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Serum adipokines as biomarkers for the therapeutic monitoring of patients with inflammatory bowel diseases (IBDs) treated with infliximab: a systematic review and meta-analysis

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Summary

Introduction: Inflammatory bowel diseases (IBDs) are idiopathic inflammations of the colon, which can often undergo remission with the use of specific anti-TNF antibodies such as the infliximab. Although that the therapeutic monitoring can provide valuable insight into the possible etiology of unfavorable outcomes and allow for an appropriate management strategy for these patients, currently none technique or biomarker have proved ideal for the evaluation of therapeutic benefices of anti-TNF antibodies in IBDs. **Aim:** To summarise current knowledge on the role of serum adipokines as potential biomarkers for the therapeutic monitoring of patients with IBDs under infliximab. **Methods:** A systematic review was carried out in the PubMed/MEDLINE, Cochrane Library, Scopus and *Biblioteca Virtual em Saúde* databases. Next, the meta-analysis was performed with the mean values of serum adipokine levels in patients with IBDs before and after the use of infliximab using the Review Manager (RevMan) ® 5.3 software. **Results:** Three studies that together included 58 patients diagnosed with IBDs and treated with inflix-

imab at 5 mg/kg were selected. According to the quantitative analysis, serum leptin levels were significantly increased after the use of infliximab (p-value=0.01; Heterogeneity: I^2=61%), which is correlated with the clinical remission of the disease. In addition, the circulating adiponectin (p-value=0.006; Heterogeneity: I^2=0%) and resistin (p-value=0.009; Heterogeneity: I^2=93%) concentrations were both reduced after the clinical remission of IBD with the use of infliximab. **Conclusion:** Serum leptin levels are significantly increased, while circulating adiponectin and resistin is reduced among IBD patients after the use of infliximab.

Keywords: Therapeutic monitoring, Infliximab, Leptin, Adiponectin, Resistin, Inflammatory Bowel Diseases.

Resumo

Adipocinas séricas como biomarcadores para monitoramento terapêutico de pacientes com doenças inflamatórias intestinais (DIIs) tratados com infliximabe: revisão sistemática e metanálise

Introdução: as doenças inflamatórias intestinais (DIIs) são inflamações idiopáticas do cólon, que muitas vezes podem sofrer remissão com o uso de anticorpos anti-TNF específicos, como o infliximabe. Embora o monitoramento terapêutico possa fornecer informações valiosas sobre a possível etiologia de desfechos desfavoráveis e permitir uma estratégia de manejo adequada para esses pacientes, atualmente nenhuma técnica ou biomarcador se mostrou ideal para a avaliação dos benefícios terapêuticos dos anticorpos anti-TNF em DIIs. **Objetivo:** resumir o conhecimento atual sobre o papel das adipocinas séricas como potenciais biomarcadores para o monitoramento terapêutico de pacientes com DII em uso de infliximabe. **Métodos:** foi realizada revisão sistemática nas bases de dados PubMed/MEDLINE, Cochrane Library, Scopus e Biblioteca Virtual em Saúde. Em seguida, foi realizada a meta-análise com os valores médios dos níveis séricos de adipocinas em pacientes com DII antes e após o uso de infliximabe, utilizando o software Review Manager (RevMan) ® 5.3. **Resultados:** três estudos que juntos incluíram 58 pacientes diagnosticados com DII e tratados com infliximabe na dose de 5 mg/kg foram selecionados. De acordo com a análise quantitativa, os níveis séricos de leptina aumentaram significativamente após o uso de infliximabe (valor de p=0,01; Heterogeneidade: I^2=61%), o que está correlacionado com a remissão clínica da doença. Além disso, as concentrações circulantes de adiponectina (valor de p=0,006; heterogeneidade: I^2=0%) e

resistina (valor de p=0,009; heterogeneidade: I^2=93%) foram ambas reduzidas após a remissão clínica da DII com o uso de infliximabe. **Conclusão:** os níveis séricos de leptina estão significativamente aumentados, enquanto a adiponectina e a resistina circulantes estão reduzidas entre os pacientes com DII após o uso de infliximabe.

Palavras-chave: Acompanhamento terapêutico, infliximabe, leptina, adiponectina, resistina,doenças inflamatórias intestinais.

Resumen

Adipocinas séricas como biomarcadores para el seguimiento terapéutico de pacientes con enfermedades inflamatorias intestinales (EII) tratados con infliximab: revisión sistemática y metanálisis

Introducción: las enfermedades inflamatorias intestinales (EII) son inflamaciones idiopáticas del colon, que en muchas ocasiones pueden entrar en remisión con el uso de anticuerpos anti-TNF específicos, como el infliximab. Aunque el seguimiento terapéutico puede proporcionar información valiosa sobre la posible etiología de los desenlaces desfavorables y permitir una estrategia de manejo adecuada para estos pacientes, actualmente ninguna técnica o biomarcador ha demostrado ser ideal para evaluar los beneficios terapéuticos de los anticuerpos anti-TNF en las EII. **Objetivo:** resumir el conocimiento actual sobre el papel de las adipocinas séricas como biomarcadores potenciales para el seguimiento terapéutico de pacientes con EII que utilizan infliximab. Métodos: Se realizó una revisión sistemática en las bases de datos PubMed/MEDLINE, Cochrane Library, Scopus y Virtual Health Library. Luego, se realizó un metanálisis con los valores medios de los niveles de adipoquinas séricas en pacientes con EII antes y después del uso de infliximab, utilizando el software Review Manager (RevMan)® 5.3. **Resultados:** se seleccionaron tres estudios que en conjunto incluyeron 58 pacientes diagnosticados de EII y tratados con infliximab a dosis de 5 mg/kg. Según el análisis cuantitativo, los niveles de leptina sérica aumentaron significativamente después del uso de infliximab (valor de p = 0,01; Heterogeneidad: I^2 = 61 %), lo que se correlaciona con la remisión clínica de la enfermedad. Además, las concentraciones circulantes de adiponectina (valor de p = 0,006; hete-

rogeneidad: $I^2 = 0$ %) y resistina (valor de p = 0,009; heterogeneidad: $I^2 = 93$ %) se redujeron después de la remisión clínica de la EII con el uso de infliximab. **Conclusión:** los niveles de leptina sérica aumentan significativamente, mientras que la adiponectina y la resistina circulantes se reducen entre los pacientes con EII después del uso de infliximab.

Palabras clave: Seguimiento terapéutico, infliximab, leptina, adiponectina, resistina, enfermedades inflamatorias intestinales.

Introduction

Inflammatory bowel diseases (IBDs) are chronic and idiopathic disorders that essentially cover Crohn's disease (CD) and ulcerative colitis (UC). IBDs are considered immune-mediated diseases without a definitive cure, since they have a chronic, progressive, and recurrent character, resulting from an inadequate immune response in genetically susceptible individuals [1-3]. Clinically, IBDs are characterized by intense inflammation of the intestinal mucosa, which evolves into structural and functional changes in the large and/or small intestine [1, 3]. Recently, a population-based systematic review showed that during the second half of the twentieth century, there was a significant increase in the incidence of IBDs in North America and Europe. Since 1990, this rate has been shown to be unstable or decreasing in these regions, but its prevalence continues to increase [4]. Currently, IBDs affect 1.3% of the American population, thus totalling 3.1 million cases [5]. Conversely, IBDs in developing countries still have a low prevalence, but with increasing incidence, so the total number of cases is expected to increase in the coming years in this region [4].

