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REVIEW

Association Between Adipokines Levels with Inflammatory Bowel Disease (IBD): Systematic Reviews

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Abstract
Background A combination of genetic and environmental factors is involved in the etiology of inflammatory bowel disease (IBD). Recent studies have shown that adipocytes play a crucial role, by actively participating in systemic immune responses in IBD patients. But findings remain controversial. To the best of our knowledge, no systematic review has evaluated the roles of adipokines in IBD, considering which this systematic review was undertaken to summarize the effects of these adipokines in IBD pathogenesis.
Methods For this review, articles published between 1980 and 2016 were identified from the PubMed, EMBASE, Scopus, and Cochrane and Google scholar databases. Thirteen articles were ultimately selected for inclusion in this systematic review.
Results Findings of the present study indicate that some of the adipokines such as leptin, adiponectin and resistin are associated with disease severity, body composition and glucose hemostasis in IBD patients, although some of these associations are stronger than others.
Conclusions Overall findings indicate that some adipokines may play a crucial role in IBD severity or other IBD related outcomes. Further studies are recommended to confirm the results.

Keywords Inflammatory bowel disease · IBD · Adipokines · Leptin · Adiponectin

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Introduction

Inflammatory bowel diseases (IBDs) are an idiopathic disease caused by the destruction of the mucosa gastrointestinal tract by the mucosal immune system. The main types of inflammatory bowel disease are Crohn's disease (CD) and ulcerative colitis (UC). Crohn's disease and ulcerative colitis present with periods of remission and relapse [1]. IBD has negative long-term economic consequences due to the rise of hospitalizations, surgery and health-related quality of life. The overall prevalence of IBD in the U.S. is 1.5 million and 2.2 million in Europe. The annual incidence rates of ulcerative colitis and Crohn's

disease are 0–19.2 per 100,000 and 0–20.2 per 100,000 in North America, respectively [2].

A combination of genetic and environmental factors strongly influences the risk for developing IBD. Cytokines have been directly and indirectly involved in the pathogenesis of IBD [3]. The modulation of cytokine function has a crucial role in the immune system's imbalance and promotion of intestinal inflammation. Adipose tissue was classically involved in energy storage and homeostasis, but it is now approached such that adipose tissue as an endocrine organ play a critical role in inflammatory processes [4]. Recent studies have shown the link between adipose tissue and the inflammatory diseases such as rheumatoid arthritis and IBD [5]. The number of adipokins mediators can influence pathogenesis of IBD such as leptin, adiponektin, resisten, visfatin, chemerin (hormones that act as adipokines) and retinoid binding protein (RBP4).

Leptin is a key parameter in the regulation of inflammation signaling pathways [6]. Initially studies have shown overexpression of leptin in mesenteric WAT of patients with Crohn's disease (CD) [7]. In IBD the levels of leptin increase particularly by LPS and proinflammatory cytokines [8].

Adiponectin as a key mediator plays a regulatory role in the pathogenesis of chronic inflammation-related metabolic disease like atherosclerosis, type 1 diabetes and cystic fibrosis [9]. Adiponectin has anti-inflammatory effects through modulating signaling pathways and, therefore, can play a critical role in IBD severity or treatment [10].

Ghrelin, as the gut-brain peptide, directly and indirectly participates in the biological activities including energy metabolism, control of food intake and stimulation of growth hormone (GH) release. Ghrelin plays a role in modulating immune responses and inflammatory processes [11].

Resistin is secreted by adipose tissues and immune cells (mainly produced by PBMC *(*peripheral blood mononuclear cells) and macrophages). Resistin may be an important link between adipose tissues and inflammatory response [10].

