

Serum adipokines in inflammatory bowel disease

Marek Waluga, Marek Hartleb, Grzegorz Boryczka, Michał Kukla, Krystyna Żwirska-Korczała

Marek Waluga, Marek Hartleb, Grzegorz Boryczka, Department of Gastroenterology and Hepatology, Medical University of Silesia, 40-752 Katowice, Poland

Michał Kukla, Krystyna Żwirska-Korczała, Department of Physiology Zabrze, Medical University of Silesia, 40-055 Katowice, Poland

Author contributions: Waluga M conceived the study, analyzed the data and drafted the manuscript; Hartleb M participated in the study design and helped prepare the manuscript; Boryczka G assisted with blood samples and data collection; Kukla M and Żwirska-Korczała K assisted with technical issues and statistical analysis; all authors read and approved the final version of the manuscript.

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Correspondence to: Marek Waluga, MD, PhD, Department of Gastroenterology and Hepatology, Medical University of Silesia, ul. Medyków 14, 40-752 Katowice, Poland. mwaluga@sum.edu.pl

Telephone: +48-32-7894401 Fax: +48-32-7894402

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Abstract

AIM: To investigate serum adipokine levels in inflammatory bowel disease (IBD) patients before treatment and after achieving clinical remission.

METHODS: Serum concentrations of six adipokines (tissue growth factor- β 1, adiponectin, leptin, chemerin, resistin, and visfatin) were studied in 40 subjects with active IBD [24 subjects with Crohn's disease (CD) and in 16 subjects with ulcerative colitis (UC)] before and after three months of therapy with corticosteroids and/or azathioprine. Clinical diagnoses were based on ileocolonoscopy, computed tomography or magnetic resonance enterography and histological examination of mucosal biopsies sampled during endoscopy. Serum levels of adipokines were assessed by an indirect enzyme-linked immunosorbent assay. The control group was comprised of 16 age- and sex-matched healthy

volunteers.

RESULTS: Baseline leptin concentrations were significantly decreased in both types of IBD compared to controls (8.0 ± 9.1 in CD and 8.6 ± 6.3 in UC vs 16.5 ± 10.1 ng/mL in controls; $P < 0.05$), and significantly increased after treatment only in subjects with CD (14.9 ± 15.1 ng/mL; $P < 0.05$). Baseline serum resistin concentrations were significantly higher in CD (19.3 ± 12.5 ng/mL; $P < 0.05$) and UC subjects (23.2 ± 11.0 ng/mL; $P < 0.05$) than in healthy controls (10.7 ± 1.1 ng/mL). Treatment induced a decrease in the serum resistin concentration only in UC subjects (14.5 ± 4.0 ng/mL; $P < 0.05$). Baseline serum concentrations of visfatin were significantly higher in subjects with CD (23.2 ± 3.2 ng/mL; $P < 0.05$) and UC (18.8 ± 5.3 ng/mL; $P < 0.05$) than in healthy controls (14.1 ± 5.3 ng/mL). Treatment induced a decrease in the serum visfatin concentrations only in CD subjects (20.4 ± 4.8 ng/mL; $P < 0.05$). Serum levels of adiponectin, chemerin and tissue growth factor- β 1 did not differ between CD and UC subjects compared to healthy controls and also were not altered by anti-inflammatory therapy. Clinical indices of IBD activity did not correlate with adipokine levels.

CONCLUSION: IBD modulates serum adipokine levels by increasing resistin and visfatin release and suppressing leptin production.

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Key words: Adipokines; Tumor growth factor- β 1; Crohn's disease; Ulcerative colitis; Inflammatory bowel disease

Core tip: Recently, many adipokines with varying metabolic effects have been discovered. A bidirectional interaction between inflammation of the gut and visceral fat may exist in cases of inflammatory bowel disease (IBD). In this work, plasma levels of selected adipokines were studied in subjects with Crohn's disease and ulcerative colitis before treatment and after achieving clinical remission. The results of this study indicate that IBD modulates serum adipokine levels by stimulating resistin

and visfatin release and suppressing leptin production.

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INTRODUCTION

Inflammatory bowel diseases (IBDs) such as Crohn's disease (CD) and ulcerative colitis (UC) are severe and difficult to treat diseases of the digestive tract. Despite considerable progress in the field, the pathophysiology of IBD remains unclear, while its prevalence continues to rise. The most important determinant of the clinical course of IBD is the balance, levels, and ratios of proinflammatory, anti-inflammatory, and immunomodulating factors.