The treatment of IBDs is usually aimed at controlling acute phase episodes and, in the long term, disease remission. Pharmacological therapy is usually started with the use of corticosteroids, aminosalicylates, and immunomodulators [1, 2]. However, in cases of moderate to severe IBDs, which do not respond well to the first therapeutic options, the use of so-called biologics drugs is indicated [6, 7]. Infliximab was the first medication (prototype) of this class to be approved against IBDs, which is indicated for the treatment of adults and children from 6 years old who live with moderate to severe CD or UC [1, 2, 8]. It is a chimeric human-murine monoclonal IgG1 antibody that is capable of strongly binding to tumour necrosis factor (TNF). After binding to TNF, infliximab prevents it from interacting with its receptors, consequently resulting in the inhibition of pro-inflammatory pathways that trigger acute and recurrent episodes of IBDs [8]. Infliximab has a half-life of approximately 14 days, is adminis-

tered intravenously (iv) by weight-based dosing, and is typically dosed every 4–8 weeks following an initial loading period (0–2–6 weeks) [9]. However, the development of anti-drug antibodies (ATIs) directed against the Fab fragment of infliximab can be observed in patients with IBDs, which is an important mechanism involved in the loss of response. The ATIs interfere with the biological activity by inhibiting the binding of TNF inhibitors to both serum and membrane-bound TNF alpha (TNF-α) molecules and by creating immune complexes that are eliminated by the reticuloendothelial system [6, 9]. Thus, the therapeutic monitoring of TNF inhibitors may, in many cases, provide insight into the mechanism of the evolving loss of response, as well as suggest a possible salvage strategy [10].

However, the therapeutic monitoring of infliximab efficacy in unresponsive IBDs is often complicated by the need for invasive procedures, such as endoscopy and recurrent biopsies [7, 9, 11]. Furthermore, the monitoring of ATI levels has important drawbacks, one being the inability to detect ATIs in the presence of infliximab in the serum by Enzyme-Linked Immunosorbent Assay (ELISA). Moreover, in the detriment of additional detection methods such as homogenous mobility shift assay and radioimmunoassay to be used in clinical practise, none demonstrate superior diagnostic value in direct comparison with ELISA techniques [10]. Thinking about this gap, several studies focused on developing new non-invasive, precise, sensitive, specific, and accessible biomarkers to be used in the therapeutic monitoring of infliximab, which led to the emergence of some serological and coprological candidates [9]. Unfortunately, all candidate biomarkers have several limitations, and none have proved relevant for the evaluation and therapeutic management of IBDs treated with infliximab [11].

Adipokines, which are peptides and bioactive proteins produced and secreted by adipose tissue, stand out as potential biomarkers because they have been shown to play an active role in relapse and even remission of IBDs [12, 13]. The ambiguous role of these adipokines is due to the fact that they may have a pro- or anti-inflammatory effect depending on their serum levels, type of adipokine, and type of receptor to which they activate [14]. Among these adipokines, adiponectin is characterised by its anti-inflammatory effects; therefore, its production is inversely proportional to the lipid content inside the adipocytes [15]. In turn, leptin, resistin, and visfatin are characterised by their known pro-inflammatory effects, and the production of these adipokines is proportional to the content of lipids and the degree of inflammation in adipocytes [16]. Studies have shown that serum levels of resistin and visfatin are increased in patients with CD or CU when compared to healthy controls [17, 18]. A recent meta-analysis by our group revealed that serum leptin levels, in turn, did not differ between patients with IBD compared to healthy patients. However, leptin levels were significantly higher in patients with CD than in patients with UC because of creeping fat (i.e. a

locally restricted hyperplasia of the mesenteric fat adjacent to the inflamed segments of the intestine), which is a pathognomonic feature of CD [19]. In turn, the effects of IBDs on serum adiponectin levels are controversial, as some studies show an increase in serum adiponectin [17], while others have found a reduction in its circulating concentration [20].

Due to its relationship with intestinal inflammation, it is suggested that serum levels of adipokines can be explored in the therapeutic monitoring of patients with IBDs, assisting in the management of treatment in these patients. Currently, despite much evidence associating changes in serum concentration of several adipokines to the efficacy of infliximab, the results are still controversial, especially considering the ambiguous effects of many of these peptides [21-23]. Thus, we aim to summarise current knowledge on the role of serum adipokines as potential biomarkers for the therapeutic monitoring of patients with IBD under the use of infliximab through a systematic review of the biomedical literature and meta-analysis of the recovered data. This study, therefore, seeks to elucidate the role and potential of these adipokines in the therapeutic management of patients with IBD who benefit from the use of this anti-TNF antibody.

Methods

Study type

This is a systematic review and meta-analysis conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24]. To assess the employability of serum adipokine levels in the therapeutic monitoring of patients with IBDs treated with infliximab, the **PICOS** strategy was used, as follows: "**P**opulation", patient with a diagnosis of IBD (CD; UC; or indeterminate IBD); "**I**ntervention", use of infliximab; "**C**ontrol", patients before the use of infliximab; "**O**utcomes", serum levels of leptin, adiponectin, visfatin, or resistin; "Study", observational before-and-after studies.

Search strategy

A systematic search was carried out in the PubMed/MEDLINE, Cochrane Library, Scopus, and *Biblioteca Virtual em Saúde* (VHL) databases. To determine the descriptors used in the search strategies, the Medical Subject Heading (MesH) terms were employed to define the keywords in English and the *Descritores Virtual em Saúde* to define the keywords in Portuguese and Spanish. The terms "Leptin" OR "Adiponectin" OR "Nicotinamide Phosphoribosyltransferase" OR "Resistin" were combined using the AND Boolean with the terms "Inflammatory Bowel Diseases" OR "Colitis,

Ulcerative" OR "Crohn's Disease". In all combinations, the term "Infliximab" was also used, as in the following examples: "Leptin" AND "Inflammatory Bowel Diseases" AND "Infliximab". The detailed search strategy used in each of the selected databases is shown in the supplementary materials.

The reference list of all included studies, as well as of prominent narrative reviews in the field of interest, was also evaluated for the selection of other possible articles that fit the inclusion criteria in the study. In addition, with the help of the Web of Science platform, all articles that cited the included papers were also screened. After the search, only articles written in Portuguese, Spanish, and English were selected, with no restrictions on the date of publication.

Inclusion and exclusion criteria

The inclusion of the studies was carried out according to the criteria defined in the PICOS strategy, described above. Thus, studies that do not fit this strategy were excluded, such as reviews, notes, e-mails, editorials, and letters to the editor. Other exclusion factors were as follows: (i) articles that did not describe the therapeutic scheme applied in association with infliximab, (ii) articles that did not describe the doses and routes of administration of infliximab, and (iii) studies that included, in a combined therapeutic protocol, other biologic drugs in addition to infliximab.

Selection of studies

For the selection of studies, the EndNote® software was used to remove duplicates and organise the articles found in a table, including author, year, title, periodic, keywords, and abstract. Next, the titles, abstracts, and keywords were analysed by two independent authors (P.A.C. and W.G.L.) in order to identify relevant studies. In cases where the article was in accordance with inclusion criteria but the full text was not available, the corresponding author was contacted by e-mail three times (with 14-day intervals between them), and the articles were included if they were received in response to the last point of contact at the latest. Any discrepancy between the two evaluators at this stage was resolved by discussion with the judge (S.O.A.F.). The pre-selected articles were then thoroughly analysed to confirm their relevance and potential inclusion in this systematic review and meta-analysis.

Data analysis

For critical interpretation, all data of interest obtained were summarised and organised in tables. The selected articles were submitted to a full analytical reading to identify and extract the variables of interest, which include the following: reference (first author and year of publication), characteristics of the population studied (age group,

sex, region of the study, number of patients included), type of IBD, and serum levels of adipokines (concentration and technique used). For the meta-analysis, the mean and standard deviation values of serum adipokines (ng/mL), determined in patients before and after the use of infliximab, were extracted. Studies that defined serum adipokine levels as nonparametric data and the median and 25th percentile were used for the meta-analysis. Some of the studies included in our review used other units (such as pg/L) to report the level of some cytokines. In these cases, the units were converted to ng/mL in order to standardise all data. Values in pg/mL were multiplied by 1,000 and converted to ng/mL.