The expression of visfatin is correlated strongly with the amount of visceral fat and mesenteric adipose tissue [12]. Visfatin could be associated with the pathogenesis of IBD by induced inflammatory pathways. Actually, visfatin stimulates human leukocytes to produce proinflammatory cytokine including TNFα, IL-6 and IL-1β [13]. Serum visfatin levels have been shown to be higher in CD patients compared with UC patients, other studies showed an increased expression of visfatin genes in IBD compared to healthy people [14]. In addition, studies have shown visfatin is associated with complications of IBD such as osteoporosis in these patients. Visfatin influences the osteoblastogenesis by stimulating osteoblast and inhibition of activated RANKL [15].

There is no systematic review that has compared the levels of adipokines in IBD patients. This systematic review focuses on the different levels of adipokines as markers or predictors of inflammation related diseases in IBD.

Methods

Literature Search and Study Selection

Articles for review were identified from the PubMed, EMBASE, Scopus, Cochrane and Google Scholar databases from 1980 to December 2016. Two researchers independently searched with a combination of free text to include: 'akipokines','leptin', 'adiponectin', 'resistin' and 'visfatin' cross-referenced with 'IBD', "Inflammatory bowel disease", "Crohn Disease" and "Colitis Ulcerative". All reference lists from.

The main articles and relevant reviews were hand searched to identify additional studies. Articles were eligible for inclusion if they had a case control study design and they compared adipokine levels between IBD groups with controls. All titles and abstracts were reviewed to by two authors to find eligible studies. Other type of studies such as randomized controlled trials, reviews, letters, editorials, systematic reviews, conference abstracts and non-human studies (i.e., cell culture or animal studies) were excluded. Figure 1 summarizes the process of the literature search and study selection.

Data Extraction

For each study, data were independently extracted by two authors and the following data were extracted from each eligible article: Surname of lead author, journal name, publication year, design of study, method of adipokines measurement, mean and standard deviation of leptin, adiponectin, visfatin and/or resistin serum levels for each group, IBD subtype and criteria for IBD diagnosis.

Risk of Bias

Methodological quality of studies was assessed using the Newcastle–Ottawa Scale for Observational Cohort and Case Control Studies because the validity of this method has been demonstrated in different studies [16]. A 'star system' has been developed in which a study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case–control