Inflammatory reactions localized in the bowel wall may penetrate the surrounding visceral adipose tissue. Imaging methods provide evidence for hypertrophy of the mesenteric adipose tissue in patients with CD^[1-3]. Moreover, submucosal fat deposition (fat halo sign) in the bowel is observed in both CD and UC patients^[4]. The anatomic proximity of the bowel and visceral fat favors the activation of adipocytes. Visceral adipose tissue is not only an energy storage site, but is also an active endocrine organ. Activated visceral adipocytes secrete many mediators, cytokines and adipokines, such as leptin, adiponectin, resistin, chemerin, and visfatin. Adipokines influence the immunologic system of the gastrointestinal tract, in some cases worsening IBD by amplifying inflammation *via* the secretion of proinflammatory interleukins, tumor necrosis factor alpha (TNF- α) and adhesion factors. Visfatin is an example of an adipokine that increases the epithelial expression of TNF- α , interleukin (IL)-1, IL-6, and adhesion molecules^[5,6]. Furthermore, the adipokines visfatin, chemerin, and resistin have increased tissue expression in many acute and chronic inflammatory diseases^[6-9].

The significance of adipokines for IBD pathophysiology is the subject of intensive research, as on one hand the adipokine levels might serve as an index of inflammatory activity and on the other hand, inhibition of specific adipokines could expand the spectrum of therapeutic interventions for this disease. The aim of the present study was to determine the serum concentrations of tumor growth factor (TGF)- β 1, adiponectin, leptin, chemerin, resistin, and visfatin in patients with active CD and UC in the pre-treatment stage and after three months of anti-inflammatory and/or immunosuppressive therapy.

MATERIALS AND METHODS

Patients and study design

This work was carried out in accordance with the Declaration of Helsinki (2000) of the World Medical As-

sociation and was approved by the Ethics Committee of the Medical University of Silesia (resolution number KNW/0022/KB1/4/13). Subjects provided written informed consent before enrollment to the study. Individuals with clinically active IBD not treated with corticosteroids or azathioprine between the ages of 19 and 60, including those on low doses of 5-aminosalicylate (up to 2 g/d), were eligible to be included in the study. Exclusion criteria included the presence of any other inflammatory, systemic, endocrine, or metabolic disease, pregnancy, or lack of participant agreement. Patients who required surgical treatment or underwent bowel resection procedures were also excluded from the study. Volunteer subjects were included if they did not have signs of any disease and did not report any associated complaints.

A total of 56 volunteers participated in the study: 24 with CD, 16 with UC, and 16 healthy subjects. Participants in all three groups were comparable regarding demographics and clinical characteristics including age, sex, body mass index (BMI), and waist and hip circumferences (Table 1). Clinical diagnosis of IBD was based on ileocolonoscopy, computed tomography, or magnetic resonance enterography, and histological examination of mucosal biopsies sampled during endoscopy. Blood morphology, serum levels of C-reactive protein, glucose, creatinine, aspartate transaminase, alanine transaminase, gamma-glutamyl transpeptidase, and alkaline phosphatase were measured from each subject. The Vienna classification, which measures the time from initial diagnosis (A), localization of lesions in the bowel (L), and the clinical course (B), was used for CD diagnosis^[10], and the activity and extent of UC was defined according to the Montreal classification^[11] (Table 1).

We synchronized all IBD subjects according to the following corticosteroid treatment schedule: prednisone at a daily dose of 0.8 mg/kg of body mass for two weeks, then tapered by 5 mg over each of the following weeks for a total of three months. Simultaneously, subjects with CD were treated with azathioprine at a constant dose of 2 mg/kg per day. All subjects were administered 5-aminosalicylate at a constant dose of 3 g/d. All subjects participated in monthly check-ups, when the subject's complaints and any abnormalities discovered by physical examination were recorded, and medication compliance was determined.

