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Inflammatory Bowel Disease in Systemic Lupus Erythematosus Patients: A Meta-analysis

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease with features of multisystem involvement, relapsing and remitting course. Gastrointestinal system affection is common in Lupus patients but coexistence of the inflammatory bowel disease (IBD) and SLE is rare. The coexistence of signs and symptoms of both diseases in the same patient represents a diagnostic challenge. Diagnoses of both diseases is difficult as both may share the same gastrointestinal features. Some of the therapies used in IBD may induce lupus. **Aim of the study:** To detect the presence of IBD in SLE patients. **Methods:** Only19 studies investigating the coexistence of IBD in SLE patients were published from January 2000 to March 2017 searching the Medline, PubMed, Ovid, Trip and Cochrane database. We excluded 16 studies (case reports) as they lacked the inclusion criteria for the meta-analysis. Only three studies were included in this systematic review. The prevalence/frequency and its 95% CI are included or estimated whenever possible. **Results:** Most of the studies that detected a statistical association between both diseases were case series and case control study that revealed the presence of IBD in some lupus patients. Criteria for the diagnosis of SLE cases and IBD cases were clearly explained in these studies, and same stratified results according to gender. The pooled results of all cases with SLE were (total 6665) showed that, there were IBD cases (total 79) associated with lupus with a frequency (95% CI) is 1.19% (0.96-1.48). **Conclusion:** The prevalence of IBD in SLE patients is rare however, the coexistence of both diseases in the same patient could occur.

Keywords: Systemic lupus erythematosus, inflammatory bowel disease, Crohn's disease, Ulcerative colitis, coexistence, gastrointestinal symptoms.

INTRODUCTION

Autoimmune diseases tend to be viewed as distinct entities, however clustering, coexistences and overlaps of autoimmune diseases can occur as the association between Inflammatory bowel disease (IBD) and Systemic lupus erythematosus (SLE). The coexistence of both diseases is rare and the presence of clinical features of both entities in a patient represents a diagnostic challenge [(1)]. SLE is a systemic chronic autoimmune disease with variable clinical presentations and immunological signs and symptoms. It mainly affects women during childbearing age [(2)]. SLE has a highly variable prognosis with benign to rapidly progressive and even fatal with remitting and relapsing course. The survival rate is higher, and the course is milder in persons with isolated skin and musculoskeletal affection than those with renal and CNS affection [(3)]. IBD is a chronic recurrent disease that includes mainly two phenotypes, Crohn's disease (CD) and ulcerative colitis (UC) which lacks an autoimmune serological marker yet, they can be present with several examples of autoimmunity [(4)]. UC that causes ulcers in the lining mucosa of colon and rectum, while CD characterized by spreading inflammation deep into the affected tissues. Both usually produce severe diarrhea, abdominal pain, fatigue and weight loss [(5)]. IBD and SLE are systemic diseases caused by abnormal immune responses, in a genetically susceptible individual due to environmental triggers [(6)]. SLE association with IBD is considered mainly if GIT symptoms develop in a well-controlled SLE patient; in such cases a colonoscopy with biopsy should be performed [(7)]. Specific alleles can confer susceptibility to both diseases so, it is possible that SLE and IBD share immunological or genetic defects. Three loci, the CARD15/NOD2 gene, the disc's large homolog 5 gene (DLG5) and the IBD5 locus on 5q31 (IBD5), have been validated as giving susceptibility to IBD [(8)].

Crohn's disease and lupus:

The occurrence of both diseases together is rare. Only few case reports are detected and common genetic susceptibility between SLE and CD is controversial as there is no evidence that the Crohn's disease-associated mutations on CARD15 contributed to SLE susceptibility, but differentiation of CD from SLE gastrointestinal symptoms is difficult, as CD may show clinical signs and symptoms similar to SLE. So, the correct diagnosis has important treatment and prognostic implications [(9)].

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Ulcerative colitis and Lupus:

The association between UC and SLE is also rare as the incidence of UC in SLE was 0.4%. the endoscopic features in SLE patient's colon were different from those of UC, as in SLE multiple "punched out" ulcers with pale mucosa were seen which is not in UC but sometimes the endoscopic findings are the same in both diseases [(1)].

