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REVIEW ARTICLE

Bariatric Surgery and Rheumatic Diseases: A Literature Review

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Abstract: ***Background*:** Obesity is a debilitating growing condition and represents a challenge for every surgeon. It is associated with the activation of the inflammatory pathway and this may have a negative impact on the natural history of some rheumatic diseases. Bariatric surgery, reducing obesity, could bring to a minor activation of the well-known inflammatory pathway with improvement of these diseases. The aim of this review is to investigate the role of weight loss, achieved through bariatric surgery, in rheumatic diseases.

***Materials and Methods*:** A systematic review of literature was undertaken to evaluate weight loss subsequent to bariatric surgery in obese patients suffering from some rheumatic diseases (Rheumatoid Arthritis, Psoriasis, Psoriatic Arthritis, Fibromyalgia, Osteoarthritis, Systemic Lupus Erythematous). Three major databases (PUBMED, EMBASE and WEB OF SCIENCE) were searched.

***Results*:** Three-hundred studies were identified. After screening of titles, abstracts and inclusion criteria sixteen articles were included. Of the selected articles, seven were reviews, five were case reports, one was a clinical report, one was a retrospective study, one was a cohort study and one was an author manuscript.

***Conclusion*:** Weight loss, obtained through bariatric surgery, seems to reduce serum inflammatory markers as a consequence of the inflammatory pathway reduction and this is connected with both the improvement of some rheumatic diseases and reduction in the use of medicaments (steroids and immunosuppressors).

Keywords: Bariatric surgery, metabolic disturbances, obesity, rheumatic diseases, rheumatic manifestations, weight loss.

1. INTRODUCTION

Obesity is defined as a body mass index (BMI) greater than 30Kg/m2 [1]. According to the World Health Organization (WHO) Global Database on Body Mass Index (BMI), 39% of adults were overweight and 13% were obese in 2014 [2]. Obesity causes a systemic inflammatory state with an increase of serum inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), estrogen status and adipokines and it is associated with many chronic diseases (arterial hypertension, coronary heart disease, cancer), immune dysfunction [3] and elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alfa (TNF-alfa) which stimulate hepatocytes to produce acute phase proteins.

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A strict connection between rheumatic diseases and metabolic disturbances, such as diabetes, is already well-known in the literature [4-6]. Furthermore, obesity has been associated with an increased risk of rheumatoid arthritis (RA) onset because of its association with pro-inflammatory pathways activation. In fact the activation of the nuclear factor kappa-beta (NF-κβ) in combination with inactive lifestyle can bring to a condition known as rheumatoid cachexia [7].

Adipokines, bioactive molecules found in adipocytes, are also implicated in RA pathogenesis inducing the production of VEGF, MMP, IL-1, IL-6 and several pro-inflammatory cytokines [8]. Nowadays, more than 50 adipokines have been identified [9] and the circulating levels of one of them, a 244-residue protein called Adiponectin, decrease in an obesity status and increase subsequently to a weight loss [8].

Several studies have highlighted a link between weight loss and pain severity in many chronic pain syndromes. In this respect, an association between obesity and a higher incidence of fibromyalgia (FM) due to the high estrogen

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levels has been also reported [10, 11]. Moreover, obesity is an important risk factor for osteoarthritis (OA) due to the degradation of cartilage matrix, inappropriate deposition of subchondral bone matrix and increased local proinflammatory cytokines [12, 13]. Coggon *et al*. reported a significant increased risk (odds ratios 13.6) of developing osteoarthritis in individuals with BMI over 36Kg/m2 compared to controls [14].

Psoriasis (P), one of the most studied chronic inflammatory skin disease, is common in overweight individuals with an association not only with the severity of the disease but also with the lack of response to biological agents [15]. Recent publications have reported complete remission of severe P following bariatric surgery [16, 17].

Obesity is also common among systemic lupus erythematous (SLE) patients [18]. Sometimes, weight loss is associated to the remission of chronic diseases such as associated to the remission of chronic diseases such as diabetes mellitus, arterial hypertension and to the reduction of serum inflammatory markers in the obese [19-22].