Blood samples were collected from subjects under fasting conditions both before and after three months of treatment. Blood was centrifuged 10 min after collection and serum samples were immediately frozen at -80 °C. Enzyme-linked immunosorbent assays (ELISA) were used to determine serum concentrations of adiponectin, leptin, and chemerin (BioVendor, Brno, Czech Republic), resistin (Millipore Corporation, Billerica, MA, United States), visfatin (Phoenix Europe GmbH, Karlsruhe, Germany), and TGF- β 1 (Gen Probe Diaclone SAS, Besancon, France).

Statistical analysis

All analyses were performed using Statistica PL version

Table 1 Subject characteristics

	Crohn's disease (n = 24)	Ulcerative colitis (n = 16)	Control group (n = 16)	P value
Female, %	54	56	50	0.902
Age, yr	31.0 ± 9.4	33.2 ± 21.9	30.3 ± 12.2	0.060
BMI, kg/m ²	21.4 ± 2.8	23.4 ± 5.6	22 ± 4.8	0.444
Waist circumference, cm	78.8 ± 9.9	78.4 ± 15.7	78.5 ± 8.5	0.090
Hip circumference, cm	91.5 ± 8.8	93.6 ± 11.9	91.1 ± 8.1	0.345
Waist/hip ratio	0.86 ± 0.08	0.84 ± 0.08	0.86 ± 0.07	0.472
Duration of IBD, yr	9.5 ± 7.9	10.5 ± 8.1	-	0.105
Activity of IBD				
CDAI	A: 241 ± 155 B: 36.6 ± 25.3	-	-	
Montreal severity classification				
S0/S1/S2/S3	-	A: 0/1/14/1 B: 8/8/0/0	-	
Vienna classification				
A1/A2	21/3	-	-	
L1/L2/L3/L4	2/5/17/0	-	-	
B1/B2/B3	14/6/4	-	-	

A: Before treatment; B: 3 mo after initiation of treatment; CDAI: Crohn's disease activity index; IBD: Inflammatory bowel disease; BMI: Body mass index.

10.0 (StatSoft Inc., Tulsa, OK, United States). Intergroup differences for each adipokine were analyzed using the Kruskal-Wallis test (nonparametric ANOVA) for global comparisons between CD, UC and healthy volunteer subjects. Adipokine levels were compared between groups using an unpaired Student's *t*-test if the data showed a normal distribution; otherwise the Mann-Whitney *U* test was used. A paired Wilcoxon test was used to independently compare data acquired before and after three months of treatment for each disease group. Linear regression analysis was performed to assess the associations between the severity of the disease, time post-diagnosis, age, waist and hip circumference, BMI (independent variables) and the levels of each adipokine (dependent variables). Data are expressed as mean ± SD, and a *P* value of 0.05 or less was considered as statistically significant.

RESULTS

All subjects completed the study. The serum concentrations of adiponectin, TGF-β1, and chemerin were not different between subjects with active IBD and healthy controls, and there was no effect of treatment (Table 2). Baseline serum leptin concentrations were significantly lower in subjects with CD and UC compared with healthy controls (*P* < 0.05), and significantly increased in CD subjects after three months of treatment (*P* < 0.05). Baseline serum resistin concentrations were significantly higher in CD and UC subjects compared with healthy controls (*P* < 0.05), and treatment induced a decrease in levels only in UC subjects (*P* < 0.05). Baseline serum concentrations of visfatin were also significantly higher in subjects with CD and UC compared to healthy controls (*P* < 0.05). Treatment induced a decrease in the serum visfatin concentration only in CD subjects (*P* < 0.05), but the post-therapy level of this adipokine remained significantly higher than that in healthy controls (*P* < 0.05) (Table 2). There were no correlations detected between

any of the adipokines examined or TGF-β1 and the clinical severity of IBD, time from initial diagnosis, age, waist or hip circumference, or BMI (Table 3).

DISCUSSION

Although the etiology of IBD remains unclear, the most prevalent hypothesis is that the disease develops due to a genetic predisposition and a hyperactive gut-associated immune response to food allergens and bacteria. Individuals with IBD exhibit hypertrophy of the mesenteric adipose tissue lying in direct proximity to the inflamed bowel as well as alterations in local or serum adipokine concentrations^[1].

Adipokines have both pro- and anti-inflammatory effects in IBD patients. Adiponectin is one of the most richly represented adipokines in the blood, exerting many metabolic effects^[12-14]. It also has anti-inflammatory effects by increasing the synthesis of an interleukin receptor antagonist and decreasing the dendritic cell release of interferon gamma. Moreover, adiponectin enhances phagocytosis by human macrophages^[15,16]. In the present study, no statistically significant increase in serum adiponectin concentration was found in either type of IBD, indicating strong adaptive mechanisms of adiponectin homeostasis.

