

Are adipocytokines inflammatory or metabolic mediators in patients with inflammatory bowel disease?

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Abstract: This study examined the adiponectin and leptin levels and insulin resistance (IR) in patients with inflammatory bowel disease (IBD) and the associations between these factors and IBD characteristics. Fasting serum leptin, adiponectin, glucose, and insulin levels, as well as inflammatory parameters, were measured in 105 patients with IBD (49 patients with Crohn's disease [CD], 56 patients with ulcerative colitis [UC]) and 98 healthy controls [HC]. IR was evaluated using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). Disease activity and severity in patients with UC were evaluated using the Truelove–Witts index, and patients with CD were evaluated using the Crohn's Disease Activity Index. Serum adiponectin levels were found to be significantly lower in patients with CD and UC ($p < 0.001$). Serum leptin levels were also found to be significantly higher in both the UC and CD groups ($p < 0.001$). When HOMA-IR levels were compared, no significant difference was detected for either the CD or UC groups compared with the controls. In conclusion, it was shown that leptin levels increased and adiponectin levels decreased in patients with IBD, which is thought to be related to chronic inflammation. The effects of adipocytokines in patients with IBD with inflammatory and metabolic processes need to be investigated in further broader studies.

Keywords: ulcerative colitis, Crohn's disease, insulin resistance, adiponectin, leptin

Introduction

Inflammatory bowel diseases (IBDs) are chronic inflammatory diseases of the gastrointestinal tract.¹ Crohn's disease (CD) and ulcerative colitis (UC) are the main forms of IBD. Chronic inflammation plays a significant role in the development of insulin resistance (IR), metabolic syndrome (MS), and diabetes via various inflammatory mediators and adipocytokines, including adiponectin and leptin.^{2–4} In recent years, it has been found that adipose tissue actively participates in local and systemic immune responses via molecules called adipocytokines secreted by adipose tissue. Activation of inflammatory cells located in visceral adipose tissue, namely, macrophages, and secretion of adipocytokines such as leptin, adiponectin, and tumor necrosis factor- α (TNF- α) have been found to activate inflammatory pathways, which leads to the development of IR, steatohepatitis, and atherosclerosis.^{5,6} Mesenteric visceral adipose tissue hyperplasia, also known as creeping fat, is a pathognomonic finding of CD. These mesenteric fat deposits are secondary to intestinal inflammation and increased by inflammatory cytokines such as TNF- α , inflammatory cells such as macrophages, and preadipocytes.⁷

The first investigated adipocytokine associated with intestinal inflammation was leptin. In experimental colitis models, intestinal inflammation was significantly

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reduced in leptin-deficient (*ob/ob*) mice.⁸ On the other hand, intrarectal leptin administration has been shown to cause mucosal inflammation in mice.⁹ It has been shown in experimental studies that leptin has an important function in many autoimmune diseases as a proinflammatory cytokine.¹⁰ Leptin, together with interleukin 1 alpha (IL-1 α), TNF- α , and interleukin 6 (IL-6), plays an active role in inflammatory processes.¹¹ Another function of leptin is to regulate food intake and energy balance. It has been shown that a lack of leptin or leptin resistance was correlated with the development of obesity, IR, and diabetes.¹²

Adiponectin, another important adipocytokine synthesized in large quantities from adipocytes, has anti-inflammatory effects. In the experimental colitis model, adiponectin (*-/-*) mice showed a significant increase in colitis severity due to adiponectin deficiency, which suggested possible protective effects of adiponectin against colitis.¹³ Studies in humans have reported conflicting results about systemic serum levels of adiponectin in patients with IBD. Some authors reported that serum adiponectin levels decrease in patients with IBD,^{14,15} whereas others reported no change or increased levels.^{16–18}

Adiponectin also plays a significant role in energy homeostasis. Adiponectin is involved in glucose regulation and fatty acid catabolism. It decreases gluconeogenesis and increases glucose uptake in cells, beta oxidation, and fat clearance. Lower serum adiponectin levels are associated with IR and metabolic diseases in the general population.¹⁹ Adiponectin may be regarded as a potential biomarker of MS.²⁰ It has been shown that cytokines lead to decreased adiponectin expression in fat tissue.

IR is a factor that has significance in the development of atherosclerosis; it forms the basis for the development of MS and diabetes and indirectly affects morbidity and mortality. This study assessed the serum adiponectin and leptin levels and IR in adult patients with IBD and the associations between these factors and characteristics of IBD.

Patients and methods

Patient population

A total of 105 patients who were followed up after being diagnosed as having IBD (56 with UC [(22 females and 34 males)], mean age 40 \pm 11 years; 49 with CD [24 females and 25 males], mean age 38 \pm 11 years) and 98 healthy controls [HC], who had similar baseline demographic values, were enrolled in the study. Patients with diabetes mellitus, thyroid diseases, chronic obstructive pulmonary disease (COPD), coronary heart disease, malignant hypertension, or renal failure; those receiving hormone replacement therapy or

corticosteroids in the past 6 months; who were pregnant; or those with liver cirrhosis were excluded. After obtaining written informed consent from the participants and approval from Istanbul University's ethics committee (2012-4873), the study was conducted in accordance with the Declaration of Helsinki. Disease activity and severity were evaluated using the Truelove–Witts (TW) index in patients with UC and the Crohn's Disease Activity Index (CDAI) in patients with CD. There were no patients with severe active colitis among patients with UC. Crohn's patients were divided into two groups as CDAI <150 and CDAI \geq 150 in terms of activity index. There were no patients with CDAI >450. Patients with UC were divided into two groups according to extension: left-sided, determined as limited distal of the splenic flexure, and extensive involvement exceeding the splenic flexure. Patients with CD were divided into two groups as ileal CD and ileocolonic CD.