Quality assay

The quality of the included studies was independently assessed by two reviewers (P.A.C. and W.G.L.) using the Newcastle-Ottawa Quality Assessment Scale to examine the selection of participants and study design, comparability of groups, ascertainment of exposure, and outcome processing [25]. Included studies were categorised into three quality groups: high quality (received 7 to 9 stars), moderate quality (received 4 to 6 stars), and low quality (received 3 to 0 stars). Furthermore, the risks of bias of studies were determined using the tool described by Munn et al [26]. This tool includes 10 items for critical assessment of the methodological quality of observational studies. For each criterion, the study was attributed "yes" or "no" or "not applicable" or "unclear". The total number of "yes" answers per study was tallied. Herein, the higher the number of "yes" means the lower the risk of bias of the study. Because a limited number of articles were available, the results of the quality assessment were not used as an inclusion/exclusion criterion.

Statistical analysis

The meta-analysis was performed with the mean values of serum adipokine levels in patients with IBD before and after the use of infliximab. Review Manager (RevMan) ® 5.3 software was used to analyse data from individual studies, which were then combined using a random-effects model to estimate the combined mean difference of the variable of interest (adipokine levels) and their confidence intervals. The heterogeneity of primary data, in turn, was analysed by the I^2 test; we considered $I^2 > 50\%$ as a criterion for substantial heterogeneity. In all procedures, the level of significance was set at 5%.

Results

Search and selection of studies

As shown in Fig. 1, 85 articles were identified during the search in the selected databases, 49 in Scopus, 22 in the Virtual Health Library, nine in PubMed/MEDLINE, and five in the Cochrane Library. With the exclusion of duplicate records using the EndNote® software, 72 studies were conducted to review the titles, abstracts, and keywords. After this stage, 10 relevant studies were selected for full-text read and evaluated according to the previously defined eligibility criteria. At the end, there were three studies that followed for critical reading and data extraction of interest [21-23]. Of these, only one was excluded from quantitative studies, as it did not present comparable data to the others [21]. The remaining two studies were included in the quantitative analysis and used to conduct a meta-analysis of the relationship between serum adipokine levels and the efficacy of infliximab in the treatment of patients with IBD.

Study characteristics

The main characteristics of the studies included in the systematic review are summarised in Table 1. Of the studies, two were prospective cohorts (2/3; 66%) [21-23] and one was a retrospective cohort (1/3; 44%) [22]. All studies were carried out in European countries, namely, Belgium [21], Germany [22], and Greece [23]. Overall, 58 patients were analysed in these studies, of which 55 were diagnosed with CD and three with UC. No cases of indeterminate IBD have been reported. The overall mean age of the patients was 26.7 years, and the majority were male (32/58; 55%). All patients were treated with 5 mg/kg of infliximab, but the administration regimens differed between the studies (Table 1).

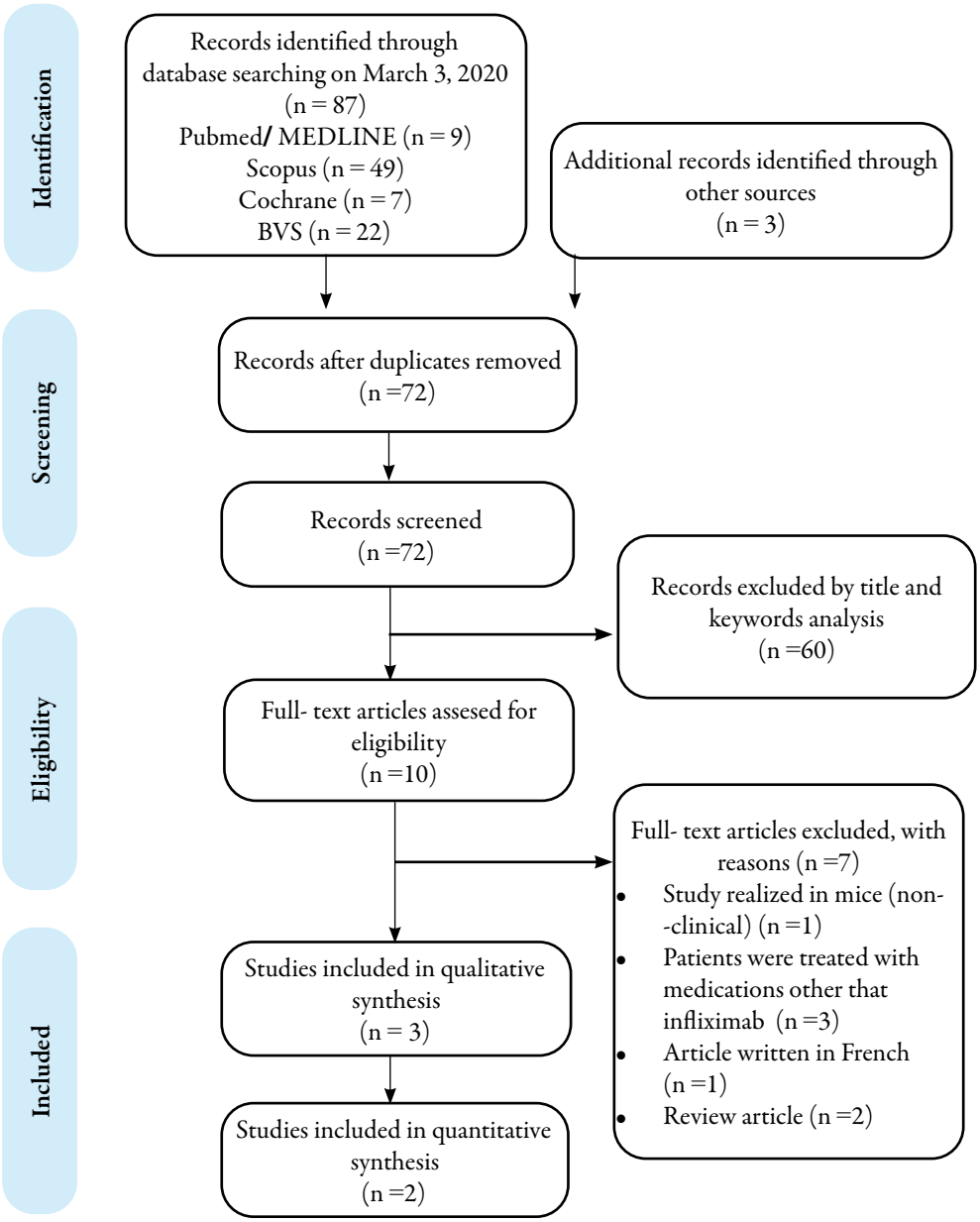

Figure 1. Flowchart of article selection for systematic review and meta-analysis according to PRISMA criteria [24].

Table 1. Main characteristics of the included studies

Study	Study design and follow-up	Country	Patients included (n)	Type of DII (DC or UC)	Age, Years	Sex, %[&]	Infliximab treatment	Outcomes associated to infliximab treatment	Number of stars
Franchimont *et al.*, 2005 [21]	Prospective cohort Single center	Belgium	20	·Active CD [CD activity index (CDAI) > 150]	26.5 ± 9.4[a]	40	·5 mg/kg ·Patients received either a three-dose administration regimen (0, 2, and 6 wk) (n = 14) or a single-dose induction (n = 6)	·Leptin levels were significantly higher after IFX administration · IFX significantly induced clinical remission in all patients at 4 wk; · The increase in serum leptin was negatively correlated with the decrease in CRPat 1 wk ·Leptin levels increased in patients treated with IFX who were entering into clinical and biological remission	7

Study	Study design and follow-up	Country	Patients included (n)	Type of DII (DC or UC)	Age, Years*	Sex, %&	Infliximab treatment	Outcomes associated to infliximab treatment	Number of stars
Frivolt *et al.*, 2018 [22]	Retrospective cohort Single center	Germany	18	CD	15.0±1.5	45	·5 mg/kg · Patients received infliximab at 0, 2, and 6 weeks, followed by a maintenance treatment every 8 weeks.	·Resistin significantly decreased under IFX ·Leptin significantly increased in CD patients under ·Adiponectin significantly increased after the first IFX infusion but decreased after 14 weeks to levels lower than at week 2	9
Karmiris *et al.*, 2007[b] [23]	Prospective cohort Single center	Greece	20	UC (3) and CD (17)	UC (43.3) CD (37.9) Overall mean: 38.7	UC (33) CD (41) Overall: 48	·5 mg/kg · Patients received infliximab at 0, 2, and 6 weeks, followed by a maintenance treatment every 8 weeks.	·Resistin significantly decreased under IFX ·Adiponectin and leptin levels were no changed after IFX infusion ·IFX induced significant increase of BMI in all patients	6

Note. *Data refer to the mean age of the groups or the age group employed. &Data were proportional to women. [a]Age at diagnosis (yr). [b]Intra-assay precision was evaluated.