Leptin, one of the most well studied adipokines, exerts many metabolic, endocrine, and immunologic effects. This adipokine stimulates the proliferation of naïve T-helper lymphocytes, but inhibits the proliferation of T-memory lymphocytes and subsequent production of cytokines^[17]. In addition, leptin activates phagocytosis by macrophages^[15] and regulates proinflammatory immune responses^[18]. The adipose tissue mass is the most important determinant of serum leptin concentration. In our study, despite similar BMI in the three groups of subjects, serum leptin levels were decreased in subjects with both types of IBD, compared with healthy controls. Low

Table 2 Serum adipokine concentrations

	Adiponectin, $\mu\text{g/mL}$	Leptin, ng/mL	TGF- β 1, pg/mL	Chemerin, ng/mL	Resistin, ng/mL	Visfatin, ng/mL
Crohn's disease						
Before treatment ($n = 24$)	14.7 \pm 19.4	8.0 \pm 9.1 ^a	3152 \pm 1137	418 \pm 193	19.3 \pm 12.5 ^a	23.2 \pm 3.2 ^a
Upon treatment ($n = 24$)	11.7 \pm 6.7	14.9 \pm 15.1 ^c	3261 \pm 1327	344 \pm 127	17.9 \pm 13.2 ^a	20.4 \pm 4.8 ^{ac}
Ulcerative colitis						
Before treatment ($n = 16$)	9.8 \pm 4.1	8.6 \pm 6.3 ^a	4378 \pm 361	421 \pm 214	23.2 \pm 11.0 ^a	18.8 \pm 5.3 ^a
Upon treatment ($n = 16$)	13.7 \pm 5.3	9.2 \pm 7.3	2877 \pm 1761	379 \pm 208	14.5 \pm 4.0 ^c	21.0 \pm 3.5 ^a
Control group						
Healthy subjects ($n = 16$)	9.3 \pm 3.0	16.5 \pm 10.1	3027 \pm 809	355 \pm 69	10.7 \pm 1.1	14.1 \pm 5.4

^a $P < 0.05$ vs control group; ^c $P < 0.05$ vs before treatment. TGF: Tumor growth factor.

Table 3 Results of correlational analyses (P values) between adipokine levels and clinical parameters

Adipokine level	A/B	Severity, points	Duration of IBD, yr	Age, yr	Waist circumference, cm	Hip circumference, cm	BMI, kg/m ²
Crohn's disease							
TGF- β 1	A	0.157	0.068	0.067	0.061	0.126	0.065
	B	0.235	0.065	0.468	0.084	0.068	0.056
Adiponectin	A	0.086	0.055	0.065	0.171	0.096	0.116
	B	0.056	0.054	0.058	0.061	0.085	0.075
Leptin	A	0.274	0.118	0.065	0.076	0.074	0.085
	B	0.065	0.086	0.081	0.070	0.085	0.268
Chemerin	A	0.066	0.129	0.063	0.088	0.115	0.095
	B	0.149	0.097	0.224	0.183	0.093	0.085
Resistin	A	0.065	0.066	0.080	0.061	0.116	0.063
	B	0.159	0.129	0.056	0.078	0.075	0.069
Visfatin	A	0.094	0.076	0.159	0.127	0.097	0.061
	B	0.085	0.085	0.054	0.075	0.087	0.105
Ulcerative colitis							
TGF- β 1	A	0.068	0.061	0.137	0.082	0.154	0.054
	B	0.073	0.137	0.193	0.156	0.954	0.068
Adiponectin	A	0.065	0.060	0.061	0.067	0.177	0.061
	B	0.106	0.070	0.070	0.090	0.095	0.271
Leptin	A	0.093	0.080	0.060	0.086	0.158	0.081
	B	0.085	0.056	0.071	0.080	0.085	0.224
Chemerin	A	0.065	0.052	0.088	0.075	0.173	0.101
	B	0.077	0.130	0.093	0.088	0.055	0.094
Resistin	A	0.064	0.060	0.061	0.073	0.084	0.070
	B	0.084	0.068	0.080	0.062	0.275	0.260
Visfatin	A	0.065	0.079	0.060	0.079	0.054	0.161
	B	0.115	0.069	0.070	0.117	0.064	0.070