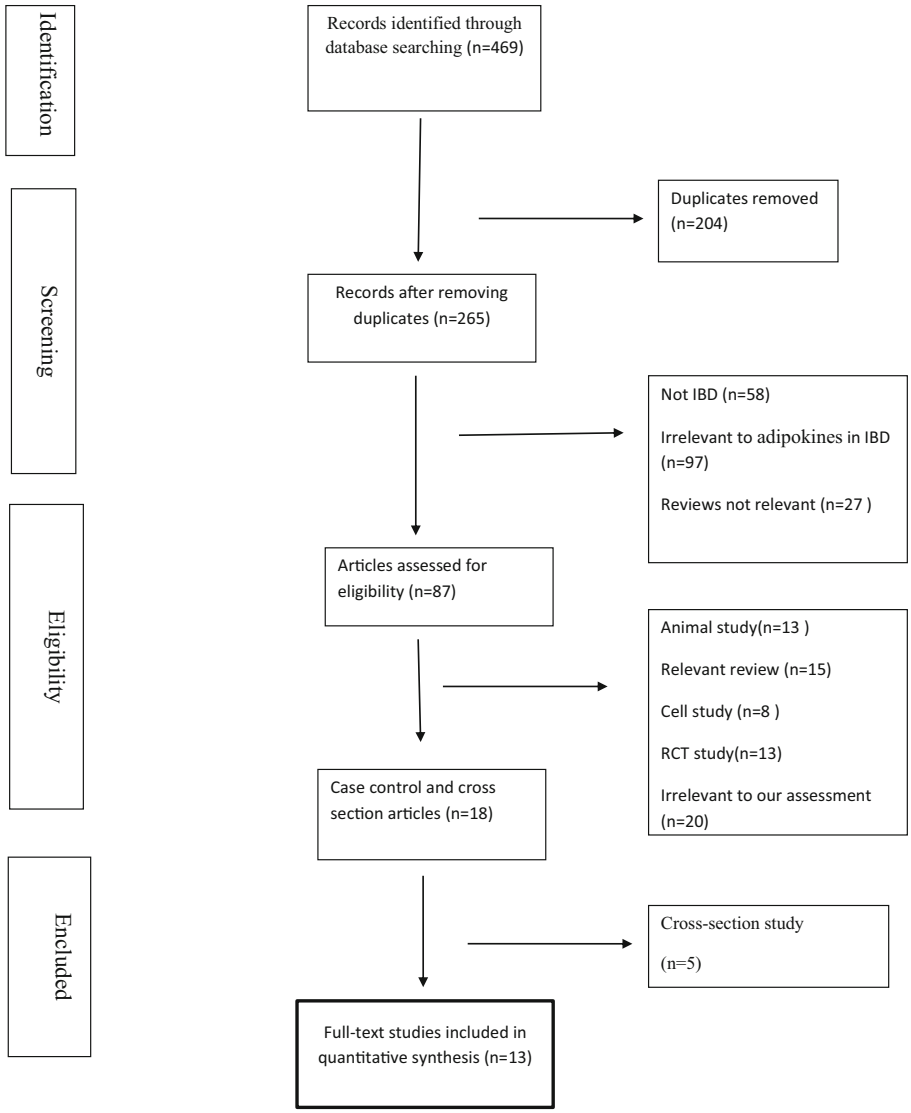

Fig. 1 Flow chart of study selection

or cohort studies, respectively. In this scale, each of the study can get one star for each item. In the "Comparability" section, each study can be awarded two stars.

If the total number of stars is greater than seven for each study, this study is rated as high quality.

Result

Characteristics of the Included Studies

Our initial literature search identified 469 studies from Pubmed, EMBASE, Scopus, Cochrane and Google Scholar databases. After the duplicate removing and first screening, 87 articles were included in second screening. In this phase, two researchers independently evaluated articles and 14 articles were ultimately selected for inclusion in the systematic review. A summary of the study characteristics included in the systematic review is presented in Table 1.

The Difference in Levels of Adipokines Eight studies on adipokines and IBD were included that have focused on circulating levels of adipokines in patients with IBD.

Serum leptin levels were assessed in children with IBD and results showed that leptin levels were lower in IBD children than the healthy group. In subgroup assessment, the leptin level was higher in children with CD in comparison to UC, although this difference is justifiable due the most mesenteric fat in the CD group ($P = 0.8$) [17].

In another study, when patients with active Crohn's disease were compared to the control group, researchers showed no significantly difference in leptin concentration [18].

Table 1 Characteristics of studies

References	Number of subjects (case/control)	Type of adipokines	Total score
Bannerman et al. [18]	17 CD/15	Leptin	4
Aurangzeb et al. [17]	23 CD, 5 UC/56	Leptin	5
Terzoudis et al. [14]	68 CD, 52 UC/120	Visfatin	6
Valentini et al. [21]	67 CD, 61 UC/37	Leptin, adiponectin, resistin	6
Weigert et al. [24]	230 CD, 80 UC/80	Adiponectin	6
Karmiris et al. [26]	54 CD, 46 UC/60	Leptin, adiponectin, resistin	5
Scoville et al. [41]	48 CD, 96 UC/46	Leptin, resistin, adiponectin	5
Abdel Kader et al. [27]	16 CD, 24 UC/20	Resistin	5
Tuzun et al. [19]	29 UC/17	Leptin	5
Konrad et al. [23]	235 CD, 112 UC/144	Resistin	7
Rodrigues et al. [20]	16 CD/6	Leptin, adiponectin	4
Dogan et al [22]	31 UC/29	Visfatin	4
Ahishali et al. [28]	11 CD, 31 UC/26	Resistin	4

CD Crohn's disease, UC ulcerative colitis

In contrast, Tuzun et al. evaluated leptin levels in 29 male patients with acute UC compared to 17 healthy controls with similar age, sex and body mass index (BMI). Crude leptin levels were significantly higher in individuals with acute UC (5.89 ± 2.06 ng/mL) compared to controls (3.64 ± 1.69 ng/mL; $P = 0.001$) [19].