Indications for bariatric surgery were for the first time formalized in 1991 [23] and the first official attempt in favor of its use in patients with type 2 DM and mild obesity occurred in 2011 [24].

Surgical procedures for bariatric surgery can be restrictive (laparoscopic adjustable gastric banding - LAGB and laparoscopic sleeve gastrectomy - LSG) or malabsorptive (roux-en-Y gastric bypass - RYGB and biliopancreatic diversion with or without duodenal switch - BPDDS) [25]. Bariatric surgery represents one of the most effective therapeutic modalities to obtain weight loss in obese patients [26, 27]. However, the effects of substantial weight loss after surgical procedures on rheumatic diseases are not completely explored.

The aim of the present study was to elucidate the impact of bariatric surgery in patients who suffer from rheumatic diseases by reviewing the existing literature.

2. MATERIALS AND METHODS

2.1. Search Strategy for Identification of Studies

A comprehensive search of three major databases (PUBMED, EMBASE, WEB OF SCIENCE) using broad search terms (bariatric surgery, obesity, weight loss, obese patients, systemic autoimmune disease, connective tissue diseases, metabolic disturbances, rheumatoid arthritis, fibromyalgia syndrome, osteoarthrosis, osteoarthritis, psoriasis, metabolic syndrome and psoriasis, psoriatic arthritis, systemic lupus erythematosus, type 2 diabetes, Bowel-associated dermatitis-arthritis syndrome, vasculitis, cryoglobulinemia, polyarthritis, purple skin rash, GLP-1) was completed. There was no restriction on the data of publication.

2.2. Study Selection

The articles resulting from the search of databases were screened by two reviewers independently (GG and GC). Only articles in the English language were considered for review. The inclusion criteria were: (1) patients aged 18 years or over; (2) patients with BMI above 25; (3) obese patients with concomitant rheumatic diseases submitted to bariatric surgery were included. Multiple publications involving the same set of patients were grouped together including only the most recent study. The cited references of the identified articles were also examined to identify additional relevant publications.

2.3. Assessment of Methodological Quality of Studies

The articles resulting from the search of databases were screened by two reviewers independently (GG and GC). Only articles in the English language were considered for review. The inclusion criteria were: (1) patients aged 18 years or over; (2) patients with BMI above 25; (3) obese patients with concomitant rheumatic diseases submitted to bariatric surgery were included. Multiple publications involving the same set of patients were grouped together including only the most recent study. The cited references of the identified articles were also examined to identify additional relevant publications.

3. RESULTS AND DISCUSSION

A total of 300 articles have been detected. After screening of titles, abstracts and inclusion criteria 16 articles assessing the connection between bariatric surgery and rheumatic diseases have been identified, as shown in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [29] (Fig. **1**).

Table **1** reports the details of each study. The number of patients ranged from 1 to 1203. Patients' age was >18 years. Subjects undergoing bariatric surgery had a BMI ranging from 25 to 56.9 Kg/m2. Patients who have been included in all studies received different kinds of bariatric surgeries: LRYGBP, RYGBP, LAGB, AGB, LSG, BPDDS, VBG, Jejunoileostomy and Ileocolostomy. All the analyzed patients were affected by rheumatic diseases such as: RA, OA, FM, ESL, P, PA, BADAS and vasculitis (Henoch-Schonlein purpura, cryoglobulinemia, purpuric skin rash).

The articles mentioned in our review underline the strict connection among bariatric surgery and several rheumatic diseases. Besides the improvement of the them, it is clear the drug use (steroid and immunosuppressant) reduction in obese patients who underwent bariatric surgery.

Sparks *et al*. [30] conducted a retrospective cohort study of 53 RA patients with a median BMI above 47.8 Kg/m2 who underwent bariatric surgery. Twelve months after the surgery, subjects lost on average 41 Kg (SD 17.3). RA disease activity showed a significant improvement during post-surgery controls ($p<0.001$). Patients showed a significant lower ESR, CRP and RA-related medication use compared to baseline ($p<0.05$). Interestingly, these effects were evident six months after bariatric surgery and persisted for years.