Methodological quality and risk of bias

The methodological quality of the included studies was generally considerable, being judged to be moderate [23] and high [21, 23] according to the criteria established in the Newcastle-Ottawa scale. The studies were signed with 9 [22], 7 [21], or 6 [23] stars, since only the studies by Frivolt *et al.* [22] clearly present the limitations and potential sources of bias and inaccuracy. None of the selected studies described the intra- and inter-trial variations related to the assessed adipokine dosages.

Overall, the included studies had a risk of bias due to not accounting for possible confounding factors and/or failure to perform subgroup analyses, except the study by Franchimont *et al.* [21], which is suitable for all these criteria (Table 2). With regard to the population analysed, none of the studies included a satisfactorily large group of patients to infer a cause-effect relationship with great statistical robustness, and furthermore, the sample size calculation is not discussed in any of the studies selected. However, the studies by Frivolt *et al.* [22] and Karmiris *et al.* [23] clearly describe the method used to recruit included patients (Table 2).

Association between circulating leptin levels and the use of infliximab

To evaluate the association between serum leptin levels and clinical remission of IBDs after infliximab use, 38 patients (35 patients with CD and three patients with CU) were pooled for this meta-analysis. As shown in Fig. 2, treatment with infliximab was associated with a significant increase in circulating leptin level (IV, -0.73; 95% CI, -1.30 to -0.16; $p = 0.01$). The heterogeneity, indicated by the I^2 statistic, was relatively high ($I^2 = 61\%$), suggesting that factors from the included population may be associated with the result observed. However, as only two articles were selected, a subgroup analysis could not be performed to determine the possible sources of heterogeneity.

Franchimont *et al.* [21] revealed that an increase in serum leptin levels accompanied the clinical remission of IBDs after the use of infliximab, suggesting that this adipokine is a potential indicator of disease remission. In addition, the study also correlated the increase in serum leptin levels after the use of infliximab with a significant reduction in plasma C-reactive protein, which is an important biomarker of disease activity (Table 1).

Table 2. Risk of bias of observational studies included according to criteria adopted by Munn *et al.* (2014).

Reference	Was the sample representative of the target population?	Were study participants recruited in an appropriate way?	Was the sample size adequate?	Were the study subjects and the setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were objective, standard criteria used for the measurement of the condition?	Was the condition measured reliably?	Was there appropriate statistical analysis?	Are all important confounding factors/ subgroups/differences identified and accounted for?	Were subpopulations identified using objective criteria?	Total number of "yes"
Franchimont *et al.*, 2005 [21]	Unclear	Unclear	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Frivolt *et al.*, 2018 [22]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Not applicable	7
Karmiris *et al.*, 2007 [23]	Unclear	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Not applicable	6

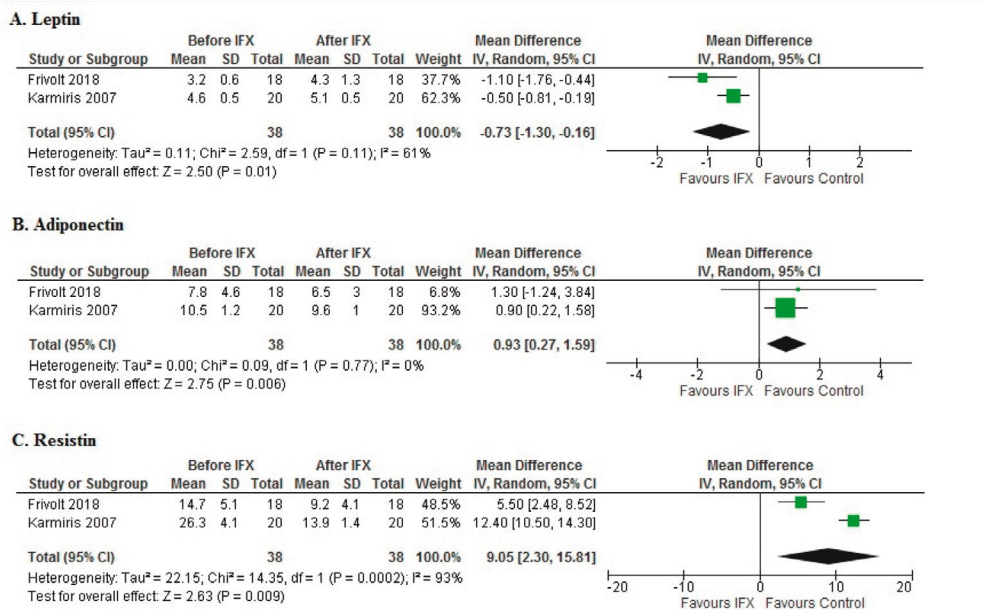

Figure 2. Meta-analysis of circulating levels of leptin, adiponectin, and resistin among patients with IBD treated with infliximab at 5 mg/kg. CI, confidence interval; IV, mean variation; SD, standard deviation.

Association between circulating adiponectin levels and the use of infliximab

Infliximab treatment was negatively and significantly related to serum adiponectin levels (IV, 0.93; 95% CI, 0.27-1.59; p = 0.006). The heterogeneity of the population included in this meta-analysis was low (I^2 = 0%), indicating good robustness in the association shown.

Association between circulating resistin levels and the use of infliximab

For this meta-analysis, 38 patients with IBDs (35 patients with CD and three patients with CU) were included. As shown in Fig. 2, serum resistin levels were significantly reduced after clinical remission of IBDs with the use of infliximab (IV, 9.05; 95% CI, 2.30-15.81; p = 0.0002). However, the heterogeneity of this population was substantial, as revealed by the I^2 statistic (I^2 = 93%). In the absence of an adequate number of studies, subgroup analysis cannot be performed to assess possible sources of heterogeneity. Interestingly, the two studies included in this meta-analysis [21, 23] used the same therapy protocol with infliximab, and both found an association between the decrease in serum resistin levels and the clinical remission of IBDs associated with anti-

TNF therapy (Table 1). Therefore, it is suggested that the therapeutic regimen does not consist of a source of heterogeneity in this case.

Discussion

IBDs are diseases that present a clinical picture characterized by idiopathic inflammation of the colon, which can often undergo remission with the use of specific biologic drugs such as infliximab [8, 9]. However, one of the biggest challenges for patients with IBD under the use of infliximab is therapeutic monitoring and management of treatment effectiveness, since many of the procedures are currently invasive and cannot be performed with frequency [2, 9]. Currently, new serological and faecal biomarkers have been studied, but none have been shown to be ideal for the therapeutic management of IBDs due to their specificity limitations [11]. In this context, certain adipokines may have great potential for the therapeutic monitoring of patients with IBDs treated with infliximab, because their serum levels have been shown to be strongly influenced by the use of anti-TNF agents. However, current studies are contradictory in terms of the precision, sensitivity, and specificity of serum adipokine levels for this purpose [17, 22]. Thus, we aimed to synthesise the available evidence on the possible use of circulating adipokines as biomarkers in the therapeutic monitoring of patients with IBDs using infliximab.

