Circulating Leptin Levels as a Potential Biomarker in Inflammatory Bowel Diseases: A Systematic Review and Meta-Analysis

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Background: The differential diagnosis of inflammatory bowel diseases (IBDs) between Crohn's disease (CD) and ulcerative colitis (UC) is important for designing an effective therapeutic regimen. However, without any adequate gold standard method for differential diagnosis currently, therapeutic design remains a major challenge in clinical practice. In this context, recent studies have showed that circulating leptin stands out as a potential biomarker for the categorization of IBDs. Thus, we aimed to summarize the current understanding of the prognostic and diagnostic value of serum leptin in patients with IBDs.

Methods: A systematic search was performed in PubMed/MEDLINE, Scopus, Cochrane Library, and Web of Science databases. Articles that aimed to study the relationship between circulating levels of leptin and IBDs were included. Finally, the meta-analysis was performed with the mean serum leptin levels in patients with IBDs and healthy controls using RevMan 5.3 software, with $I^2 > 50\%$ as a criterion for substantial heterogeneity.

Results: Nineteen studies were included. Serum leptin levels among patients with IBDs and healthy controls did not show a significant difference (95% CI, −2.15 to 0.57; I^2, 86%, $P \leq 0.00001$). Similarly, there was no association of leptin levels with the activity of IBDs (95% CI, −0.24 to 0.06; I^2, 50%; $P = 0.13$). However, serum leptin levels were significantly higher in patients with CD than those in patients with UC (95% CI, −2.09 to −0.37; I^2, 7%; $P \leq 0.36$).

Conclusion: This review suggested that serum leptin levels might be a promising biomarker to help in the differentiation between CD and UC.

Key Words: adipokines, Crohn's disease, ulcerative colitis, prognosis, differential diagnosis

INTRODUCTION

Inflammatory bowel diseases (IBDs) are chronic idiopathic disorders characterized by intense inflammation of the intestinal mucosa, which evolves into structural and functional changes in the large and/or small intestine.[1, 2] These clinical conditions primarily include Crohn's disease (CD) and ulcerative colitis (UC), which affect 1.3% of US adults (an estimated 3.1 million patients).[3] Clinically, CD is characterized by the appearance of discontinuous transmural lesions that can affect any region along the gastrointestinal tract (ie, from the mouth to the anus); however, it is more commonly seen in the colon and terminal ileum.[4, 5] Ulcerative colitis manifests as continuous superficial ulcers that normally appear in the rectum and extend proximally, therefore being restricted to the colon.[6] Both forms of IBDs are often associated with major impairment to the quality of a patient's life, as they usually manifest in younger individuals in different cycles of relapse and remission. Furthermore, IBDs are characterized by symptoms that have a considerable impact on their patients, such as abdominal pain, diarrhea, dysentery, and extraintestinal complications such as joint, skin and eye injuries.[2] Moreover, patients with decompensated IBDs are at increased risk of developing severe complications such as colon and rectal cancer.[4, 5]

Despite recent advances in the epidemiology and pathophysiology of IBDs, great efforts are still being made to identify potential biomarkers that may be employed for clinical and therapeutic monitoring of these patients.[7] Currently, the differential diagnostic of IBDs in CD and UC is based on clinical, endoscopic, radiologic, and histologic criteria.[1, 2] However, the distinction between the initial presentation of IBD and acute colitis of another etiology, or the same distinction between UC and CD, is complicated by the clinical and anatomo-pathological similarities between these conditions.[8, 9] Thus, the differential diagnosis of IBDs remains a major challenge in clinical practice. In fact, the distinctive categorization between CD and UC remains unelucidated in about 10% of

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the cases of IBDs in the United States and Europe.[8] Moreover, prospective and population-based studies suggest that approximately 1 in 20 patients with IBD will have a diagnosis of indeterminate colitis.[10, 11] Therefore, the design of a new biomarker that is readily available, noninvasive, precise, sensitive, specific, and accessible is essential for optimization of the confirmatory and differential diagnosis of IBDs. An important difference in the physiopathology of CD and UC, which can be used for diagnostic purposes, is the role of adipocytes and adipokines in each condition. The transmural lesions of CD are known to increase bacterial translocation to regions adjacent to the intestine, such as the adipose tissue.[12, 13] These microorganisms and their subproducts promote the proliferation and activation of adipocytes and preadipocytes, thereby inducing hyperplasia of the mesenteric adipose tissue.[12] Imaging in patients with CD using magnetic resonance shows adipocyte hyperplasia, which appears as creeping fat and covers more than 50% of the gut circumference.[14] This signal pathognomic of CD is absent in UC carriers because the superficial ulcers associated with this form discretely increase bacterial translocation.[15]

Morphologically, creeping fat refers to a set of significantly smaller adipocytes with cell density about 4 times greater than that of adjacent mesenteric adipose tissue. Creeping fat also shows large numbers of immune cells such as lymphocytes, macrophages, neutrophils, and natural killer (NK) cells.[16] This specialized set of adipocytes plays an active role in CD, thus being responsible for transmural inflammation, fibrosis, and muscular hypertrophy of this form of IBD.[15, 17] Adipocytes present in creeping fat secrete several cytokines and adipokines capable of modulating gastrointestinal functions and the immune system.[18] Among these adipokines is leptin, a hormone ("leptos" meaning "lean") produced and secreted by adipose tissue, stomach, and muscle, which acts mainly in the hypothalamus-mediated regulation of food intake and energy expenditure.[19, 20] Although the gut is not a classical target tissue for leptin, several studies indicate that this hormone determines important physiological effects on intestinal growth and differentiation and maturation of enterocytes.[21, 22] As these developmental phenomena are greatly affected in patients with IBDs, leptin is expected to play a central role in the cascade of events that culminates in the development and relapse of the disease. In this direction, preclinical studies have confirmed the involvement of leptin in IBDs. Animals deficient in leptin (ob/ob mice) present a reduction of more than 70% in the severity of sodium dextran sulfate (DSS) and trinitrobenzene sulfonic acid (TNBS)–induced colitis. Further, the authors demonstrated that the administration of exogenous leptin restores the susceptibility to the lesions in the intestinal mucosa induced by these chemical agents, indicating that leptin deficiency, not obesity, is related in resistance to colitis.[23] In addition, intrarectal administration of leptin induces intense damage to the wall of the intestinal epithelium and neutrophil infiltration, indicating that the proinflammatory effects of this hormone are associated with direct intraluminal signaling in colonic cells.[24]

Despite the preclinical evidence of involvement of leptin in pathophysiology of IBDs, clinical studies have shown that the association between circulating leptin and CD or UC are still inconclusive. Although much evidence supports the diagnostic and prognostic potential of leptin in these patients, the results are still controversial because these adipokines are known for their pro- and anti-inflammatory effects.[23–26] Therefore, we aimed to summarize the current knowledge about the prognostic and diagnostic value of serum leptin levels in patients with CD or UC by systematically searching and performing a meta-analysis of the data available in the biomedical literature. In addition, using subgroup analysis, we identified potential sources of heterogeneity that may contribute to the discrepancies between the results obtained in previous studies.