In a retrospective review including 16 patients with autoimmune disorders or chronic steroid use (SLE, Sarcoidosis, Renal Transplant, RA, ulcerative colitis, Grave's disease and celiac disease) [31], the authors demonstrated that the LAGB performed in RA immunosuppressed patients is attainable

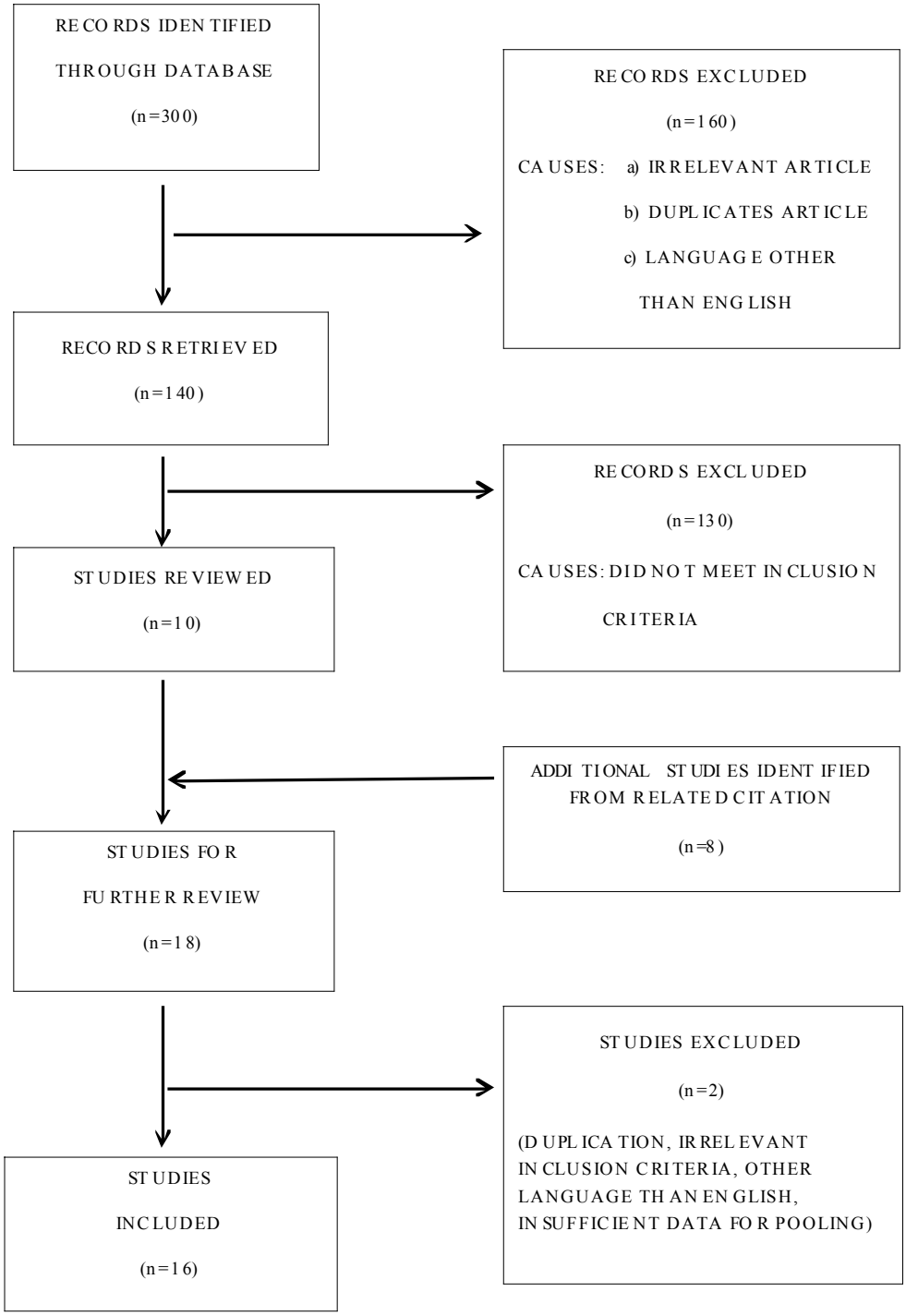

Fig. (1). PRISMA flow diagram.