Two cohorts and one case-control that included 58 patients (mean age, 26.7 years) diagnosed with IBDs (55 with CD and three with CU) and treated with infliximab at 5 mg/kg were selected. According to the quantitative analysis of the main outcomes of each study, serum leptin levels were significantly increased after the use of infliximab (IV, -0.73; 95% CI, -1.30 to -0.16; $p = 0.01$), which is correlated with the clinical remission of the disease. In addition, the circulating adiponectin (IV, 0.93; 95% CI, 0.27-1.59; $p = 0.006$) and resistin (IV, 9.05; 95% CI, 2.30-15.81; $p = 0.009$) levels were reduced after clinical remission of IBD with the use of infliximab. To the best of our knowledge, this is the first systematic review and meta-analysis that highlights the potential of serum leptin, adiponectin and resistin levels as biomarkers for monitoring the clinical remission of IBDs induced by infliximab use.

The influence of infliximab on serum adipokines levels may, at least in part, be justified by its effect on TNF-α. The mesenteric adipose tissue of patients with IBDs is characterised by the involvement of an important inflammatory process associated with increased tissue concentrations of TNF-α [12, 27]. Infliximab is able to bind to soluble (sTNF) and transmembrane (tmTNF) forms of TNF-α, which is a key mediator in the inflammatory cascade associated with the activity of CD and UC [28]. In this direc-

tion, it is expected that infliximab may also inhibit the inflammatory process associated with mesenteric adipose tissue, which is known to regulate circulating adipokine levels in patients with IBDs [12, 29]. In vitro studies showed that the exposition of TNF-α (10 ng/ml) by 48 h decreased leptin production by 30-50% and gene expression by 80–90% in adipocytes from human abdominal subcutaneous adipose tissue [30]. Similarly, leptin release from subcutaneous adipocytes was inhibited by 17.7%, 21.6%, and 37.1% by 1, 10, and 100 ng/mL TNF-α, respectively, after 48 h in culture, indicating a dose-dependent effect [31]. In addition, Bokarewa *et al.* [32] showed that stimulation of human peripheral blood mononuclear cells (PBMCs) with TNF-α (10 ng/mL) resulted in upregulation of resistin mRNA and increased resistin levels in the supernatants after 48 h of stimulation. Taken together, these results suggest that the action of TNF-α on the mesenteric adipocytes of patients with IBD is associated with the inhibition of expression, synthesis, and release of leptin. Moreover, the activity of TNF-α on macrophages into mesenteric adipose tissue induces an increase in the expression and synthesis of resistin. In this direction, it is expected that the use of infliximab will reverse the effects of TNF-α on mesenteric adipose tissue, allowing an increase in leptin content and a reduction in resistin, which is in accordance with the findings of this meta-analysis.

Leptin is an appetite-depressing (anorexigenic) peptide that has a direct relationship with body fat mass and has several metabolic functions associated with the regulation of glucose and lipid homoeostasis [33]. However, in addition to its function as an anti-obesity factor, leptin may play an important role in acute and chronic inflammatory conditions. In patients with acute inflammation, such as sepsis, leptin concentrations are increased up to three-fold from baseline levels [34]. In contrast, under conditions of chronic inflammation, like IBDs, leptin release is inhibited [22]. In fact, most studies showed that the circulating leptin levels were found to be decreased in patients with IBDs compared with healthy controls [13, 18, 35]. The decreased serum leptin levels of patients with IBD could be partially attributed to an elevated circulating TNF-α, which has already been shown to inhibit the expression, synthesis, and release of leptin in vitro [30, 31]. In this direction, suggesting that the chronic inhibitory effect of TNF-α on leptin release is blocked by anti-TNF antibodies, justifying the increased leptin levels shown in this review after the use of infliximab. Therefore, monitoring serum leptin levels is a good indicator of the efficacy of anti-TNF therapy and can thus be a valuable tool in the therapeutic monitoring of patients with IBDs treated with infliximab. Furthermore, the increase in leptin levels after infliximab use might also be associated with increased appetite and weight gain when patients enter remission [22]. However, because several studies indicate that leptin does not seem to influence food behaviour in humans to the same extent as in mice [33, 36, 37], this mechanism may be less relevant.

Resistin (or "resistance to insulin") is a peptide proposed as a link between obesity and diabetes, which was named for its ability to resist (interfere with) insulin action [38]. The expression patterns of resistin differ considerably between species, as the murine resistin is expressed primarily by adipocytes, while, in human resistin, is predominantly expressed by PBMCs and macrophages [39]. Thus, although resistin is postulated to contribute to insulin resistance in mice, human resistin plays a major regulatory role in the inflammatory response [17, 39, 40]. In line with this, human resistin stimulates the secretion of pro-inflammatory cytokines such as TNF-α, IL-6, IL-12, and monocyte chemoattractant protein (MCP)-1 in PBMCs, macrophages, and hepatic stellate cells via the nuclear factor-κB (NF-κB) pathway in vitro [32, 41]. Furthermore, serum resistin levels have been found to be elevated in inflammation-related diseases such as type 2 diabetes mellitus, coronary atherosclerosis, chronic kidney disease, rheumatoid arthritis, and/or sepsis [41]. In IBD patients, serum resistin levels were found to be elevated, and in the creeping fat from CD patients, resistin mRNA is overexpressed, suggesting that this pro-inflammatory adipokine may play an important role in the pathophysiology of IBDs (especially in CD) [35]. Interestingly, TNF-α, but not other pro-inflammatory cytokines such as IL-6 and IL-1β, induced resistin mRNA expression, suggesting that this adipokine is markedly elevated in IBD patients as a response to the sustained increase in TNF-α levels in these patients [32]. Infliximab treatment, in turn, inhibits the local and systemic effects of TNF-α in patients with IBDs, causing a significant decrease in circulating resistin levels, as shown in this review. Consistent with our study, Wistar rats with colitis induced by repeated intracolonic trinitrobenzene sulphonic acid (TNBS) instillations showed a significant increase in resistin mRNA in mesenteric adipose tissue after infliximab administration (5 mg/kg intraperitoneally), which was associated with the restoration of adipocyte morphology and PPAR-γ expression [42]. In fact, it has been shown that the expression and release of resistin in PBMCs are downregulated by PPAR-γ [32, 41, 43], indicating that infliximab increases resistin levels by activating this pathway in macrophages from mesenteric adipose tissue of patients with IBDs.

Adiponectin is the most abundant peptide secreted by adipocytes and has been extensively studied for its involvement in obesity and associated morbidities such as cardiovascular disease, metabolic syndrome, and type 2 diabetes [44]. There is much evidence that adiponectin is a potent anti-inflammatory agent associated with the inhibition of pro-inflammatory cytokines (e.g. TNF-α, IL-6, IL-1β, and chemokine) and to the induction of anti-inflammatory ones (e.g. IL-10), downregulation of adhesion molecule expression (e.g. ICAM-1 and VCAM-1), antagonism of toll-like receptors and their ligands (e.g., LPS), and inhibition of pro-inflammatory pathways (e.g. NF-κB) [45]. However, the relationship between serum adiponectin levels in patients with

IBD is controversial [46]. This is because some studies have shown high levels of this adipokine in patients with active IBD, indicating a negative feedback mechanism on the ongoing inflammatory process [17, 47, 48], while others point to reduced circulating adiponectin levels as a triggering mechanism of disease activity [20]. In addition, the study by Frivolt *et al.* [22] indicates that the effects of infliximab on serum levels of adiponectin is significantly influenced by the temporary effect of this biologic drug. In this study, the authors showed that adiponectin increased two weeks after the use of infliximab to a level higher than that observed before treatment. However, after the fourteenth week, the values decreased considerably and did not differ from the baseline values before treatment, even if the clinical remission of the disease maintained. Thus, the marked early increase of the potent anti-inflammatory adiponectin may contribute to the rapid response to infliximab in IBD, but this adipokine is not a good biomarker to assess the long term therapeutic benefit of the drug.