In the Rodrigues et al. [20] study, which had eight patients with active type of CD, eight remission CD and six healthy controls, researchers found that plasma levels of adiponectin were significantly lower in the active patients compared to the control group [6828.5 vs. 911.4 ($P < 0.01$)], but no significant difference in remission CD group with control. Although, leptin levels were not significantly different in CD patients compared to healthy individuals ($P > 0.05$).

Terzoudis et al. [14] has found no difference in plasma visfatin concentration in patients with IBD compared to healthy controls, although serum visfatin levels in CD group were significantly higher than UC ($P = 0.039$).

In another study, an increased visfatin concentration was observed in active UC but not in CD, remission and controls. However, a significant decrease was observed in adiponectin levels in both active and remission disease compared with controls ($P < 0.001$) [21].

Dogan et al. [22] found a significant difference in visfatin levels in patients with active disease (7.77 ± 2.41 ng/ml) rather than remission (6.18 ± 2.04 ng/ml) and healthy individuals (6.54 ± 2.20 ng/ml; $P < 0.01$).

In another study, which was performed in active and remission IBD patients, resistin levels was increased in patients with both active and remission disease as compared to controls ($P < 0.0001$) [23]. The difference between adiponectin levels between patients with IBD and controls was influenced by gender, disease duration, localization and type of disease.

Adipokines and Severity of Disease Ten studies on adipokines and disease activity were included in this systematic review.

Weigert et al. [24] showed that the adiponectin level was significantly higher in UC patients compared to the control group, but this relationship was inverted in CD patients. However, levels of adiponectin depended on the stage of disease; active male patients had lower levels of adiponectin compared to inactive patients.

Aurangzeb et al. [17] found no correlation between serum leptin levels and CRP (C-reactive protein), ESR or Disease Activity Index in the children with IBD. Another study has found similar relationship between serum leptin concentrations with and disease activity and CRP [18].

On the contrary, in children with IBD, leptin but no adiponectin were related to inflammation and disease activity in UC children. A negative correlation was detected between serum leptin and disease activity which was quantified using the Pediatric Crohn's Disease Activity Index and Pediatric Ulcerative Colitis Activity Index [25].

Therefore, phase of disease induces the release and intracellular pools of adipokines. Serum leptin concentrations were lower in active UC ($P < 0.05$) but adiponectin and resistin were higher than inactive UC and healthy controls [26].

In another study, the serum resistin level has a positive association with disease activity and inflammatory parameters (CRP and ESR) [27]. Similarly, Konrad et al. [23] evaluated resistin plasma levels in 235 patients with CD and 112 patients with UC patients (44 females, 68 males)

vs sex, BMI and WBC matched controls ($n = 144$). The authors reported that resistin levels were significantly associated with WBC count ($P < 0.0001$, $r = 0.4598$ for CD, $r = 0.4146$ for UC), CRP ($P < 0.0001$) and disease activity ($P < 0.0001$) in IBD patients and suggested that resistin levels can be used as a predictor of disease activity and inflammation in patients with CD.

Elevated plasma resistin concentration was observed in the active IBD but not in remission and controls, and concluded that serum resistin levels depend on disease activity or severity ($P < 0.05$). In addition, serum levels of leptin presented a significant positive association with rate of relapse in 3 months ($P < 0.026$), nevertheless, there was no correlation between leptin and inflammatory mediators [21].

Adipokines and Body Composition in IBD Few studies have examined the relationship between adipokines and body composition in IBD, and these results were inconclusive.