and safe with no infectious complications. There is no definitive literature to determine the best choice of bariatric surgery for this population of obese patients. Postoperative absorption of medications, complications related to immunosuppressive medications, alteration of anatomy, and the effect that some of the autoimmune diseases may have on the motility of the esophagus, are all factors that need to be considered before the surgical approach choice.

Corcelles *et al*. [18] described 31 SLE obese patients who underwent bariatric surgery. Of these, 24 patients (77.4%) were taking immunosuppressive medications for SLE. Multivariate analysis identified immunosuppressive therapy to be significantly associated with postoperative complications (p=0.05). Three years after surgery, 13 patients (42%) showed a reduction in the number of immunosuppressive medications and 6 (19.3%) were completely off steroid intake.

Twenty-four percent of fibromyalgia patients are obese with a BMI higher than 30 [32] and it has been shown that a 5% body weight loss is related to mild improvement of

Table 1. Studies included.

Authors/ Year/ Study Design	Aim	Number of Patients	Mean Age (years)	Preoperative Mean BMI (Kg/m^2)	Rheumatic Disease (RD)	Bariatric Surgery
Corcelles *et al.*/2014 Review Surg Obes Rel Dis [18]	*Postoperative outcames among SLE patients undergoing bariatric surgery*	31	52.8±9.4	44.3±9	SLE	RYGBP LSG LAGB
Sparks *et al.*/2016 Retrospective cohort study Arth Care Res [30]	*Investigated the effect of weight loss after bariatric surgery among patients with rheumatoid arthritis*	53	47.9	47.8	RA	RYGBP LAGB LSG
Del Prado *et al.*/2014 Review Obes Surg [31]	*Experience with placament of LAGB in patients with autoimmune disease or chronic steroid use*	16	46.5	46.8	RA	LAGB
Vincent *et al.*/2012 Review Ost Supp [35]	*Bariatric surgery associated with lower joint pain and increased physical function*	NA	NA	NA	OA	LAGB LSG VBG
Saber *et al.*/2008 Review Obes Surg [34]	*Incidental finding of improvement of fibromyalgia following laparoscopic Roux-en-Y gastric bypass*	10	47.2	49.4	FM	LRYGBP
Gill *et al.*/2011 Review Obes Rev [38]	*Bariatric surgery may benefit obese patients with hip or knee osteoarthritis*	14 to 1203	<18	<30	OA	LAGB RYGBP LSG BPDDS
Egeberg *et al.*/2016 Population based cohort study JAMA Surg [41]	*Incidence and prognosis of P and PA in patients undergoing bariatric surgery*	12.364+1071	41	NA	P PA	RYGBP LAGB
Sako *et al.*/2014 Review J Am Acad Dermatol [42]	*Effect of bariatric surgery on psoriasis Severity*	50	NA	>38.7	P	RYGB Jejunoileostomy Ileocolostomy AGB
Farias *et al.* 2012 Clinical Report Obes Surg [43]	*Impact on QoL of patients with P who underwent bariatric surgery Remission of P after RYGB*	10	41.2	25 to >39.9	P	LRYGB LSG

(Table 1) contd.....