A: Before treatment; B: 3 mo after initiation of treatment; BMI: Body mass index; IBD: Inflammatory bowel disease; TGF: Tumor growth factor.

leptin concentrations in CD and UC subjects, which are consistent with previous studies^[19], may be the result of TNF- α hyperactivity. TNF- α stimulates the temporary release of substantial amounts of leptin in response to inflammation eventually leading to a decrease in leptin-mediated chronic inflammation. Moreover, serum leptin levels increase in CD subjects treated with the TNF- α antagonist infliximab confirming the role of TNF- α in the regulation of leptin release by adipocytes^[20]. Similarly, our study showed that a 3-month treatment period with corticosteroids alone or with azathioprine leads to increased blood leptin concentrations, which is particularly noticeable in CD subjects. Interestingly, while some studies report increased expression of leptin mRNA in the mesenteric adipose tissue or increased concentrations of leptin in large bowel lavage fluid from patients with mild to severe CD or UC^[3,21], leptin is not detected in

normal colonic epithelium. However, it is detected in the subapical region of the epithelial cells during conditions of inflammation^[21]. This finding explains the differences between leptin concentrations measured in the serum, tissue, or gut lumen.

Recent studies suggest that TGF- β 1 decreases symptoms of IBD by suppressing the immunologic system in the gut and the bowel epithelium through inhibition of immature dendritic cells^[22,23]. In our study, TGF- β 1 serum concentrations were not significantly different in IBD subjects versus healthy controls, and anti-inflammatory treatment had no effect on TGF- β 1 serum levels. These data indicate that any potential role of TGF- β 1 in IBD is limited to the mucosa and potential changes in the local concentration of this cytokine cannot be monitored in the systemic circulation.

Chemerin acts as either an activator (initiating stage)

or inhibitor (later stages) of inflammation^[24,25]. Weigert *et al*^[8] reported elevated serum concentrations of chemerin in IBD patients, especially those with CD. Surprisingly, the highest levels of this adipokine were observed in patients with the non-active form of CD. However, results from this study failed to show significant differences in the baseline chemerin concentrations, though serum levels tended to be higher in IBD patients before treatment.

Resistin is a proinflammatory agent, as it stimulates the synthesis and secretion of TNF- α , IL-12, and adhesive factors upon nuclear factor kappa B activation^[26]. Expression of resistin in the mesenteric adipose tissue is elevated in patients with severe CD compared to those with colon cancer^[27]. Adipose tissue is not a unique source of resistin as it is also found in mononuclear blood cells, macrophages, and stem cells^[28]. The production of resistin by mononuclear cells may be increased by lipopolysaccharides, TNF- α , IL-1, and IL-6^[29]. Karmiris *et al*^[19] reported elevated serum levels of resistin in IBD patients, irrespective of disease type. Consistent with these findings, results of this study found significantly higher serum resistin concentrations in both CD and UC subjects compared to healthy controls. Resistin levels returned to baseline levels following three months of treatment in UC, but not CD, subjects.

Adipose tissue produces large amounts of visfatin. Apart from its role in the regulation of insulin receptor sensitivity^[30], visfatin also inhibits apoptosis in a neutrophilic response to inflammatory factors^[31], and induces the synthesis of interleukins by CD14+ monocytes^[5]. Increased serum concentrations of visfatin have been detected during active IBD symptoms^[9] and correlate with indices of IBD activity^[32]. The findings of the present study confirm this role of visfatin in IBD, as levels were significantly higher in CD and UC subjects compared with healthy controls. Moreover, three months of treatment significantly lowered visfatin levels in CD subjects, indicating that azathioprine-mediated immunosuppression affects the visfatin level.

In summary, bowel inflammation is responsible for elevation of serum levels of some adipokines (resistin, visfatin), while others are not significantly altered (adiponectin, chemerin) or are even suppressed (leptin). In general, the treatment of IBD led to a normalization of adipokine serum levels, though it is unknown if the improvement in leptin and visfatin levels observed only in CD patients is related to disease specificity or the use of azathioprine. Overall, the findings suggest that adipokines are involved in the pathogenesis of IBD. However, the lack of a direct correlation between serum levels and IBD activity implies that adipokines are modulators rather than determinants of IBD severity.