Bannerman et al. [18] examined the association between serum leptin concentrations and body composition among 17 patients with Crohn's disease with 15 healthy controls. Researchers observed a significant positive correlation between the serum leptin concentrations and fat percent in patients with active Crohn's disease ($P < 0.001$).

Moreover, it has been shown that the BMI z score are positively correlated with serum leptin level in children with IBD ($P < 0.001$) [17]. But this result was not confirmed in another study [19]. Terzoudies et al. [14] showed that serum visfatin exhibited no association with fat mass in patients with IBD.

Adipocytes and Glucose Homeostasis in IBD Three studies on adipocytes and glucose homeostasis were included and have focused on alterations in serum adipokine levels and levels of insulin and glucose. There was a significant trend between change in the levels of adiponectin and insulin concentration in 128 IBD patients, 18-70 years old. Patients with hyperinsulinemia had a significantly lower adiponectin values than other patients ($r < 0.572$, $P < 0.001$). However, this relationship was not seen in the other adipokines [21].

The Chouliaras et al. [25] studies evaluated leptin and adiponectin association with insulin resistance, and suggested that leptin concentration elevated with increase in HOMA2-IR but was not associated between adiponectin and HOMA2-IR ($r = 0.29$, $P = 0.045$).

In another study, was performed in 42 IBD patients (31 ulcerative colitis, 11 Crohn's disease) with those of 26 healthy volunteers. No significant correlations between visfatin and any of insulin resistance states parameters (including fasting serum glucose levels and IR values) were observed [28].

Discussion

To the best of our knowledge, the current systematic review is the first to assess the association between various adipokines and inflammatory bowel diseases (IBDs). The results of this systematic review indicate that some of the adipokines can be involved in IBD severity and this relates to clinical and preclinical risk factors.

Inflammation is one of the main components in the etiology of IBD. In previous studies, researchers have shown that there was a strong correlation between levels of adipokines and inflammation severity. On the other hand, some of the proinflammatory adipokines was produced by adipose tissue involved in the development of insulin resistance and disease severity. However, results of the studies are contradictory.

Leptin is one of the most important adipokines that is released from adipose tissue. Increased circulating leptin level has been observed in inflammatory diseases. One of the first adipokines to be related to intestinal inflammation was leptin. Therefore, leptin is considered a proinflammatory adipokine that is involved in the inflammatory pathway, especially in obese subjects. In the present systematic review, association between leptin levels in IBD patients compared to control groups was different. Perhaps one of the reasons for this paradox is the difference in weight and age of the study population. So that in obese and adult patients with IBD due the higher amount of adipose tissue, leptin secretion can be higher compared to children. In acute intestinal inflammation, leptin induces the activation of Th1 and promotes the release of IL-1a, IL-1b, IL-2, IL-6 and TNF- α. Conversely, TNF-α and IL-1β enhance the expression of leptin mRNA in adipose tissue. This interaction forms a loop with components that influence each other in promoting inflammation. In addition, leptin promotes neutrophil infiltration and histologic epithelial damage in IBD [8]. Despite the existing hypothesis, after the evaluation of included studies, we did not observed linear association between leptin levels with IBD severity. In one of the studies [25], a negative association between leptin levels with IBD severity was observed. In explanation, some of studies indicated that, whereas TNF-a increase acute release of leptin, it decreases leptin secretion in chronic inflammation [29]. Furthermore, in some studies, after the treatment of IBD patients with infliximab, an anti-TNF-a agent, leptin levels were increased [30]. Actually, serum leptin levels are highly dependent on TNF-a,

and TNF-α regulates leptin levels at inflammatory conditions. Interactions between IL-1α and TNF-α can control leptin. Therefore, probably one of the reasons for lower leptin levels in IBD patient is interference by TNF-a.