Clinical features:

The coexistence of the IBD and SLE is rare. The coexistence of signs and symptoms of both diseases in the same patient represents a diagnostic challenge [(10)]. IBD can occur as GIT feature of SLE as patient with SLE may present with mesenteric vasculitis with symptoms like diarrhea, abdominal pain, and bowel infarction. Also, IBD can cause joint affection and skin lesions mainly CD. Identical imaging and endoscopic finding may occur like segmental thickening of bowel wall, enhancement of mesenteric fat, diminished vascular pattern, friability and diffuse or focal ulcerations. Furthermore, ANA and anti-ds DNA antibodies which are typical for SLE, may be present in up to 53% of CD patients and 35% in those under anti-TNF treatment [(11)].

Diagnosis*:*

SLE was diagnosed before IBD in 70% of the cases and usually at an earlier age than patients with SLE alone. At the time of diagnosis of IBD, SLE disease was not active and both diseases had a benign course. Patients with concomitant IBD and SLE tended to have less photosensitivity, less arthritis, and less serositis than patients with SLE alone and none of them had neurological or renal involvement [(8)].

Treatment:

Majority of cases had a good response to treatment with steroids associated with azathioprine or hydroxychloroquine [(8)]. While sulfasalazine (5-ASA) used in IBD treatment may induce lupus like syndrome with serositis, joint affection, skin rash and positivity of anti-dsDNA and anti-histones and anti-ANA antibodies [(1)].

Prognosis:

Prognosis of SLE-related IBD is generally good with remission rate not differ from patients with isolated SLE as many cases achieved remission with favorable prognoses following development of CD or successful treatment, while with UC, there was no subsequent relapse of SLE and serious organ involvement was rarely seen. There are no clear differentiating criteria between IBD and SLE, moreover the presence or absence of histological vasculitis is useful for differentiating between the gastrointestinal complications of SLE and concurrent IBD, despite difficulties in differentiation, endoscopic and histological findings remain the standard in their diagnosis [(6)].

MATERIALS AND METHODS

For the current systematic review, we collected all available published studies in the literature that discuss presence of IBD in lupus patients from January 2000 to March 2017 using key words Lupus, IBD, coexistence, Crohn's disease, Ulcerative colitis that is searched in Medline, PubMed, TRIP Database and OVID. Studies were identified using the following search strategy: Case series* OR case report* OR case control* OR cohort* OR observational studies. The included studies were in all languages. Prevalence/Frequency and its 95% CI that is included or estimated whenever possible.

Finally, we localized 19 published studies. One case report study in 2001 by ***Toulemonde et al.*** [(12)] about association of disseminated lupus erythematosus with CD. In 2004, two case reports were reported by ***Principi et al.*** [(13)] and ***Burson et al.*** [(14)] respectively about concomitant lupus nephritis and CD and lupus patient developed CD later on. In 2006, ***Nieradko-Iwanicka et al.*** [(15)] described two case reports with SLE who develop lupus nephritis and concomitant UC. Also, ***Nitzan et al.*** [(16)] published ten cases, one case report and nine in the literature from them six cases with concomitant SLE and UC and four cases with CD. ***De Jager et al.*** [(17)] described a multi-center case series study in 2006 also about genetic association between SLE and IBD and found that 21 cases developed IBD from 1305 case with SLE. In 2008 ***Lee et al.*** [(18)] reported one SLE case with rectal bleeding who was identified as UC; she was diagnosed as SLE prior to UC.

Also, ***Su et al.*** [(19)] and ***Bourikas et al.*** [(20)] described one SLE case with CD who developed massive intestinal bleeding and one SLE case developed UC respectively. In 2009 one case report was found by ***Medeiros et al.*** [(21)] about SLE and UC, while ***Tian et al.*** [(22)] in 2010 reported about 27 SLE cases who developed UC. In 2012, ***Konstantinos et al.*** [(1)] described five case reports, one case with UC and four cases with CD and ***Roudrigouz et al.*** [(7)] published one SLE case with CD, and ***Yamashita et al.*** [(23)] described one SLE case with CD. In 2013,

Siwiec et al. [24] reported a case series study of 342 SLE cases from them five cases developed UC during the disease course. ***Michalopoulos et al.*** [11] in 2015 found one case report with CD, and in 2016 ***Alves et al.*** [8] published five SLE cases with UC and ***Shor et al.*** [4] described a case control study from the medical records of a large medical Clait health services in Tel Aviv, Israel, from 5018 SLE cases they found 53 IBD cases (20 UC and 33 CD). And lastly in 2017, ***Mansour et al.*** [25] published one case report who was diagnosed as SLE and developed UC later on.