However, this relationship between serum adipokine levels and IBD activity is poorly understood.

Research frontiers

Although many functions of adipokines in inflammatory diseases have been investigated, their impact on the exacerbation of IBD, as well as the impact of therapy-induced remission on serum levels of adipokines, is unknown.

Innovations and breakthroughs

This study examined serum levels of six adipokines in IBD patients before treatment and after 3 mo of immunosuppression leading to clinical remission. Results indicate that serum adipokine levels differ in IBD patients compared to a healthy population. Their profile and reaction to immunosuppressive treatment seems to depend on type of disease (Crohn's disease vs ulcerative colitis) and not clinical indices of IBD activity.

Applications

Understanding the biochemical and immunological relationship between IBD the surrounding adipose tissue may influence the future therapy of IBD.

Terminology

IBD refers to a group of chronic inflammatory diseases usually involving the ileocecal region (Crohn's disease) or the large bowel (ulcerative colitis). Adipokines are hormones mostly produced in adipose tissue and have an impact on many metabolic, endocrine and inflammatory pathways.

Peer review

This paper reports differential changes in serum levels of adipokines, including adiponectin, leptin, chemerin, resistin, visfatin and TGF- β 1, in individuals with Crohn's disease and ulcerative colitis, before and after treatment and after achieving clinical remission.

REFERENCES

- 1 Schöffler A, Schölmerich J, Büchler C. Mechanisms of disease: adipocytokines and visceral adipose tissue--emerging role in intestinal and mesenteric diseases. *Nat Clin Pract Gastroenterol Hepatol* 2005; **2**: 103-111 [PMID: 16265128 DOI: 10.1038/ncpgasthep0090]
- 2 Maconi G, Greco S, Duca P, Ardizzone S, Massari A, Cassinotti A, Radice E, Porro GB. Prevalence and clinical significance of sonographic evidence of mesenteric fat alterations in Crohn's disease. *Inflamm Bowel Dis* 2008; **14**: 1555-1561 [PMID: 18521926 DOI: 10.1002/ibd.20515]
- 3 Barbier M, Vidal H, Desreumaux P, Dubuquoy L, Bourreille A, Colombel JF, Cherbut C, Galmiche JP. Overexpression of leptin mRNA in mesenteric adipose tissue in inflammatory bowel diseases. *Gastroenterol Clin Biol* 2003; **27**: 987-991 [PMID: 14732844]
- 4 Ahualli J. The fat halo sign. *Radiology* 2007; **242**: 945-946 [PMID: 17325078 DOI: 10.1148/radiol.2423041600]
- 5 Moschen AR, Kaser A, Enrich B, Mosheimer B, Theurl M, Niederegger H, Tilg H. Visfatin, an adipocytokine with proinflammatory and immunomodulating properties. *J Immunol* 2007; **178**: 1748-1758 [PMID: 17237424]
- 6 Luk T, Malam Z, Marshall JC. Pre-B cell colony-enhancing factor (PBEF)/visfatin: a novel mediator of innate immunity. *J Leukoc Biol* 2008; **83**: 804-816 [PMID: 18252866 DOI: 10.1189/jlb.0807581]
- 7 Tilg H, Moschen AR. Role of adiponectin and PBEF/visfatin as regulators of inflammation: involvement in obesity-associated diseases. *Clin Sci (Lond)* 2008; **114**: 275-288 [PMID: 18194136 DOI: 10.1042/CS20070196]
- 8 Weigert J, Obermeier F, Neumeier M, Wanninger J, Filarczyk M, Bauer S, Aslanidis C, Rogler G, Ott C, Schöffler A, Schölmerich J, Buechler C. Circulating levels of chemerin and adiponectin are higher in ulcerative colitis and chemerin is elevated in Crohn's disease. *Inflamm Bowel Dis* 2010; **16**: 630-637 [PMID: 19714754 DOI: 10.1002/ibd.21091]
- 9 Valentini L, Wirth EK, Schweizer U, Hengstermann S, Schaper L, Koernicke T, Dietz E, Norman K, Buning C, Winkhofer-Roob BM, Lochs H, Ockenga J. Circulating adipokines and the protective effects of hyperinsulinemia in in-

COMMENTS

Background

Severe inflammatory reactions localized in the bowel wall may extend into surrounding visceral adipose tissue. Activated adipocytes may in turn produce numerous adipokines modulating inflammatory bowel disease (IBD) activity.