METHODS

Systematic review and meta-analysis were performed according to the principles described in the Cochrane Handbook.[27] The steps of searching, selecting, extracting the data of interest, and analyzing results were performed according to the rules of the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA).[28]

Search Strategy

Articles that aimed to investigate leptin serum levels in patients with UC or CD were screened from PubMed/MEDLINE, Scopus, Cochrane Library, and Web of Science databases (last search: March 9, 2019). The descriptors employed were defined according to the terms of the Medical Subject Heading (MeSH); we selected 2 different populations: (1) "Inflammatory Bowel Diseases" OR "Bowel Diseases, Inflammatory" OR "Colitis, Ulcerative" OR "Crohn Disease" OR "Colitis" OR "Colitis, Granulomatous" OR "Crohn's Disease" OR "Crohn's Enteritis" OR "Enteritis, Granulomatous" OR "Enteritis, Regional" OR "Ileitis, Regional" OR "Ileitis, Regional" OR "Ileitis, Terminal" OR "Ileocolitis" OR "Inflammatory Bowel Disease 1" OR "Regional Enteritis" OR "Duodenitis" OR "Enterocolitis" OR "Ileitis"; and (2) "Leptin" OR "Ob Gene Product" OR "Ob Protein" OR "Obese Gene Product" OR "Obese Protein." The different populations of descriptors were combined using the term "AND" between them; the combinations of descriptors were searched in each database according to characteristics and limitations of each one. The details of these searches are summarized in the supplementary materials. Limits were established in Portuguese, Spanish, and English, with no restriction on the date of publication.

Eligibility and Exclusion Criteria

After performing the search as described previously, the criteria for selecting studies were defined by the "PECOS" strategy,[29] as follows: "population," patients of any age, ethnicity, and gender; "exposure," confirmatory differential diagnosis of CD or UC; "control," patients with negative diagnosis

for some IBD; "outcome," serum leptin levels; and "study," analytical observational studies. Review articles, notes, e-mails, editorials, letters, papers presented at scientific events, and articles that had no original material were excluded. In addition, other articles were excluded based on the following criteria: (1) differential diagnosis between CD and UC not closed; (2) leptin levels from only the asymptomatic stage of IBD reported; and (3) lack of information regarding the study population.

Selection of Studies and Data Extraction

Two independent researchers (LGFC and WGL) carried out the search and selection of articles according to the inclusion and exclusion criteria established. First, a preliminary reading of the title, abstract, and keywords for identification and preselection of the articles of interest was carried out. Subsequently, the preselected articles were read completely to confirm their inclusion in this study. Discrepancies between the 2 researchers were resolved by discussion with a third researcher (SOAF) to reach a consensus regarding the inclusion or exclusion of articles. To define the concordance rate among the different researchers, the kappa index was determined, and values higher than 0.8 were considered significant.[30]

The selected articles were submitted to an integral analytical reading to identify and extract the variables of interest, which were reference (first author and year of publication), characteristics of the population studied (age, gender, time of diagnosis, number of patients included), type of IBD and diagnostic criteria used, and serum levels of leptin (concentration and technique employed). For the meta-analysis and subgroup study, the mean and standard deviation values of serum leptin (ng/mL) were extracted from patients and healthy controls. Studies that referred to leptin levels as nonparametric, median, and 25th percentile were used in the meta-analysis. Some studies included in our review used other units, such as pg/L, to report leptin serum levels. In this case, the units were converted to ng/mL to standardize all data. Values in pg/mL were multiplied by 1000 and converted to ng/mL.

Evaluation of Methodological Quality and Risk of Bias

The quality of the selected studies was independently assessed by 2 researchers (LGFC and WGL) using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[31] All included studies were analyzed and categorized into 3 groups according to methodological quality: high (fulfills more than 80% of STROBE criteria); moderate (fulfills 80%–50% of STROBE criteria); and low (fulfills less than 50% of the STROBE criteria). Because a limited number of articles were found in the biomedical literature, quality was not used here as a criterion for exclusion from work. In addition, we assessed potential publication bias with a funnel plot.

Statistical Analysis

The meta-analysis was performed with the mean serum leptin levels in patients with CD or UC and healthy individuals (without IBD). Review Manager (RevMan) 5.3 software was used to analyze data from individual studies, which were then combined using a random effects model to estimate the combined mean difference of the variable of interest (represented by abbreviation IV) and their confidence intervals. The heterogeneity of the primary data, in turn, was analyzed by the I^2 test; we consider $I^2 > 50\%$ as a criterion for substantial heterogeneity. In all procedures, the level of significance was 5%.[32] Subgroup analysis was performed to evaluate the influence of age, study quality, ethnic-racial factors, gender, type of IBD, and study design on the heterogeneity of the analyses performed.