The inclusion criteria for considering studies for the meta-analysis:

Case control or case series studies that have frequency and/or odds ratio (95% CI), or sufficient data to calculate them including SLE patients, any age, gender and disease severity and there is presence or prevalence of IBD in lupus patients.

Data extraction:

Data was extracted from identified studies by first reviewer (A.I.A) and cross checked by second reviewer (H.E.M).

The identified studies that detect UC in SLE patients:

They were 12 studies from the total 19 studies. these studies were the case control study in 2016 [4] by ***shor et al.*** with total number of SLE cases was 5018 from them 20 UC cases were detected with frequency (95% CI) of0.4(0.26 – 0.62), and the case series study in 2013 [21], from 342 SLE cases only 5 UC cases were reported with frequency (95% CI) of 1.46 (0.62 – 3.37). And 21 UC cases were reported in 2006 from the multi-center case series study [17] from 1305 SLE cases with frequency (95% CI) of 1.61(1.06 – 2.45). The remainder were case report studies in 2006, two case reports [15] by ***Nieradko-Iwanicka et al.*** and 6 case report studies by ***Nitzan et al.*** [16] , one case report in 2008 by ***Lee et al.*** [18], one case by ***Bourikas et al.*** [20], one case report in 2009 by ***Medeiros et al.*** [21], 27 cases in 2010 by ***Tian et al.*** [22], one case by ***Katsanos et al.*** [1] in 2012 and 5 cases in 2016 by ***Alves et al.*** [8] and one case in 2017 by ***Mansour et al.*** [25]. The total identified SLE cases were 6718 and the total UC cases were 91 with frequency (95% CI) of 1.35 (1.1-1.606).

The identified studies that detect CD in SLE patients:

They were 11 studies from the total 19 published studies. These studies were the case control study in 2016 by ***Shor et al.*** [4] with total number of SLE cases was 5018 from them 33 CD cases were detected with frequency (95% CI) of 0.66 (0.47 – 0.92), and 21 CD cases were reported in 2006 by ***De jager et al.*** [17] with frequency (95% CI) of 1.6 (1.06-2.45). The remainder were one case report by ***Toulemonde et al.*** [12] in 2001, one case report by ***Burson et al.*** [14] in 2004, one case by ***Principi et al.*** [13] in 2004, four cases by ***Nitzan et al.*** in 2006 [16], four cases by ***Katsanos et al.*** [1] in 2012 and one case by ***Rodríguez et al.*** in 2012 [7]. Also, one case by ***Yamashita et al.*** in 2012 [23] and one case in 2015 by ***Michalopoulos et al.*** [11]. The total identified SLE cases were 6345 and the total number of CD cases were 69 with frequency (95% CI) of 1.09 (0.86-1.38).

The exclusion criteria for considering studies that were not included for the meta-analysis:

Case report and review of literature studies that haven't frequency or accurate relation between both diseases and lacked the inclusion criteria. The excluded studies that were excluded from the meta-analysis were 16 studies from total 19 published studies.

RESULTS

The overall studies were 19 studies with only 3 studies that fulfilled the inclusion criteria for the meta-analysis in this review (tables1, 2 and 3). The studies detected the statistical relation between both diseases were case series and case control study that revealed the presence of IBD in some lupus patients. Criteria for the diagnosis of SLE cases and IBD cases were explained in the3 studies, same stratified for gender. In addition, ORs and 95% CI of UC and CD in lupus patients were reported.

Table (1): Meta-analysis of the three studies that detect the presence of UC in SLE patients.