This meta-analysis has some limitations. First, the number of articles included was small, which reflects the limited number of studies on this topic. Due to this limitation, it was not possible to perform subgroup analysis to determine the possible sources of heterogeneity for each of the studied outcomes. Second, the difference in the dosing period for adipokines after the start of infliximab use between studies may have interfered with the association shown, especially in the case of adiponectin where temporality is a relevant factor. Third, as a result of the small number of patients included in this review, the extrapolation of the associations found in other populations is limited. Fourth, only three of the patients included in the selected studies were diagnosed with UC, which makes it difficult to say that the result obtained for this meta-analysis is considerable for this group. Fifth, none of the selected studies described the intra- and inter-trial variations related to the adipokine dosages, thus increasing the bias in the results. Finally, it is emphasised that the associations shown in the meta-analysis do not imply causality and are always sensitive to residual confounding factors, especially in this case where the included studies present the observational design.

Conclusion

In summary, this systematic review and meta-analysis indicates that serum leptin levels are significantly increased, while circulating adiponectin and resistin is reduced among IBD patients after the use of infliximab. This effect is coupled with the activity of infliximab on TNF-α, which a cytokine is known to inhibit the expression, synthesis, and release of leptin by the mesenteric adipose tissue of patients with IBD and stimulate the expression and synthesis of adiponectin and resistin. However, it was possible to verify that clinical studies aimed at evaluating the use of adipokines as biomarkers in the

therapeutic monitoring of patients with IBD undergoing treatment with infliximab are still scarce, especially when it comes to patients with UC. In this direction, large randomised and controlled clinical trials need to be conducted to define the real role of these adipokines in the therapeutic monitoring of patients with CD or CU treated with anti-TNF agents such as infliximab.

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Compliance with Ethical Standards

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References

1. J.T. Chang, Pathophysiology of Inflammatory Bowel Diseases, *New England Journal of Medicine*, **383**, 2652-2664 (2020).
2. H.-J. Su, Y.-T. Chiu, C.-T. Chiu, Y.-C. Lin, C.-Y. Wang, J.-Y. Hsieh, S.-C. Wei, Inflammatory bowel disease and its treatment in 2018: Global and Taiwanese status updates, *Journal of the Formosan Medical Association*, **118**, 1083-1092 (2018).
3. K.B. Gecse, S. Vermeire, Differential diagnosis of inflammatory bowel disease: imitations and complications, *The Lancet, Gastroenterology & Hepatology*, **3**, 644-653 (2018).

4. S.C. Ng, H.Y. Shi, N. Hamidi, F.E. Underwood, W. Tang, E.I. Benchimol, R. Panaccione, S. Ghosh, J.C.Y. Wu, F.K.L. Chan, J.J.Y. Sung, G.G. Kaplan, Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies, *Lancet (London, England)*, **390**, 2769-2778 (2018).

5. J.M. Dahlhamer, E.P. Zammitti, B.W. Ward, A.G. Wheaton, J.B. Croft, Prevalence of inflammatory bowel disease among adults aged ≥18 years — United States, 2015, *Morbidity and Mortality Weekly Report*, **65**, 1166-1169 (2016).

6. J. Côté-Daigneault, M. Bouin, R. Lahaie, J.F. Colombel, P. Poitras, Biologics in inflammatory bowel disease: what are the data?, *United European Gastroenterology Journal*, **3**, 419-428 (2015).

7. P. Rawla, T. Sunkara, J.P. Raj, Role of biologics and biosimilars in inflammatory bowel disease: Current trends and future perspectives, *Journal of Inflammatory Research*, **11**, 215-226 (2018).

8. R. Ferreiro, M. Barreiro-de Acosta, Infliximab in inflammatory bowel disease, in: A.D. Medrano-Acevedo (editor), *Infliximab: Pharmacology, Uses and Limitations*, Nova Science Publishers, Inc., 2012, pp. 39-74.

9. A.N. Sasson, A.N. Ananthakrishnan, M. Raman, Diet in Treatment of Inflammatory Bowel Diseases, *Clinical Gastroenterology and Hepatology*, **19**, 425-435 (2021).

10. U. Kopylov, S. Ben-Horin, E. Seidman, Therapeutic drug monitoring in inflammatory bowel disease, *Annals of Gastroenterology*, **27**, 304-312 (2014).

11. E.L. Barnes, R. Burakoff, New biomarkers for diagnosing inflammatory bowel disease and assessing treatment outcomes, *Inflammatory Bowel Disease*, **22**, 2956-2965 (2016).

12. C. Fink, I. Karagiannides, K. Bakirtzi, C. Pothoulakis, Adipose tissue and inflammatory bowel disease pathogenesis, *Inflammatory Bowel Disease*, **18**, 1550-1557 (2012)

13. M. Waluga, M. Hartleb, G. Boryczka, M. Kukla, K. Zwirska-Korczala, Serum adipokines in inflammatory bowel disease, *World Journal of Gastroenterology*, **20**, 6912-6917 (2014).

14. T. Karrasch, A. Schaeffler, Adipokines and the role of visceral adipose tissue in inflammatory bowel disease., *Annals of Gastroenterology*, **29**, 424-438 (2016).

15. V.S. Rodrigues, M. Milanski, J.J. Fagundes, A.S. Torsoni, M.L.S. Ayrizono, C.E.C. Nunez, C.B. Dias, L.R. Meirelles, S. Dalal, C.S.R. Coy, L.A. Velloso, R.F. Leal, Serum levels and mesenteric fat tissue expression of adiponectin and leptin in patients with Crohn's disease, *Clinical & Experimental Immunology*, **170**, 358-364 (2012).

16. N. Ouchi, J.L. Parker, J.J. Lugus, K. Walsh, Adipokines in inflammation and metabolic disease, *Nature Revew Immunology*, **11**, 85-97 (2011).

17. K. Karmiris, I.E. Koutroubakis, C. Xidakis, M. Polychronaki, T. Voudouri, E.A. Kouroumalis, Circulating levels of leptin, adiponectin, resistin, and ghrelin in inflammatory bowel disease, *Inflammatory Bowel Disease*, **12**, 100-105 (2006).

18. F. Trejo-Vazquez, I. Garza-Veloz, G.A. Villela-Ramirez, Y. Ortiz-Castro, P. Mauricio-Saucedo, E. Cardenas-Vargas, M. Diaz-Baez, M.A. Cid-Baez, R. Castañeda-Miranda, J.M. Ortiz-Rodriguez, L.O. Solis-Sanchez, M.L. Martinez-Fierro, Positive association between leptin serum levels and disease activity on endoscopy in inflammatory bowel disease: A case-control study, *Experimental and Therapeutic Medicine*, **15**, 3336-3344 (2018).

19. L.G.F. de Carvalho, W.G. Lima, L.G.V. Coelho, V.N. Cardoso, S.O.A. Fernandes, Circulating leptin levels as a potential biomarker in inflammatory bowel diseases: A systematic review and meta-analysis, *Inflammatory Bowel Disease*, **27**, 169-181 (2021)

20. R. Kahraman, T. Calhan, A. Sahin, K. Ozdil, Z. Caliskan, E.S. Bireller, B. Cakmakoglu, Are adipocytokines inflammatory or metabolic mediators in patients with inflammatory bowel disease?, *Therapeutics and Clinical Risk Management*, **13**, 1295-1301 (2017).

21. D. Franchimont, S. Roland, T. Gustot, E. Quertinmont, Y. Toubouti, M.-C. Gervy, J. Deviere, A. Van Gossum, Impact of infliximab on serum leptin levels in patients with Crohn's disease, *The Journal of Clinical Endocrinology & Metabolism*, **90**, 3510-3516 (2005).

22. K. Frivolt, T. Schwerd, S.B. Schatz, F. Freudenberg, C. Prell, K.J. Werkstetter, P. Bufler, S. Koletzko, Hyperadiponectinemia During Infliximab Induction Therapy in Pediatric Crohn Disease, *Journal of Pediatric Gastroenterology and Nutrition,* **66**, 915-919 (2018).