RESULTS

Search and Selection of Studies

As shown in Figure 1, 645 articles were identified by searching in the selected databases (178 from PubMed/MEDLINE, 309 from Scopus, 6 from Cochrane Library, 152 from Web of Science). After excluding duplicate records and reviewing titles, abstracts, and keywords, 47 relevant studies were selected for reading the full text and further evaluation following the selected eligibility criteria. From these articles, 28 were excluded based on the criteria described in Figure 1; the remaining 19 studies[32–50] were followed-up for the critical reading and extraction of the variables of interest. Of these, 16[32–35, 37, 38, 40–48, 50] were included in the quantitative studies and used to conduct the meta-analysis of the relationship between circulating levels of leptin and IBDs. The degree of agreement between the 2 authors responsible for the search and selection of articles was substantial, as revealed by the kappa concordance index (Kappa = 0.852).[30]

Characteristics of Included Studies

The main characteristics of each study selected in the systematic review are summarized in Table 1. Of the studies, 11 were prospective cross-sectional (11 of 17, 64.7%),[33, 34, 37–39, 41–43, 45–49] 3 were cohort (3 of 17, 17.7%),[36, 45, 49] and 3 were case-control (3 of 17, 17.7%) studies.[33, 42, 44] Most studies were conducted in European countries (Germany,[33, 37, 40, 49] Scotland,[34] Greece,[38, 39] England,[41, 43, 48] and Poland[46, 51]), followed by Asian countries (Turkey,[35] Saudi Arabia,[42] Korea,[45] and Japan[50]), Latin America (Mexico[34] and Brazil[47]), and Oceania (Australia[36]). Samples from a total of 1403 individuals were analyzed in these studies, of which 860 had IBDs (525 diagnosed with CD and 335 with UC), and 543 were healthy controls. The age of included patients ranged from 2.6 to 78 years (with a general mean of 32.8 ± 11.6), and the majority were female (57 ± 23.9%). Of the analyzed samples, 84% (722 of 860) were from patients with

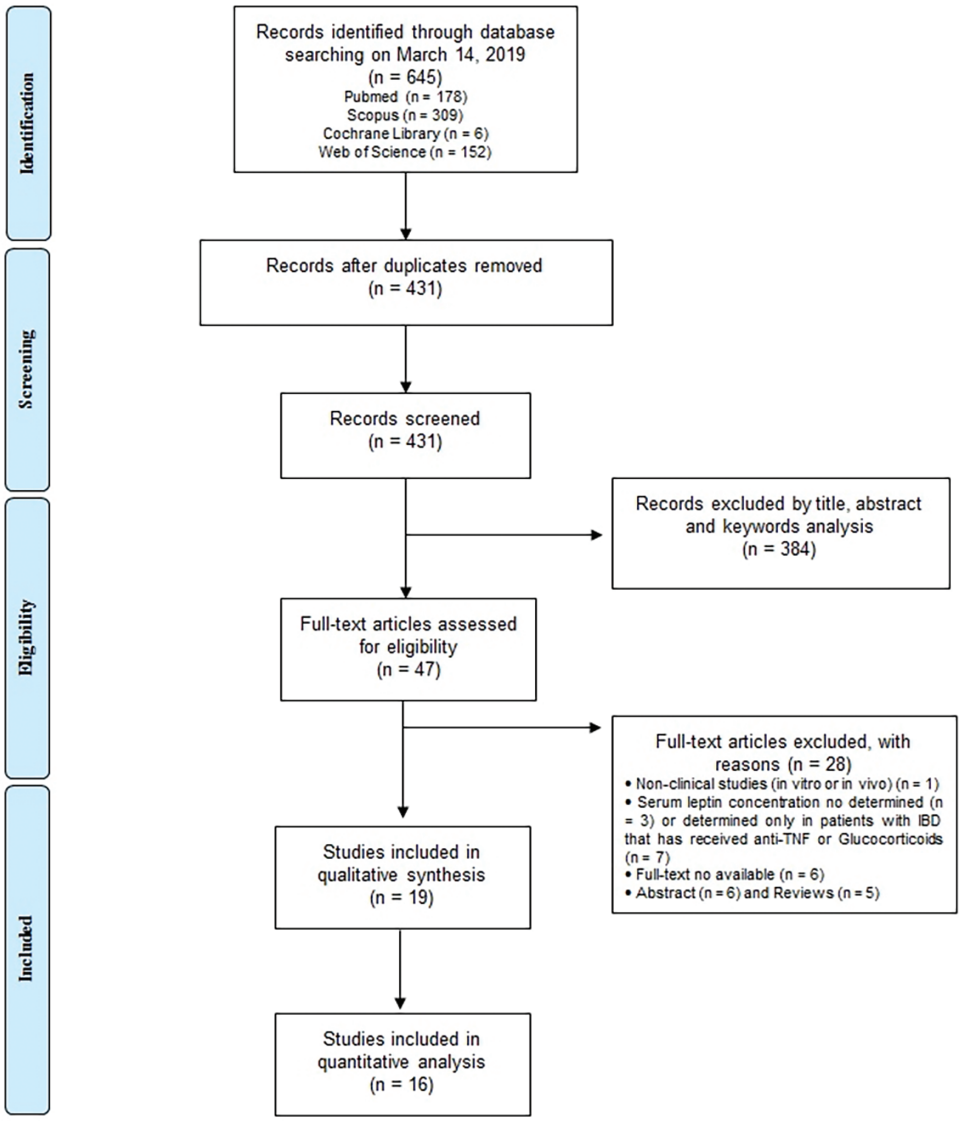

FIGURE 1. Flowchart of article selection for systematic review and meta-analysis according to PRISMA criteria.[28]

active disease, and 16% (138 of 860) were from patients with inactive disease.

The confirmatory diagnosis of IBDs and the differential diagnosis of CD and UC were performed based on ileocolonoscopy, computed tomography, magnetic resonance imaging, and/or histological examination of mucosal biopsies sampled during endoscopy. In addition, some complementary tests such as hemogram, serum C-reactive protein, blood glucose, creatinine, aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transpeptidase (Gama-GT), and alkaline phosphatase (PAL) were performed with the objective of evaluating the prognosis and degree of disease in each included patient (data not shown). The categorization of clinical activity/disease activity was obtained from endoscopy by appropriate scales such as UC Mayo endoscopic score (UC-MES), UC endoscopic index of severity (UCEIS), UC/CD Montreal classification, CD activity index (CDAI), simple endoscopic scale for CD (SES-CD), and Truelove-Witts score.