Authors/ Year/ Study Design	***Aim***	**Number of Patients**	**Mean Age (years)**	**Preoperative Mean BMI (Kg/m2)**	**Rheumatic Disease (RD)**	**Bariatric Surgery**
Hossler *et al*. 2013 Author manuscript Br J Dermatol [44]	*Effects of weight loss surgery on the severity of psoriasis*	34	50	48.5	PA	RYGB AGB NA (n1)
Halawi *et al*. 2013 Review Obes Surg [46]	*Effects of bariatric surgery on the skin*	NA	NA	NA	BADAS P V	RYGB
Faurschou *et al*. 2011 Case reports Med Hypo [53]	*Involvement of GLP-1 (glucagon like peptide-1) in the remission of P observed after bariatric surgery*	NA	NA	NA	P	RYGB
Higa Sansone *et al*./2004 Case Report Obes Surg [54]	*Outcame of a 55 year old male with P underwent L-RYGB*	1	55	41	P	LRYGBP
Ettinger *et al*. 2006 Case report Obes Surg [55]	*Improvement of P after bariatric surgery*	1	55	46.9	P	RYGB
Pérez Pèrez *et al*. 2008 Case report View Derm [56]	*Improvement of P after bariatric surgery*	1	52	56.9	P	NA
Hossler *et al*. 2010 Case reports J Am Acad Dermatol [57]	*Improvement of PA after bariatric surgery*	2	34-42	52-55	P	*RYGB*

fibromyalgia symptoms [33]. In a series of 194 patients undergone LRYGBP with a follow-up of 24.5 months, 5.15% (10 patients) had fibromyalgia. In these patients, postoperative decrease of BMI was associated with a significant improvement of the median pain score and median points of tenderness (p=0.001) [34].

The relationship between obesity and the development of osteoarthritis has already been described [35] with a pivotal role of leptin and adiponectin as well as for the psychosomatic component [36, 37]. Coggon *et al*. [14] reported a significantly increased risk for the development of knee osteoarthritis in individuals with BMI over 36 kg/m2 compared to the controls [11]. According to Gill *et al*., bariatric surgery may benefit obese patients with hip or knee osteoarthritis. In this systematic review, they have analyzed a total of six studies for qualitative analysis and have concluded that bariatric surgery may lead to the improvement of hip and knee pain and function in obese patients with osteoarthritis. Unfortunately, of these six studies five were case series and one was a controlled study. Therefore, further prospective studies are needed to confirm this trend [38]. Bariatric surgery can elicit massive weight loss when postsurgical instructions are followed. Joint pain can be attenuated or abolished in morbidly obese patients with hip, knee, ankle, foot, spine, neck, shoulder, elbow, wrist, and hand pain [35].

The association between psoriasis and obesity is the subject of a recent evidence-based review [39]. There is indirect evidence that the immunological and metabolic alterations

associated with obesity may be linked with the pathophysiology of psoriasis [40]. Macrophages in adipose tissue produce TNF-alfa, IL-1, IL-6, IL-17 and IFN-γ. These adipocytokines, as well as leptin, are recruited and stimulated in obesity and may have an autocrine and paracrine effect on nearby skin. Leptin levels have been shown to correlate with psoriasis severity. There is increasing evidence that progressive weight loss can produce significant improvements in the severity of psoriasis [40].

Egeberg *et al*. [41] identified 12,364 patients undergoing gastric bypass and 1,071 patients undergoing gastric banding. The outcomes were the incidence of P or PA, or progression to severe P. in patients who undergone gastric bypass there was a significantly decreased risk of P (adjusted HR, 0.52; 95% CI, 0.33-0.81), severe P (adjusted HR, 0.44; 95% CI, 0.23-0.86), and PA (adjusted HR, 0.29; 95% CI, 0.12-0.71). Interestingly, there were no significant differences in risk of P (adjusted HR, 1.23; 95% CI, 0.40-3.75), severe P (adjusted HR, 1.18; 95% CI, 0.12-11.48), or PA (adjusted HR, 0.53; 95% CI, 0.08-3.56), after gastric banding.

A review performed by Sako *et al*. [42], offers an overview of the effect of bariatric surgery on P severity and discusses its role in P management. Authors concluded that bariatric surgery procedures, in particular the RYGB, may be an effective option or obese patients with refractory P but more evidence is needed before definitive conclusions can be drawn about the effect of bariatric surgery on P.