23. K. Karmiris, I.E. Koutroubakis, C. Xidakis, M. Polychronaki, E.A. Kouroumalis, The effect of infliximab on circulating levels of leptin, adiponectin and resistin in patients with inflammatory bowel disease, *European Journal of Gastroenterology & Hepatology*, **19**, 789-794 (2007).

24. A. Liberati, D.G. Altman, J. Tetzlaff, C. Mulrow, P.C. Gøtzsche, J.P.A. Ioannidis, M. Clarke, P.J. Devereaux, J. Kleijnen, D. Moher, The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration, *PLoS Medicine*, **6**, e1000100 (2009).

25. G.A. Wells, B. Shea, D. O'Connell, J. Peterson, V. Welch, M. Losos, P. Tugwell, The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, 2009; URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp, Accessed in February 26, 2020.

26. Z. Munn, S. Moola, D. Riitano, K. Lisy, The development of a critical appraisal tool for use in systematic reviews addressing questions of prevalence, *International Journal of Health Policy and Management*, **3**, 123-128 (2014)

27. A. Gambero, M. Maróstica, M.J.A. Saad, J. Pedrazzoli, Mesenteric adipose tissue alterations resulting from experimental reactivated colitis, *Inflammatory Bowel Disease*, **13**, 1357-1364 (2007)

28. S. Danese, Mechanisms of action of infliximab in inflammatory bowel disease: an anti-inflammatory multitasker, *Digestive and Liver Disease*, **40**, S225-S228 (2008).

29. C. Büning, C. von Kraft, M. Hermsdorf, E. Gentz, E.K. Wirth, L. Valentini, V. Haas, Visceral adipose tissue in patients with Crohn's disease correlates with disease activity, inflammatory markers, and outcome, *Inflammatory Bowel Disease*, **21**, 2590-2597 (2015).

30. J.M. Bruun, S.B. Pedersen, K. Kristensen, B. Richelsen, Effects of pro-inflammatory cytokines and chemokines on leptin production in human adipose tissue *in vitro*, *Molecular and Cellular Endocrinology,* **190**, 91-99 (2002).

31. R.L. Fawcett, A.S. Waechter, L.B. Williams, P. Zhang, R. Louie, R. Jones, M. Inman, J. Huse, R.V. Considine, Tumor necrosis factor-α inhibits leptin production in subcutaneous and omental adipocytes from morbidly obese humans, *Journal of Clinical Endocrinology and Metabolism*, **85**, 530-535 (2000).

32. M. Bokarewa, I. Nagaev, L. Dahlberg, U. Smith, A. Tarkowski, Resistin, an adipokine with potent proinflammatory properties, *Journal Immunology*, **174**, 5789-5795 (2005).

33. G.H. Marques-Oliveira, T.M. Silva, W.G. Lima, H.M.S. Valadares, V.E. Chaves, Insulin as a hormone regulator of the synthesis and release of leptin by white adipose tissue, *Peptides*, **106**, 49-58 (2018).

34. S.R. Bornstein, J. Licinio, R. Tauchnitz, L. Engelmann, A. Negrão, P. Gold, G.P. Chrousos, Plasma leptin levels are increased in survivors of acute sepsis: Associated loss of diurnal rhythm in cortisol and leptin secretion, *Journal of Clinical Endocrinology and Metabolism*, **83**, 280-283 (1998).

35. K. Karmiris, I.E. Koutroubakis, E.A. Kouroumalis, Leptin, adiponectin, resistin, and ghrelin - Implications for inflammatory bowel disease, *Molecular Nutrition & Food Research*, **52**, 855-866 (2008).

36. M. Rosenbaum, M. Nicolson, J. Hirsch, E. Murphy, F. Chu, R.L. Leibel, Effects of weight change on plasma leptin concentrations and energy expenditure, *Journal of Clinical Endocrinology and Metabolism*, **82**, 3647-3654 (1997).

37. M. Rosenbaum, R.L. Leibel, J. Hirsch, Obesity, *New England Journal of Medicine*, **337**, 396-407 (1997).

38. M.S. Jamaluddin, S.M. Weakley, Q. Yao, C. Chen, Resistin: Functional roles and therapeutic considerations for cardiovascular disease, *Brazilian Journal of Pharmacology*, **165**, 622-632 (2012).

39. H.K. Park, R.S. Ahima, Resistin in Rodents and Humans, *Diabetes and Metabolism Journal*, **37**, 404-414 (2013).

40. H.K. Park, M.K. Kwak, H.J. Kim, R.S. Ahima, Linking resistin, inflammation, and cardiometabolic diseases, *Korean Journal of Internal Medicine*, **32**, 239-247 (2017).

41. L. Patel, A.C. Buckels, I.J. Kinghorn, P.R. Murdock, J.D. Holbrook, C. Plumpton, C.H. Macphee, S.A. Smith, Resistin is expressed in human macrophages and directly regulated by PPARγ activators, *Biochemical and Biophysical Research Communications,* **300**, 472-476 (2003).

42. T.R.L. Clemente, A.N. Dos Santos, J.N. Sturaro, É.M.F. Gotardo, C.C. De Oliveira, S.C. Acedo, C.R.E.P. Caria, J. Pedrazzoli, M.L. Ribeiro, A. Gambero, Infliximab modifies mesenteric adipose tissue alterations and intestinal inflammation in rats with TNBS-induced colitis, *Scandinavian Journal of Gastroenterology*, **47**, 943-950 (2012).

43. S. Kaser, A. Kaser, A. Sandhofer, C.. Ebenbichler, H. Tilg, J.. Patsch, Resistin messenger-RNA expression is increased by proinflammatory cytokines in vitro, *Biochemical and Biophysical Research Communications*, **309**, 286–290 (2003).

44. A.E. Achari, S.K. Jain, Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction, *International Journal of Molecular Sciences,* **18**, 1321 (2017).

45. G. Fantuzzi, Adiponectin in inflammatory and immune-mediated diseases, *Cytokine*, **64**, 1-10 (2013).

46. C. Weidinger, J.F. Ziegler, M. Letizia, F. Schmidt, B. Siegmund, Adipokines and their role in intestinal inflammation, *Frontiers in Immunology*, **9**, 1974 (2018).

47. K. Yamamoto, T. Kiyohara, Y. Murayama, S. Kihara, Y. Okamoto, T. Funahashi, T. Ito, R. Nezu, S. Tsutsui, J.-I. Miyagawa, S. Tamura, Y. Matsuzawa, I. Shimomura, Y. Shinomura, Production of adiponectin, an anti-inflammatory protein, in mesenteric adipose tissue in Crohn's disease, *Gut*, **54**, 789-796 (2005).

48. H.S.H. Al-Khalidy, R.M. Hasan, B.M. Mahdi, Role of adiponectin in patients with inflammatory bowel disease unclassified, *Journal of Coloproctology*, **38**, 320-323 (2018).