Methodological Quality and Risk of Bias

The quality of the experimental designs was categorized as moderate (11 of 19; 57.9%)[31, 32, 34–36, 39–41, 44, 45, 49] or low (8 of 19; 42.9%)[35, 36, 39–41, 43, 47, 48] according to the STROBE criteria. The potential sources of bias were discussed only in some of the included studies, and 14 studies (73.7%) clearly described the exclusion criteria used during patient selection, the most used being diabetes, autoimmune diseases, presence of other inflammatory diseases or infectious diseases, pregnancy, and lactation. None of the included studies described intra- and inter-assay variation in leptin dosages of the included samples.

TABLE 1. Description of the Main Characteristics of the Included Studies

Reference	Study Design	Country	Groups (n) Cases (UC e CD)	Groups (n) Healthy Control	Age of Cases, Years[a]	Sex of cases, %[b]	Main Outcomes	Methodological Quality
Kahraman et al., 2017[35]	Prospective	Turkey	CD (49) UC (56)	98	**CD:** 38 ± 11 **UC:** 40 ± 11	**CD:** 96 **UC:** 64.7	• ↑ Leptin in patients with IBD in relation to healthy control patients • None correlation with disease activity • None correlation with lesion location	Low
Frivolt et al., 2018[33]	Case-control	Germany	CD (18)	15	15.0 ± 1.5	90	• Leptin levels were similar between patients with CD and healthy control patients • ↑ Leptin after the use of Infliximabe	Moderate
Bannerman et al., 2001[34]	Prospective	Scotland	CD (9[I] e 8[A])	15	39 (24–65)[I] e 34 (24–53)[A]	6	• ↑ Leptin in patients with active CD in relation to healthy control patients	Moderate
Aurangzeb et al., 2011[36]	Cohort	Australia	CD (23) UC (5)	56	9.5 (2.6–14.6)	35.7	• ↓ Leptin in patients with IBD in relation to healthy control patients • None correlation with disease activity	Low
Valentini et al., 2008[37]	Prospective	Germany	CD (49[I] e 18[A]) UC (44[I] e 17[A])	37	**CD:** 36 (27, 45)[I] e 32 (26, 43)[A] **UC:** 42 (30, 56)[I] e 42 (33, 52)[A]	**CD:** 74[I] e 72[A] **UC:** 64[I] e 71[A]	• Leptin levels similar between patients with IBD and healthy control patients • In patients with UC, the level of leptin is higher among patients with relapse within 3 months than in patients without relapse	Moderate
Chouliaras et al., 2013[38]	Prospective	Greece	CD (32) UC (18)	-	**CD:** 10.7 ± 3.3 **UC:** 9.9 ± 3.7	**CD:** 66 **UC:** 55	• ↑ Leptin after remission of CD • None correlation with disease activity in CD and good correlation in patients with UC	Moderate
Karmiris et al., 2006[39]	Prospective	Greece	CD (54) UC (46)	60	**CD:** 37 **UC:** 46	**CD:** 48 **UC:** 35	• ↓ Leptin in patients with UC, but not among those with CD compared with healthy control. • None correlation with the location of the disease	Low
Moran et al., 2013[41]	Prospective	England	CD (17)	13	39.85 ± 4.6	82	• Leptin levels similar between patients with CD and healthy control patients	Low
Tuzun et al., 2004[40]	Prospective	Germany	UC (29)	17	32.1 ± 10	54	• ↑ Leptin in patients with UC in relation to healthy control patients • Leptin levels were significantly higher in patients with total bowel involvement than in patients with left or distal disease	Low
Ghomraoui et al., 2017[42]	Case-control	Saudi Arabia	CD (14[A] e 6[I]) UC (8[A] e 3[I])	41	30.8 ± 11	73	• ↓ Leptin in patients with active IBD in relation to healthy control patients • There was no correlation with IBD activity	Moderate

TABLE 1. Continued

Reference	Study Design	Country	Groups (n) Cases (UC e CD)	Groups (n) Healthy Control	Age of Cases, Years[a]	Sex of cases, %[b]	Main Outcomes	Methodological Quality
Ballinger et al., 1998[43]	Prospective	England	CD (54) UC (20)	35	34 ± 13	53	• ↓ Leptin in patients with IBD in relation to healthy control patients	Low
Trejo-vazquez et al., 2018[44]	Case-control	Mexico	CD (11) UC (23)	19	59 (26–78)	83	• ↓ Leptin in patients with IBD in relation to healthy control patients	Moderate
Kim et al., 2017[45]	Cohort	Korea	CD (25[A] e 19[I])	-	36.1 ± 10.0	19	• Similar leptin levels between patients with active CD and those with CD in remission • None correlation with the location of IBD	Moderate
Waluga et al., 2014[46]	Prospective	Poland	CD (24) UC (16)	16	**CD:** 31.0 ± 9.4 **UC:** 33.2 ± 21.9	**CD**: 54 **UC**: 56	• ↓ Leptin in patients with IBD in relation to healthy control patients • ↑ Leptin after treatment with infliximab	Moderate
Capristo et al., 1998[48]	Prospective	England	CD (20)	20	32 ± 9.6	40	• ↓ Leptin in patients with CD in relation to healthy control patients	Low
Rodrigues et al. 2012[47]	Prospective	Brazil	CD (8[A] e 8[I])	6	33·6 (16–49)[A] e 37·3 (24–53)[I]	50	• Leptin levels similar among patients with CD and healthy control patients	Low
Büning et al. 2015[49]	Cohort	Germany	CD (31)	19	38.6 ± 10	100	• Leptin levels similar among patients with CD and healthy control patients	Moderate
Nishi et al. 2005[50]	Prospective	Japan	CD (28)	46	32 (18–56)	43	• Leptin levels similar among patients with CD and healthy controls patients • None correlation with the location of the disease	Moderate
Biesiada et al., 2012[51]	Prospective	Poland	UC (50)	30[c]	38 (18–64)	60	• ↑ Leptin in patients with UC in relation to patients with infectious diarrhea • ↑ Leptin in patients with active UC in relation to patients with UC in remission	Moderate

Abbreviations: A, Active disease; I, Inactive disease
[a]Data refer to mean ± standard deviation or median (minimum-maximum age).
[b]Data were proportional to women.