Farias *et al.* [43] reviewed eight patients that underwent L-RYGB and two underwent L-SG (BMI 38.8 ± 5.2 kg/m). All patients were affected by P. They assessed surgical complications, weight progression and psoriasis-related outcomes. The Dermatology Life Quality Index was used retrospectively to assess life quality (QoL) before and after the operation. The QoL improved from 14.9 ± 6.8 before surgery to 5 ± 6.3 after surgery (p=0.005) and they concluded that bariatric surgery for positive metabolic, skin, and QoL results must to be taken in account as a useful adjuvant therapy for obese patients with P.

Hossler *et al.* [44] identified 104 patients with obesity and P underwent RYGB. A significant decrease in psoriasis treatment was noted after surgery (p=0.046). Age at the time of surgery was significantly associated with a change in psoriasis after surgery (p=0.039). It has been shown a consistent downgrade in psoriasis treatment and interestingly, all the men reported a non-statistically significant improvement (p=0.416). Those who worsened ended to be younger (mean age: 38.5 years).

Despite the improvement in the already described rheumatic diseases, some skin and autoimmune disorders, such as vasculitis (HSP), cryoglobulinemia, polyarthritis and purple skin rash are triggered by bariatric surgery [45] or may represent a complication of surgery itself, such as bowel-associated dermatitis-arthritis syndrome (BADAS) [46].

The role of hormones in the pathophysiological connection between obesity and rheumatic diseases is beyond any doubt. GLP-1 (glucagone like peptide-1), a 30-amino acid peptide hormone with incretin function produced in the intestinal epithelial endocrine L-cells and discovered in 1923 as a hyperglycemic substance present in pancreatic extracts [47] is essential for glycemic control and secreted in response to nutrients in the intestinal lumen [48]. GLP-1 receptor, a class 2 G protein-coupled receptor, has been found in cultured skin cells and is expressed in several region of the brain involved in the regulation of food intake [49]. It has been reported that GLP-1 inhibits chemokine induced CD4 positive lymphocyte migration *in vitro* through the inhibition of the PI3-kinase pathway [50], as well as anti-inflammatory actions of GLP-1 in adipocytes and mesenteric endothelium have been found [51, 52]. Levels of GLP-1 have been shown to increase up to 20 times after gastric bypass surgery [53]. Therefore, it seems possible that the rise in GLP-1 could be involved in the immediate improvement in psoriasis symptoms following RYGB.

CONCLUSION

Besides many metabolic, cardiovascular and neoplastic diseases, obesity is also associated with some rheumatic diseases. This literature review demonstrated that weight loss obtained through bariatric surgery seems to determine the improvement and, in some cases, the disappearance of these conditions. Furthermore, the bariatric surgery decreases the use of steroid and immunosuppressor drugs in patients who suffer from rheumatic diseases improving their quality of life. Nonetheless several complications after bariatic surgery have been described and the safety of this kind of surgery applied to patients afflicted with rheumatic diseases and who make use of steroid medicaments is still debated. Obviously prospective controlled studies are needed to elucidate these key points.

LIST OF ABBREVIATIONS

AGB	=	Adjustable gastric banding
BADAS	=	Bowel-associated dermatosis-arthritis syndrome
BPDDS	=	Biliopancreatic diversion with or without duodenal switch
FM	=	Fibromyalgia
LAGB	=	Laparoscopic adjustable gastric banding
LRYGBP	=	Laparoscopic roux-en-Y gastric bypass
LSG	=	Laparoscopic sleeve gastrectomy
NA	=	Not available
OA	=	Osteoarthritis
P	=	Psoriasis
PA	=	Psoriatic arthritis
QoL	=	Quality of life
RA	=	Rheumatoid arthritis
RYGBP	=	Roux-en-Y gastric bypass
SLE	=	Systemic lupus erythematous
V	=	Vasculitis

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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- Emilia De Luca: Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

- Angelo Iannicelli, Guido Sciaudone and Gianluca Pellino: acquisition, analysis, or interpretation of data for the work

- Rosario Sacco, Francesco Selvaggi and Giuseppe Sammarco: Drafting the work or revising it critically for important intellectual content

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