peptic ulcer were on NSAIDs. This was despite six patients already being on acid suppression therapy. Two of these patients developed potentially life-threatening GI bleeding. A strong association between NSAIDs use and acute upper GI emergency admission has been shown.[26] Hence, physicians treating rheumatology patients should be vigilant for silent adverse GI events.

There are a few limitations with our study. Our small sample size may not give an accurate prevalence of the GI symptoms among patients with rheumatic disorders. Our mixture of patients may affect the results. Certain rheumatic conditions, such as scleroderma, are known to have higher prevalence of GI complaints than others.[1,14] Due to the small number of certain groups of patients, we were not able make any direct comparisons and instead compared them as a group. Comparisons between the various groups did not show significant differences.

Results from a single centre may not be generalised to other geographical locations; however, our results are comparable to published findings. Furthermore, there are many cultural and ethnic similarities in the Southeast Asian region. In conclusion, our study showed that GI symptoms are common among our patients with rheumatic disorders. Furthermore, our results showed that use of NSAIDs does not significantly increase the prevalence of GI complaints, suggesting that the underlying conditions themselves predispose patients to GI complaints. Overall, the use of multiple medications with adverse GI effects increases certain GI symptoms. Knowing the prevalence of GI symptoms is helpful in the clinical management of these patients with chronic medical disorders.

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