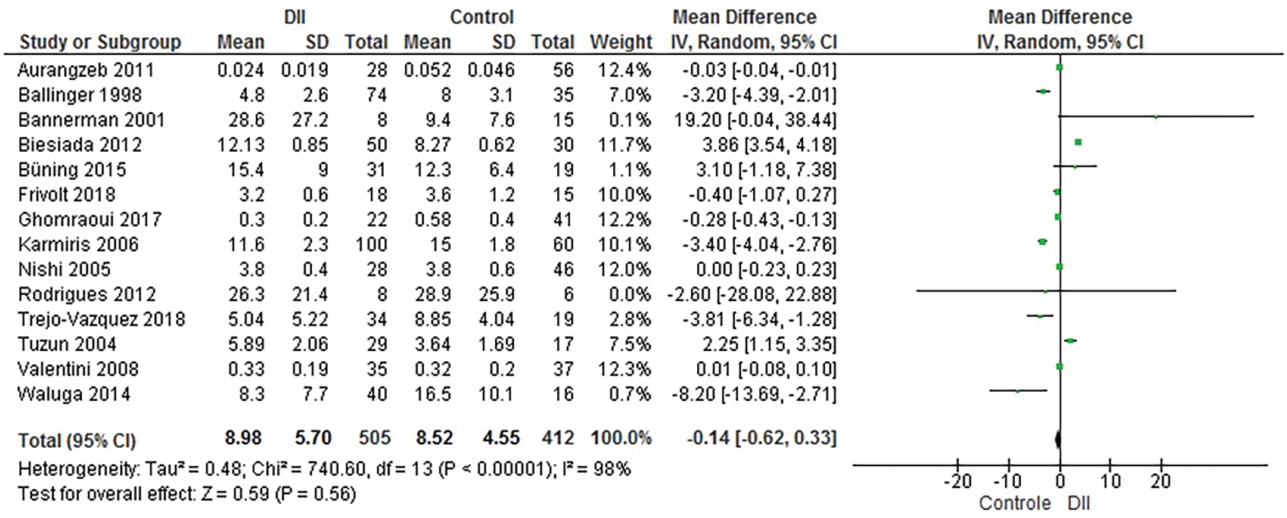

FIGURE 2. Meta-analysis of circulating levels of leptin among patients with IBD and healthy control patients.

The funnel plot, however, showed good symmetry, suggesting low publication bias (Fig. 3).

Circulating Leptin Levels in the Confirmatory Diagnosis of IBDs

Fourteen[31–34, 36, 37, 39–41, 43, 44, 46, 47, 49] of the 17 articles selected for quantitative assessment, which included 917 patients (505 patients with IBD and 412 healthy controls), were selected in this meta-analysis. As showed in Figure 2, serum leptin levels were negatively, but not significantly, correlated with the presence of IBDs (IV, −0.14; 95% confidence interval [CI], −0.62 to 0.33; I^2, 98%; P = 0.00001). This result was not influenced by the type of IBD considered, and even when analyzing CD (IV, −0.79; 95% CI, −2.15 to 0.57; I^2, 86%; $P \leq 0.0001$) and UC (IV, −1.91; 95% CI, −6.51 to 2.69; I^2, 99%; $P \leq 0.00001$) alone (Fig. S1, Supplementary Material), serum leptin levels were similar to those in the control group. This suggests that levels of circulating leptin is not a good biomarker for screening patients with IBD in the general population.

The heterogeneity (indicated by I^2) was considerably high in the included population (I^2, 98%; $P \leq 0.00001$), and the subgroup analysis showed that ethnic-racial factors and the age group considered contributed significantly to the observed high variation (Table 2). The heterogeneity in the Latin American population was considerably lower, and within this group, serum leptin levels were negatively and significantly (P = 0.003) correlated with the presence of IBDs (IV, −3.80; 95% CI, −6, 31 to −1.28; I^2, 0%; P = 0.93). Further, among children, the heterogeneity was low; however, the association between serum levels of leptin and IBDs was not found (P = 0.57) in this population (IV, −0.06; 95% CI, 0.26 to 0.14; I^2, 16%; P = 0.27). In studies that present higher methodological accuracy and level of evidence, such as those with moderate quality according to STROBE criteria (IV, 0.21; 95% CI, −0.73 to 1.16; I^2, 99%; P = 0.00001) and cohort design (IV, 0.77; 95% CI, −1.90 to 3.45; I^2, 51%; P = 0.15), leptin levels were also not correlated with the IBDs. Similarly, among the study populations that included mainly women, leptin levels were not shown to be different between healthy controls and patients with IBD (IV, 0.44; 95% CI, −0.75 to 1.62; I^2, 99%; $P \leq 0.00001$; P = 0.47).

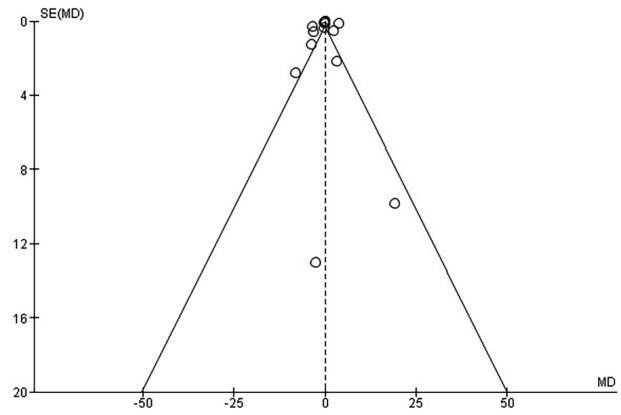

FIGURE 3. Funnel plot of the association between the estimated effect size and its standard error in individual studies.