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Supplementary file

Serum adipokines as biomarkers for the therapeutic monitoring of patients with inflammatory bowel diseases treated with infliximab: a systematic review and meta-analysis

Search strategy

1. PubMed

Search ((((((((((Leptin[Text Word] OR Ob Gene Product[Text Word] OR Ob Protein[Text Word] OR Obese Gene Product[Text Word] OR Obese Protein[Text Word]))) OR "Leptin"[Mesh])) OR (("Adiponectin"[Mesh]) OR ((Adiponectin[Text Word] OR ACRP30 Protein[Text Word] OR Adipocyte Complement-Related Protein 30-kDa[Text Word] OR Adipocyte, C1q[Text Word] AND Collagen Domain Containing Protein[Text Word] OR Adipose Most Abundant Gene Transcript 1[Text Word] OR apM-1 Protein[Text Word])))) OR (("Nicotinamide Phosphoribosyltransferase"[Mesh]) OR ((Nicotinamide Phosphoribosyltransferase[Text Word] OR NAMPT Protein[Text Word] OR NAmPRTase[Text Word] OR NMN Pyrophosphorylase[Text Word] OR Pre-B-Cell Colony-Enhancing Factor[Text Word] OR Visfatin[Text Word])))) OR (("Resistin"[Mesh]) OR ((Resistin[Text Word] OR Adipocyte Cysteine-Rich Secreted Protein FIZZ3[Text Word])))) OR (("Visfatin"[Mesh]) AND ((Inflammatory Bowel Diseases[Text Word] OR Bowel Diseases, Inflammatory[Text Word])))) OR (("Colitis, Ulcerative"[Mesh]) OR ((Colitis, Ulcerative[Text Word] OR Colitis Gravis[Text Word] OR Idiopathic Proctocolitis[Text Word] OR Inflammatory Bowel Disease Ulcerative Colitis type[Text Word] OR Ulcerative Colitis[Text Word])))) OR (("Crohn Disease"[Mesh]) OR ((Crohn Disease[Text Word] OR Colitis, Granulomatous[Text Word] OR Crohn's Disease[Text Word] OR Crohn's Enteritis[Text Word] OR Enteritis, Granulomatous[Text Word] OR Enteritis, Regional[Text Word] OR Ileitis, Regional[Text Word] OR Ileitis, Terminal[Text Word] OR Ileocolitis Inflammatory Bowel Disease 1[Text Word] OR Regional Enteritis[Text Word])))))) AND (("Infliximab"[Mesh]) OR ((Infliximab[Text Word] OR Inflectra[Text Word] OR Infliximab-abda[Text Word] OR Infliximab-dyyb[Text Word] OR MAb cA2[Text Word] OR Monoclonal Antibody cA2[Text Word] OR Remicade[Text Word] OR Renflexis[Text Word])))

2. Cochrane library

ID	Search Hits	
#1	MeSH descriptor: [Leptin] this term only	975
#2	Leptin OR Ob Gene Product OR Ob Protein OR Obese Gene Product OR Obese Protein	6090
#3	#1 OR #2	6090
#4	MeSH descriptor: [Adiponectin] this term only	838
#5	Adiponectin	3475
#6	#4 OR #5	3475
#7	MeSH descriptor: [Nicotinamide Phosphoribosyltransferase] explode all trees	45
#8	Nicotinamide Phosphoribosyltransferase OR NAMPT Protein OR NAmPRTase OR NMN Pyrophosphorylase OR Pre-B-Cell Colony-Enhancing Factor OR Visfatin	209
#9	#7 OR #8	209
#10	MeSH descriptor: [Resistin] this term only	113
#11	Resistin OR Adipocyte Cysteine-Rich Secreted Protein FIZZ3	478
#12	#10 OR #11	478
#13	#3 OR #6 OR #9 OR #12	9411
#14	MeSH descriptor: [Inflammatory Bowel Diseases] this term only	461
#15	Inflammatory Bowel Diseases OR Bowel Diseases, Inflammatory	2015
#16	#14 OR #15	2015
#17	MeSH descriptor: [Colitis, Ulcerative] explode all trees	1415
#18	Colitis, Ulcerative OR Colitis Gravis OR Idiopathic Proctocolitis OR Inflammatory Bowel Disease OR Ulcerative Colitis type OR Ulcerative Colitis	4758
#19	#17 OR #18	4758
#20	MeSH descriptor: [Crohn Disease] this term only	1431

ID	Search Hits	
#21	Crohn Disease OR Colitis, Granulomatous OR Crohn's Disease OR Crohn's Enteritis OR Enteritis, Granulomatous OR Enteritis, Regional OR Ileitis, Regional OR Ileitis, Terminal OR Ileocolitis Inflammatory Bowel Disease 1 OR Regional Enteritis	5127
#22	#20 OR 21	260746
#23	#16 OR #19 OR #22	265135
#24	MeSH descriptor: [Infliximab] this term only	662
#25	Infliximab OR Inflectra OR Infliximab-abda OR Infliximab-dyyb OR MAb cA2 OR Monoclonal Antibody cA2 OR Remicade OR Renflexis	2567
#26	#24 OR #25	2567
#27	#13 AND #23 AND #26	7

3. Scopus

(TITLE-ABS-KEY ("Leptin" OR "Adiponectin" OR "Nicotinamide Phosphoribosyltransferase" OR "Resistin") OR INDEXTERMS ("Leptin" OR "Adiponectin" OR "Nicotinamide Phosphoribosyltransferase" OR "Resistin")) AND (TITLE-ABS-KEY ("Inflammatory Bowel Diseases"OR "Colitis, Ulcerative" OR "Crohn's Disease") OR INDEXTERMS ("Inflammatory Bowel Diseases"OR "Colitis, Ulcerative" OR "Crohn's Disease")) AND (TITLE-ABS-KEY ("Infliximab") OR INDEXTERMS ("Infliximab"))

4. Biblioteca virtual em Saúde (Portal Regional da BVS)

(mh:("Leptin")) OR (tw:("Leptin" OR "Leptina" OR "Gene Product, Ob" OR "Gene Product, Obese" OR "Ob Gene Product" OR "Ob Protein" OR "Obese Gene Product" OR "Obese Protein")) OR (mh:("Adiponectin")) OR (tw:("Adiponectin" OR "Adiponectina" OR "ACRP30 Protein" OR "Adipocyte Complement Related Protein 30 kDa" OR "Adipocyte Complement-Related Protein 30-kDa" OR "Adipocyte, C1q and Collagen Domain Containing Protein" OR "Adipose Most Abundant Gene Transcript 1" OR "apM 1 Protein" OR "apM-1 Protein")) OR (mh:("Nicotinamide Phosphoribosyltransferase")) OR (tw:("Nicotinamide Phosphoribosyltransferase" OR "Nicotinamida Fosforribosiltransferasa" OR "Nicotinamida Fosforribosiltransferase" OR "Colony-Enhancing Factor, Pre-B-Cel"l OR "NAMPT Protein" OR

"NAmPRTase" OR "NMN Pyrophosphorylase" OR "Phosphoribosyltransferase, Nicotinamide" OR "Pre B Cell Colony Enhancing Factor" OR "Pre-B-Cell Colony-Enhancing Factor" OR "Visfatin")) OR (mh:("Resistin")) OR (tw:("Resistin" OR "Resistina" OR "Adipocyte Cysteine Rich Secreted Protein FIZZ3" OR "Adipocyte Cysteine-Rich Secreted Protein FIZZ3")) AND (mh:("Inflammatory Bowel Diseases")) OR (tw:("Inflammatory Bowel Diseases" OR "Enfermedades Inflamatorias del Intestino" OR "Doenças Inflamatórias Intestinais" OR "Bowel Diseases, Inflammatory" OR "Inflammatory Bowel Disease")) OR (mh:("Colitis, Ulcerative")) OR (tw:("Colitis, Ulcerative" OR "Colitis Ulcerosa" OR "Colite Ulcerativa" OR "Colitis Gravis" OR "Idiopathic Proctocolitis" OR "Inflammatory Bowel Disease, Ulcerative Colitis Type" OR "Ulcerative Colitis")) OR (mh:("Crohn Disease")) OR (tw:("Crohn Disease" OR "Enfermedad de Crohn" OR "Doença de Crohn" OR "Colitis, Granulomatous" OR "Crohn's Disease" OR "Crohn's Enteritis" OR "Crohns Disease" OR "Enteritis, Granulomatous" OR "Enteritis, Regional" OR "Granulomatous Colitis" OR "Granulomatous Enteritis" OR "Ileitis, Regional" OR "Ileitis, Terminal" OR "Ileocolitis" OR "Inflammatory Bowel Disease 1" OR "Regional Enteritis" OR "Regional Ileitides" OR "Regional Ileitis" OR "Terminal Ileitis")) AND (mh:("Infliximab")) OR (tw:("Infliximab" OR "Inflectra" OR "Infliximab-abda" OR "Infliximab-dyyb OR "MAb cA2" OR Monoclonal Antibody cA2" OR "Remicade" OR "Renflexis" OR "cA2, Monoclonal Antibody"))