- inflammatory bowel disease. *Nutrition* 2009; **25**: 172-181 [PMID: 18849144 DOI: 10.1016/j.nut.2008.07.020]
- 10 **Satsangi J**, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006; **55**: 749-753 [PMID: 16698746 DOI: 10.1136/gut.2005.082909]
 - 11 **Silverberg MS**, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, Caprilli R, Colombel JF, Gasche C, Geboes K, Jewell DP, Karban A, Loftus EV, Peña AS, Riddell RH, Sachar DB, Schreiber S, Steinhart AH, Targan SR, Vermeire S, Warren BF. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005; **19** Suppl A: 5A-36A [PMID: 16151544]
 - 12 **Yamamoto K**, Kiyohara T, Murayama Y, Kihara S, Okamoto Y, Funahashi T, Ito T, Nezu R, Tsutsui S, Miyagawa JI, Tamura S, Matsuzawa Y, Shimomura I, Shinomura Y. Production of adiponectin, an anti-inflammatory protein, in mesenteric adipose tissue in Crohn's disease. *Gut* 2005; **54**: 789-796 [PMID: 15888786 DOI: 10.1136/gut.2004.046516]
 - 13 **Nishihara T**, Matsuda M, Araki H, Oshima K, Kihara S, Funahashi T, Shimomura I. Effect of adiponectin on murine colitis induced by dextran sulfate sodium. *Gastroenterology* 2006; **131**: 853-861 [PMID: 16952554 DOI: 10.1053/j.gastro.2006.06.015]
 - 14 **Fayad R**, Pini M, Sennello JA, Cabay RJ, Chan L, Xu A, Fantuzzi G. Adiponectin deficiency protects mice from chemically induced colonic inflammation. *Gastroenterology* 2007; **132**: 601-614 [PMID: 17258715 DOI: 10.1053/j.gastro.2006.11.026]
 - 15 **Batra A**, Zeitz M, Siegmund B. Adipokine signaling in inflammatory bowel disease. *Inflamm Bowel Dis* 2009; **15**: 1897-1905 [PMID: 19408337 DOI: 10.1002/ibd.20937]
 - 16 **Wolf AM**, Wolf D, Rumpold H, Enrich B, Tilg H. Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1RA in human leukocytes. *Biochem Biophys Res Commun* 2004; **323**: 630-635 [PMID: 15369797 DOI: 10.1016/j.bbrc.2004.08.145]
 - 17 **Lord GM**, Matarese G, Howard JK, Baker RJ, Bloom SR, Lechler RI. Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. *Nature* 1998; **394**: 897-901 [PMID: 9732873 DOI: 10.1038/29795]
 - 18 **Loffreda S**, Yang SQ, Lin HZ, Karp CL, Brengman ML, Wang DJ, Klein AS, Bulkley GB, Bao C, Noble PW, Lane MD, Diehl AM. Leptin regulates proinflammatory immune responses. *FASEB J* 1998; **12**: 57-65 [PMID: 9438411]
 - 19 **Karmiris K**, Koutroubakis IE, Xidakis C, Polychronaki M, Voudouri T, Kouroumalis EA. Circulating levels of leptin, adiponectin, resistin, and ghrelin in inflammatory bowel disease. *Inflamm Bowel Dis* 2006; **12**: 100-105 [PMID: 16432373 DOI: 10.1097/01.MIB.0000200345.38837.46]
 - 20 **Franchimont D**, Roland S, Gustot T, Quertinmont E, Toubouti Y, Gervy MC, Deviere J, Van Gossum A. Impact of infliximab on serum leptin levels in patients with Crohn's disease. *J Clin Endocrinol Metab* 2005; **90**: 3510-3516 [PMID: 15784704 DOI: 10.1210/jc.2004-1222]
 - 21 **Sitaraman S**, Liu X, Charrier L, Gu LH, Ziegler TR, Gewirtz A, Merlin D. Colonic leptin: source of a novel proinflammatory cytokine involved in IBD. *FASEB J* 2004; **18**: 696-698 [PMID: 14977884]