Circulating Leptin Levels in the Prognosis of IBDs

Three studies[37, 42, 45] that included 203 patients with confirmed IBD diagnosis (82 patients with active IBD and 121 with inactive IBD) were included in the meta-analysis to assess the prognostic value of serum leptin levels (Fig. 4). Serum leptin levels were negatively, but not significantly (P = 0.25), correlated with the prognosis of IBDs (IV, −0.09; 95% CI, −0.24 to 0.06; I^2, 50%; P = 0.13). Leptin concentrations in the blood of patients with IBDs were similar between carriers of active and inactive disease (Fig. 4). The heterogeneity in this population

TABLE 2. Subgroup Analysis for the Association of Circulating Leptin Levels with Inflammatory Bowel Disease

Subgroup	Total Mean of Serum Leptin[a] (No. cases/total patients) IBD	Healthy controls	Effect Size No. Studies	IV	95% CI	Heterogeneity I^2 (P)	P (Overall effect)	References
IBD type								
Ulcerative colitis	11.00 ± 4.41 (164 of 355)	7.27 ± 3.29 (142 of 338)	5	−1.91	−6.51; 2.69	99 ($P < 0.00001$)	0.42	Biesiada et al., 2012[51]; Karmiris et al., 2006[39]; Trejo-Vazquez et al., 2018[44]; Tuzun et al., 2004[40]; Waluga et al., 2014[46]
Crohn´s disease	12.74 ± 9,40 (191 of 355)	11.98 ± 9,31 (196 of 338)	8	−0.79	−2.15; 0.57	86 ($P < 0.0001$)	0.26	Bannerman et al., 2001[34]; Büning et al., 2015[49]; Frivolt et al., 2018[33]; Karmiris et al., 2006[39]; Nishi et al., 2005[50]; Rodrigues et al., 2012[47];Trejo-Vazquez et al., 2018[44]; Waluga et al., 2014[46]
Region of studies								
Asia	2.05 ± 0.30 (50 of 477)	2,19 ± 0,50 (87 of 396)	2	−0.15	−0.43; 0.12	75 ($P = 0.04$)	0.27	Ghomraoui et al., 2017[42]; Nishi et al., 2005[50]
America	15.67 ± 13.31 (42 of 477)	18.88 ± 14.67 (25 of 396)	2	−3.80	−6.31; −1.28	0 ($P = 0.93$)	0.003	Trejo-Vazquez et al., 2018[44]; Rodrigues et al., 2012[47]
Europe	10.03 ± 5.83 (385 of 477)	8,56 ± 3.63 (284 of 396)	9	−0.21	−2.05; 1.63	99 ($P < 0.00001$)	0.82	Bannerman et al., 2001[34]; Biesiada et al., 2012[51]; Ballinger et al., 1998[43]; Büning et al., 2015[49]; Frivolt et al., 2018[33]; Karmiris et al., 2006[39]; Tuzun et al., 2004[40]; Valentini et al., 2008[37]; Waluga et al., 2014[46]
Sex								
> 60% of woman's	6.07 ± 2.68 (190 of 326)	5.65 ± 2.14 (161 of 292)	6	0.44	−0.75; 1.62	99 ($P < 0.00001$)	0.47	Biesiada et al., 2012[51]; Büning et al., 2015[49]; Frivolt et al., 2018[33]; Ghomraoui et al., 2017[42]; Trejo-Vazquez et al., 2018[44]; Valentini et al., 2008[37];
> 60% of men's	13.41 ± 9.84 (136 of 326)	8.15 ± 3.15 (131 of 292)	3	−1.12	−4.42; 2.18	98 ($P < 0.00001$)	0.51	Aurangzeb et al. 2011[36]; Bannerman et al., 2001[34]; Karmiris et al., 2006[39]
Study design								
Cohort	7.71 ± 4.51 (59 of 505)	6.18 ± 3.22 (79 of 416)	2	0,77	−1,90; 3,45	51 ($P = 0.15$)	0,57	Aurangzeb et al. 2011[36]; Büning et al., 2015[49]
Cross-sectional	11.31 ± 7.19 (372 of 505)	10.43 ± 5.73 (262 of 416)	9	−0,34	−1,76; 1,08	99 ($P < 0.00001$)	0,64	Bannerman et al., 2001[34]; Biesiada et al., 2012[51]; Ballinger et al., 1998[43]; Karmiris et al., 2006[39]; Nishi et al., 2005[50]; Rodrigues et al., 2012[47]; Tuzun et al., 2004[40]; Valentini et al., 2008[37]; Waluga et al., 2014[46]
Case-control	2.85 ± 2.01 (74 of 505)	4.34 ± 1.88 (75 of 416)	3	−0,63	−1,43; 0,18	74 ($P = 0.02$)	0,13	Frivolt et al., 2018[33]; Trejo-Vazquez et al., 2018[44]; Ghomraoui et al., 2017[42]

TABLE 2. Continued

Subgroup	Total Mean of Serum Leptin[a] (No. cases/total patients) IBD	Healthy controls	Effect Size No. Studies	IV	95% CI	Heterogeneity I² (*P*)	*P* (Overall effect)	References
Age								
Children (≤ 15 years)	1.61 ± 0.31 (46 of 505)	1.83 ± 0.62 (71 of 412)	2	−0,06	−0,26; 0,14	16 (*P* = 0.27)	0,57	Aurangzeb et al. 2011[36]; Frivolt et al., 2018[33]
Adults (> 18 years)	10 ± 6.59 (459 of 505)	9.63 ± 5.20 (341 of 412)	12	−0,35	−1,26; 0,57	98 (*P* < 0.00001)	0,46	Bannerman et al., 2001[34]; Biesiada et al., 2012[51]; Ballinger et al., 1998[43]; Karmiris et al., 2006[39]; Nishi et al., 2005[50]; Rodrigues et al., 2012[47]; Tuzun et al., 2004[40]; Valentini et al., 2008[37]; Waluga et al., 2014[46]; Trejo-Vazquez et al., 2018[44]; Ghomraoui et al., 2017[42]; Büning et al., 2015[49]
Methodological quality								
Low	9.72 ± 5.68 (239 of 505)	11.12 ± 6.51 (174 of 412)	5	−1,11	−3,29; 1,07	97 (*P* < 0.00001)	0,32	Aurangzeb et al. 2011[36]; Ballinger et al., 1998[43]; Karmiris et al., 2006[39]; Rodrigues et al., 2012[47]; Tuzun et al., 2004[40]
Moderate	8.57 ± 5.71 (266 of 505)	7.07 ± 3.46 (238 of 412)	9	0,21	−0,73; 1,16	99 (*P* < 0.00001)	0,66	Frivolt et al., 2018[33]; Bannerman et al., 2001[34]; Biesiada et al., 2012[51]; Nishi et al., 2005[50]; Valentini et al., 2008[37]; Waluga et al., 2014[46]; Trejo-Vazquez et al., 2018[44]; Ghomraoui et al., 2017[42]; Büning et al., 2015[49]

[a]Each value is the mean ± standard deviation of serum lipid levels.