Authors	Year	Type of the study	No. of SLE Patients:	No. of UC Patients:	Frequency (95% CI)
Shor et al.	2016	Case control	5018	20	0.4 (0.26 – 0.62)
Siwiec et al.	2013	Case series	342	5	1.46 (0.62 – 3.37)
De Jager et al.	2006	Multi center case series	1305	21	1.61 (1.06 – 2.45)
Pooled results	6665			46	0.69 (0.25 – 0.92)

In the case control study, the number of SLE cases were 5018 and the number of UC cases were 20 with frequency of 0.4%, 95% CI (0.26-0.62). In the case series study, the number of SLE patients were 342 and 1305 respectively and the

number of UC patients were 5 and 21 respectively with frequency (95% CI) of 1.46(0.62-3.37) and 1.61 (1.06-2.45) respectively. The pooled result of the total number of SLE cases were 6665 and total number of UC patients were 46 with frequency (95% CI) of 0.69 (0.25-0.92).

Table (2): Meta-analysis of 2 studies from the 3 studies with the inclusion criteria that detect CD in SLE patients.

Authors	Year	Type of the study	No. of SLE	No. of CD	Frequency (95% CI)
Shor et al.	2016	Case control	5018	33	0.66 (0.47 - 0.92)
De Jager et al.	2006	Multi center case series	1305	21	1.61 (1.06 - 2.45)
Pooled results	6323			54	0.85 (0.65 - 1.11)

Table (3): Meta-analysis of the all 3 studies with inclusion criteria that detect total number of IBD in SLE patients.

Authors	Year	Type of the study	No. of SLE	No. of IBD	Frequency (95% CI)
Shor et al.	2016	Case control	5018	53	1.06 (0.81 - 1.38)
Siwiec et al.	2013	Case series	342	5	1.46 (0.62 - 3.37)
De Jager et al.	2006	Multi center case series	1305	21	1.6 (1.06 - 2.45)
Pooled results	6665			79	1.19 (0.96 - 1.48)

The studies were case control and case series studies, as total number of SLE cases were 6665 and total number of IBD cases were 79 with frequency (95% CI) of 1.19(0.96-1.48).

DISCUSSION

Considerable overlaps do occur between various autoimmune rheumatic diseases, either from the beginning of the illness or at any point during the disease course. This may pose a considerable diagnostic challenge [(26)]. This can occur as in the association between IBD and SLE, however the coexistence of both diseases is rare [(1)]. We have found that only 19 studies that have reported the association of IBD with SLE cases (either UC or CD) at any point of course of the disease. Some cases were initially having IBD then developed SLE and others are the reverse &in some cases both diseases occur simultaneously, from these 19 studies only 3 studies were included that have the inclusion criteria for the meta-analysis.

These studies were the case control study that was done to search for proper coexistence of SLE and IBD utilizing data collected from the medical data base of a large Clait Health Services in Tel-Aviv, Israel, in this study the association between CD and SLE was observed as the proportion of CD among lupus patients was higher than the proportions in the controls (0.69 and 0.3 respectively). Also, the proportion of UC in Lupus patients was higher than the control (0.4 and 0.2 respectively) [(4)].

The second study was case series study about coexistence of IBD in various rheumatic diseases, among 342 patients with SLE from them only 5 UC cases were reported. The proportion of IBD in SLE patients was higher than other various rheumatic diseases with frequency (95% CI) of 1.46% (0.62-3.37) as, the coexistence of IBD with a rheumatic disease was found in 0.38% of all rheumatic patients [(24)].

In addition, in a multi-center case series study, there was a controversial data concerning the genetic association between IBD and SLE and multiple sclerosis (MS), as IBD risk alleles appear to have an effect in SLE. Specifically, the CARD15 allele appears to have a strong effect on risk to SLE, whereas the IBD5haplotype may potentially have a weak effect as among 1305 patients with lupus, 21 IBD case carried the CARD15 allele with frequency (95% CI) of 1.6(0.80–1.44) [(17)].

The pooled results of the all 3 studies detected that the proportion of IBD in lupus patients is higher than that of general populations with frequency (95% CI) of 1.19% (0.96 -1.48).

CONCLUSION

From this study we concluded that lupus patients have higher risk to develop IBD later on during the disease course more than general population by frequency of about 1.19%.

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