 - 22 **Cai Z**, Zhang W, Li M, Yue Y, Yang F, Yu L, Cao X, Wang J. TGF-beta1 gene-modified, immature dendritic cells delay the development of inflammatory bowel disease by inducing CD4(+)Foxp3(+) regulatory T cells. *Cell Mol Immunol* 2010; **7**: 35-43 [PMID: 20081874 DOI: 10.1038/cmi.2009.107]
 - 23 **Suenaert P**, Maerten P, Van Assche G, Van Driessche W, Geboes K, Bulteel V, Simaels J, Augustijns P, Ceuppens JL, Rutgeerts P, Perrier C. Effects of T cell-induced colonic inflammation on epithelial barrier function. *Inflamm Bowel Dis* 2010; **16**: 1322-1331 [PMID: 20155850 DOI: 10.1002/ibd.21211]
 - 24 **Yoshimura T**, Oppenheim JJ. Chemerin reveals its chimeric nature. *J Exp Med* 2008; **205**: 2187-2190 [PMID: 18809717 DOI: 10.1084/jem.20081736]
 - 25 **Cash JL**, Hart R, Russ A, Dixon JP, Colledge WH, Doran J, Hendrick AG, Carlton MB, Greaves DR. Synthetic chemerin-derived peptides suppress inflammation through ChemR23. *J Exp Med* 2008; **205**: 767-775 [PMID: 18391062 DOI: 10.1084/jem.20071601]
 - 26 **Silswal N**, Singh AK, Aruna B, Mukhopadhyay S, Ghosh S, Ehtesham NZ. Human resistin stimulates the pro-inflammatory cytokines TNF-alpha and IL-12 in macrophages by NF-kappaB-dependent pathway. *Biochem Biophys Res Commun* 2005; **334**: 1092-1101 [PMID: 16039994 DOI: 10.1016/j.bbrc.2005.06.202]
 - 27 **Paul G**, Schäffler A, Neumeier M, Fürst A, Bataillle F, Buechler C, Müller-Ladner U, Schölmerich J, Rogler G, Herfarth H. Profiling adipocytokine secretion from creeping fat in Crohn's disease. *Inflamm Bowel Dis* 2006; **12**: 471-477 [PMID: 16775490 DOI: 10.1097/00054725-200606000-00005]
 - 28 **Patel L**, Buckels AC, Kinghorn IJ, Murdock PR, Holbrook JD, Plumpton C, Macphee CH, Smith SA. Resistin is expressed in human macrophages and directly regulated by PPAR gamma activators. *Biochem Biophys Res Commun* 2003; **300**: 472-476 [PMID: 12504108 DOI: 10.1016/S0006-291X(02)02841-3]
 - 29 **Kaser A**, Kaser A, Sandhofer A, Ebenbichler CF, Tilg H, Patsch JR. Resistin messenger-RNA expression is increased by proinflammatory cytokines in vitro. *Biochem Biophys Res Commun* 2003; **309**: 286-290 [PMID: 12951047 DOI: 10.1016/j.bbrc.2003.07.003]
 - 30 **Fukuhara A**, Matsuda M, Nishizawa M, Segawa K, Tanaka M, Kishimoto K, Matsuki Y, Murakami M, Ichisaka T, Murakami H, Watanabe E, Takagi T, Akiyoshi M, Ohtsubo T, Kihara S, Yamashita S, Makishima M, Funahashi T, Yamanaoka S, Hiramatsu R, Matsuzawa Y, Shimomura I. Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. *Science* 2005; **307**: 426-430 [PMID: 15604363 DOI: 10.1126/science.1097243]
 - 31 **Jia SH**, Li Y, Parodo J, Kapus A, Fan L, Rotstein OD, Marshall JC. Pre-B cell colony-enhancing factor inhibits neutrophil apoptosis in experimental inflammation and clinical sepsis. *J Clin Invest* 2004; **113**: 1318-1327 [PMID: 15124023 DOI: 10.1172/JCI19930]
 - 32 **Moschen AR**, Geiger S, Gerner R, Tilg H. Pre-B cell colony enhancing factor/NAMPT/visfatin and its role in inflammation-related bone disease. *Mutat Res* 2010; **690**: 95-101 [PMID: 19583971 DOI: 10.1016/j.mrfmmm.2009.06.012]

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