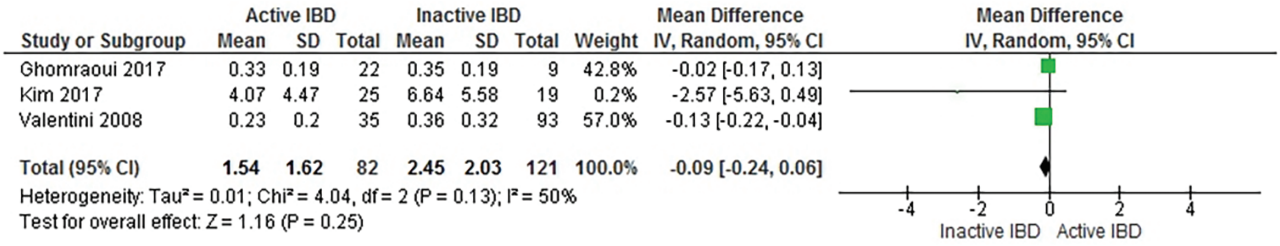

FIGURE 4. Meta-analysis of circulating levels of leptin among IBD carriers in their active or inactive form.

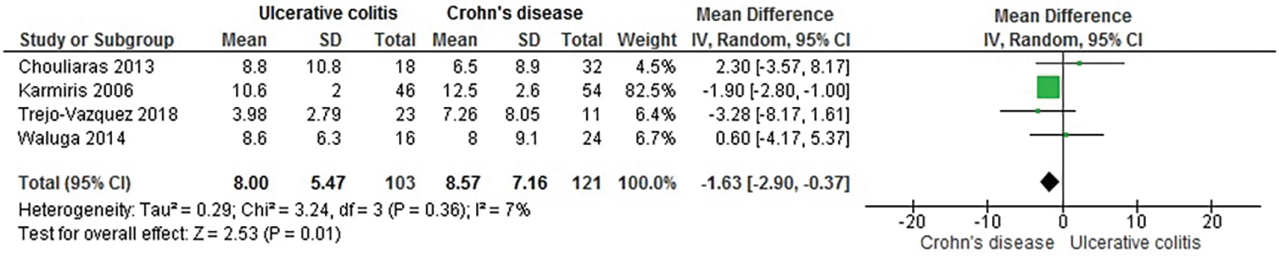

FIGURE 5. Meta-analysis of circulating levels of leptin among patients with Crohn's disease and ulcerative colitis.

was considerably low, indicating that the association is robust. Thus, circulating levels of leptin are not a good biomarker to screen for disease activity among the IBD carrier populations.

Circulating Leptin Levels in the Differential Diagnostic of IBDs

Four studies[38, 39, 44, 46] associating circulating levels of leptin between patients with CD and UC, totaling 224 patients (103 diagnosed with UC and 121 with CD), were included in this meta-analysis (Fig. 5). In contrast to the confirmatory diagnosis and prognosis of IBD, serum leptin levels were negatively and significantly ($P = 0.01$) correlated with patients with UC than with patients with CD (IV, −1.63; 95% CI, −2.09 to −0.37), thus highlighting the potential of this adipokine in the differential diagnosis between these 2 forms of IBDs. As shown in Figure 5, patients with CD (8.56 ± 7.16 ng/mL) have higher serum leptin levels than patients with UC (7.99 ± 5.47 ng/mL). The heterogeneity of this population was significantly low (I^2, 7%; $P = 0.36$).

DISCUSSION

Inflammatory bowel diseases, such as Crohn's disease (CD) and ulcerative colitis (UC), are serious diseases of the digestive tract that are difficult to diagnose and treat.[2] The strategies currently used for the confirmatory and differential diagnosis of these clinical conditions present several limitations.[1, 12] In this context, serum leptin has emerged as a readily available, noninvasive, and affordable biomarker in these patients, but current studies are contradictory as to the accuracy, sensitivity, and specificity of adipokines in the confirmatory diagnosis, prognosis, and differential diagnosis of IBDs.[15, 21] Thus, in this meta-analysis, we propose to synthesize the available evidence on the potential of circulating leptin as a biomarker in patients with inflammatory bowel diseases, such as CD and UC.

Although inversely proportional to the presence and degree of IBDs, serum leptin levels were not significantly associated with CD or UC, thus showing that this peptide has no appeal as a biomarker to differentiate between healthy individuals and patients. Similarly, the prognostic potential of leptin was considerably low, and this anorexigenic peptide was unrelated to the activity of IBDs. In contrast, our review showed that blood levels of leptin are significantly higher among patients with CD compared with those among patients with UC, indicating their potential as a biomarker for the differential diagnosis between CD and UC. To the best of our knowledge, this is the first meta-analysis that highlights the value of leptin in differentiating patients with IBDs between CD and UC carriers. However, it is important to highlight that the mean difference in serum leptin levels among patients with CD and UC was only 0.57 ng/mL. This shows that although serum leptin levels can be explored in the differential diagnosis of IBDs, this should only be a supportive method for endoscopic, imaging, and clinical examination due real possibilities of false-positive and false-negative diagnoses using serum leptin.

Despite the absence of association between circulating levels of leptin and the presence and activity of IBDs, several studies have indicated its involvement in the pathophysiology of IBDs.[15, 23, 24] The role of leptin in the development of IBDs is known to involve enterocytes present in the intestinal mucosa,[52] the immune machinery of the lamina propria (especially

T cells),[53] and mesenteric adipocytes.[14] Initially, leptin expressed and secreted at high levels by the inflamed mesenteric adipocytes common in IBDs binds to leptin receptors present on immune cells residing on the lamina propria and enterocytes of the colon and small intestine, culminating in the activation of nuclear factor kappa B (NF-κB).[24] This phenomenon induces the damage of the epithelium that covers the intestinal mucosa, promotes the apoptosis of cells of the villi and crypts, induces neutrophil infiltration, stimulates the production of reactive oxygen species, and regulates cell proliferation.[54] These changes in the intestinal mucosa are often found in biopsies of patients with IBD, indicating the importance of leptin in the pathophysiology of these conditions.