Furthermore, leptin is an adipocyte-derived hormone that links fat mass with nutritional status and immune functions. Leptin has been associated with anorexia in IBD patients. Weight loss in IBD patients may be leading to a decrease in circulating leptin [31]. On the other hand, an increase in serum leptin levels in Crohn's disease is associated with the unregulated leptin gene expression in white adipose tissue (WAT) [32].

Adiponectin is an anti-inflammatory adipokine that seems to play a protective role in IBD patients. These anti-inflammatory features include a regulatory effect on toll-like receptors (TLRs), inhibition of nuclear factor kappaB (NF-κB) and upregulation of IL-10 secretion [33, 34]. Studies that evaluated the adiponectin level in IBD patients have reached conflicting conclusions. In some studies were reported reduced adiponectin levels in active CD patients compared to the control group [20], but others reported no difference between adiponectin concentrations in UC as compared with controls and CD [35]. In explanation of higher adiponectin concentrations in CD patients, researchers have suggested increased expression of adiponectin mRNA in mesenteric adipose tissue of CD patients [36]. Furthermore, researchers reported that adiponectin concentration was dependent on the phase of the disease. In the active phase of UC, the concentration of this adipokine increases.

Resistin and visfatin can be act as pro-inflammatory adipokines through the activation of NF-κB inflammatory pathways. In addition, visfatin stimulates production and releasing of special cytokines. In analysed studies, most studies showed a linear relationship between visfatin and resistin with IBD severity. Previous studies have shown that TNF-a as well as interleukin-6 (IL-6) significantly increased resistin mRNA expression in human peripheral blood mononuclear cells in vitro [37]. Furthermore, other studies suggested that resistin acts as a stimulant of TNF-a secretion and activation of NF-κB [38].

Most of the adipokines are associated with insulin resistance. In IBD patients, because of the alteration in fat distribution and increasing visceral fat mass, an hypothesis has been created that adipokines can exacerbate IBD severity from the alteration in glucose homeostasis [39]. When we analyzed studies, among the adipokines, it seems that leptin and adiponectin are associated with glucose hemostasis and insulin resistance. In one study, IBD patients with insulin resistance had a lower adiponectin concentration compared to the control group [21]. Perhaps it is due to an anti-inflammatory effect of adiponectin and its interaction with pro inflammatory cytokines that are involved in insulin resistance pathogenesis [40]. Leptin, due to the pro inflammatory effect, acts as a stimulant of insulin resistance [25].

Recently, some studies have been focused on the role of proinflammatory adipose tissue cytokines (adipokines) in the pathogenesis of IBD. Various hypotheses regard the role of different adipokines in the progression of intestinal inflammatory processes. Obesity is associated with systemic pro inflammation conditions, and an alteration in circulating adipokines levels.

Mesenteric adipose tissue (MAT) in patients with Crohn's disease, are characterized by increased concentrations of adipokines within the mesenteric fat source. In another mechanism, some of adipokines have anti-inflammatory effects. It reduces the release of proinflammatory cytokines such as TNF-a and IL-6 [38, 40].

This systematic review and meta-analysis has several strengths. First, we did a full and rigorous systematic review methodology. Second, for the first time we pooled and evaluated all of the studies that assessed the relation between adipokines levels with IBD related parameters. Third, we investigated the quality of the all included studies using the Newcastle–Ottawa quality rating scale. Studies included in this systematic review were of high quality.

Our study also had several limitations. First, population of some studies was limited. Second, because of the study design (case control) there is always some confounding factor present in some studies.

Conclusions and Future Research Directions

In conclusion, this systematic review provides evidence that some of the adipokines can play an important role in IBD severity. Also, insulin resistance is observed in more of the IBD patients related to leptin and adiponectin levels. But, present findings are inconsistent and, for approval, need to strengthen studies with a large population and a more uniform methodology in future studies (i.e., a better control of confounders).

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Compliance with ethical standards

Conflict of Interest The authors declare no competing financial interests relevant to the present work.

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