However, it is important to note that serum levels of leptin are sensitive to different physiological and pathological conditions, which makes this peptide a biomarker influenced by multiple variables.[55] The heterogeneity between the patients with IBD and healthy individuals was considerable, suggesting that the results were probably influenced by intrinsic factors of each population evaluated. This may help explain the absence of the association between leptinemia and the confirmatory diagnosis and prognosis of IBDs. In this regard, the subgroup analysis showed that the ethnic-racial difference, besides being preponderant for the high heterogeneity found, significantly influenced the association between serum leptin and IBDs. Among Latin Americans, for example, circulating levels of leptin were negatively and significantly related to IBDs. Recent studies[56, 57] have raised concern about the potential influence of ethnic-racial difference on circulating levels of leptin; however, the detailed mechanism underlying this remains to be elucidated. In nonwhite patients, leptin levels are generally lower;[56, 57] therefore, it seems likely that ethnic variation might in fact be important in the correlation between leptinemia and IBD.

A relevant result found in this meta-analysis was the significant difference in circulating levels of leptin between patients with CD and UC. Unlike UC, 2 pathognomic symptoms of CD are mesenteric adipose tissue hyperplasia and the presence of creeping fat.[58] These deposits of adipose tissue are known as an important source of production and excretion of biologically active molecules, including leptin. Interestingly, the concentration of leptin is higher in the creeping fat of patients with CD than in the cells of the mesenteric adipose tissue of patients with UC.[59, 60] In addition, preclinical studies have shown that mesenteric adipose tissue from mice or rats with trinitrobenzene sulfonic acid-induced colitis has reduced diameter and increased expression of tumor necrosis factor (TNF)-α, interleukin (IL)-10, inducible nitric/oxide synthase (iNOS), and Toll-like receptor 4 (TLR-4), but it does not alter the secretion of leptin in relation to healthy animals.[61, 62] Thus, this differential pattern of the expression and secretion of adipokines between the patients with CD and UC justifies the higher levels of leptin shown for CD in the present meta-analysis. These studies, therefore, provide a possible biochemical basis for the use of circulating leptin levels as a biomarker for the differential diagnosis of CD and UC.

Differences in leptin between patients with CD and UC are not restricted to serum levels but also reflect the differential pathophysiology of these 2 clinical conditions. As previously mentioned, despite being primarily recognized for its anorectic role in the central nervous system, leptin acts as an important regulator of the immune system.[63] For example, leptin is recognized by modulating the T-cell response via dendritic cells, activating pathways associated with the helper T lymphocyte type 1 (responsible for regulating the innate monophagocytic immune response).[64] This effect, in part, is related to the activation of proinflammatory pathways by leptin, which can be corroborated by the stimulation of IL-12, IL-6, and L-1 secretion, in addition to reduction in IL-10 expression in dendritic cells derived from monocytes stimulated with exogenous leptin in vitro.[65] The influence of leptin on dendritic cells may be a key event in its association with CD. In fact, in patients with CD—but not with UC—dendritic cells have the ability to migrate from the lamina propria to the mesenteric lymph nodes by activating a decompensated immune response, which occurs after expression of the C-C chemokine receptor type 7 (CCR7) motif.[66] Leptin, in this context, has the ability to induce the activation of dendritic cells to promote the expression of the CCR7 receptor, thus stimulating its transmigration to the lymph nodes and the activation of a pro-inflammatory mechanism. Interestingly, only the dendritic cell population producing CCR7 can express the isoform b leptin receptor (LepRb), indicating that this isoform plays a vital role in the inflammation of the mucosa associated with CD.[66]

Leptin also has a strong influence on macrophages in the context of CD.[17, 67] Leptin activates the production of different pro-inflammatory cytokines (eg, TNF-α, IL-1β, and IL-6) and chemokines (eg, CCL1, CCL5, CXCL9, and CXCL10) in recovered M2 macrophages from patients with CD. These macrophages, which are characterized by the activation of Th2 cells, are present in large numbers in the creeping fat of patients with CD but are rare in the mesenteric adipose tissue of patients with UC.[67] Together, these results indicate that the effect of leptin on dendritic cells is important for the initiation of inflammation associated with the CD; already the influence of this adipokine on M2 cells is involved with the modulation of the intensity and localization of inflammatory response.

This meta-analysis has some limitations. First, the methodological quality of the included studies was mostly poor, which makes the association shown strongly influenced by the biases of each study. Second, the heterogeneity of the association between patients with IBDs and healthy controls was considerably high, which weakens the robustness of the results obtained. Third, the small number of patients included in each study limits the extrapolation of the results to other populations. Fourth, several studies do not clearly identify the possible confounding factors and the exclusion criteria,

which may compromise the associations observed in each case. Fifth, many of the studies did not describe the use of drugs such as anti-inflammatories, corticosteroids, and anti-TNF at the time of analysis, which may certainly influence the association studied. In particular, 2 of the included studies showed that leptin levels are elevated after the use of anti-TNF therapy (infliximab). Finally, it is important to note that the associations shown in the meta-analysis do not imply causality and are always sensitive to residual confounding factors, especially if the included studies present the observational design.

CONCLUSION

In summary, our meta-analysis shows that leptinemia has low specificity and selectivity to differentiate carriers of IBDs from the general population. In addition, circulating levels of leptin do not differ between patients with CD or UC in their active and inactive forms. However, we showed that serum leptin concentration may be a promising biomarker for the differential diagnosis of IBDs between CD and UC. As the diagnoses remain incomplete without successful differentiation between CD and UC, circulating leptin levels can be used as a low-cost, easy-to-execute tool to assist in this difficult task. In addition, many studies emphasize that leptin plays a central role in the pathophysiology of IBDs, especially CD. Thus, our results clearly show that leptin is a potential therapeutic target for the development of novel enteroprotective drugs against CD. However, large randomized controlled trials are required to verify the true value of leptin as a biomarker in IBDs or as a promising pharmacological target in CD, especially because the difference in serum leptin between patients with CD and UC found in this review was slight (only 0.57 ng/mL between the groups).

SUPPLEMENTARY DATA

Supplementary data is available at *Inflammatory Bowel Diseases* online.

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