Laboratory analysis

Blood samples were taken from antecubital vein using 20-gauge needles between 8:30–10:30 am after fasting for 8–12 hours. The levels of glucose, insulin, cholesterol, triglyceride, low-density lipoprotein (LDL), high-density lipoprotein (HDL), very-low-density lipoprotein (VLDL), complete blood count, sedimentation, C-reactive protein (CRP), and hemoglobin A1c (HbA1c) levels were studied on the same day. Blood samples taken for the measurement of adiponectin were centrifuged for 6 minutes at 5,000 rpm, and the obtained 1–2 mL serum samples were stored at -80°C . All materials used during the study were in compliance with the specifications of kits identified in the operation manual, and the steps in the operating manual were carefully observed while performing each test. Serum adiponectin and leptin levels were evaluated by commercial enzyme-linked immunosorbent assay (ELISA) kits (AssayMax Human ELISA, AssayPro, St Charles, MO, USA).

Assessing IR

IR was calculated in the patient and HC group. The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index was used to assess IR. The HOMA-IR formula used is as follows: HOMA-IR = fasting plasma glucose (mmol/L) \times fasting plasma insulin (mU/L)/22.5. HOMA \geq 2.5 was accepted as IR.²¹

Statistical methods

All data obtained at the end of the study were analyzed using the Statistical Package for the Social Sciences (SPSS), version 20 (IBM Corporation, Armonk, NY, USA). The

analysis of variance (ANOVA) test and Student's *t*-test were used to compare averages of variables in more than two groups. The calculation of differences between sexes was made using the chi-square test. For the assessment of correlation between the variables, Pearson's and Spearman's correlation analyses were conducted for parametric and nonparametric variables, respectively. A *p*-value of <0.05 was considered as statistically significant. The Shapiro–Wilk test and Kolmogorov–Smirnov test were used to evaluate the distribution of the variables. Categorical variables were presented as frequencies and percentages. Normally distributed continuous variables are expressed as mean ± standard deviation, and skewed distributed continuous variables are expressed as median (interquartile range).

Results

The demographic and laboratory data of patients with CD and UC and HC are presented in Table 1. When the patient and control groups were compared, there was no difference in terms of age, sex, or body mass index (BMI). In the UC group, serum glucose levels were found to be significantly higher than that of the control group (*p*=0.004), however in the CD group, cholesterol and LDL levels were found to be significantly lower than that of the control group (*p*=0.007, *p*=0.002 respectively, Table 1).

Assessment of leptin, adiponectin, and HOMA-IR index in the study groups is shown in Table 2. CRP levels were significantly higher in patients with CD compared with the control group (*p*=0.04, Table 2). Serum adiponectin levels were found to be significantly lower both in patients with CD

and UC compared with the HC (*p*<0.001; Figure 1). Serum leptin levels were also found to be significantly higher in both the UC and CD groups compared with the HC group (*p*<0.001; Figure 2). When HOMA-IR levels were compared, no significant difference was detected for either the CD or UC group compared with the HC. The HOMA-IR index and BMI were clearly correlated (*r*=0.43, *p*<0.001 and *r*=0.43, *p*<0.001, respectively) in the IBD and control groups.

Serum leptin, adiponectin, and HOMA-IR index were assessed for patients with UC and CD with normal and high CRP levels, and no significant difference was found (Table 3).

In UC patients, serum adiponectin levels were significantly higher in patients with BMI <25 kg/m² than BMI ≥25 kg/m² (*p*=0.04). In CD patients, HOMA-IR levels were significantly increased in patients with BMI ≥25 kg/m² compared with those of BMI <25 (*p*=0.03, Table 3).

Disease activity and IR, HOMA-IR index, leptin, and adiponectin were assessed according to the disease activity in UC as mild and moderate TW index; no significant correlation with disease activity was detected. When patients with CD who had CDAI values <150 and ≥150 were compared in terms of adiponectin, leptin, and the HOMA-IR index, no significant difference was found (Table 3).

When patients with UC were divided into two groups according to localization as limited to the distal of splenic flexure (proctitis: 5, rectosigmoiditis: 15, left side: 12; n=32) and exceeding the splenic flexure (extensive: 4, pancolitis: 19; n=23), no significant difference was noted regarding serum leptin level (551±116 vs 590±150; *p*=0.38), adiponectin level

Table 1 Demographic data for patients with CD, UC, and the HC group

	HC (n=98)	CD (n=49)	<i>p</i> -value ^a	UC (n=56)	<i>p</i> -value ^b
Age	38±10	38±11	0.803	40±11	0.301
Sex (female/male), n	51/47	24/25	0.726	22/34	0.12
Disease duration (months)	–	39.41±46.83		54.79±49.58	
BMI (kg/m ²)	26.34±3.64	24.76±6.25	0.116	25.28±5.57	0.16
Glucose (mg/dL)	90.83±9.55	95.10±16.31	0.096	95.70±10.42	0.004
Smoking, n (%)			0.050		0.003
No	62 (63.3)	24 (49.0)		34 (60.7)	
Yes	30 (30.6)	16 (32.7)		9 (16.1)	
Ex-smoker	6 (6.1)	9 (18.4)		13 (23.2)	
Cholesterol (mg/dL)	188.89±36.22	170.71±39.7	0.007	183.02±47.43	0.398
HDL (mg/dL)	49.27±12.49	51.24±17.31	0.436	53.59±26.26	0.259
LDL (mg/dL)	115.80±32.46	97.80±33.24	0.002	107.62±40.0	0.182
Current treatment, n (%)					
Mesalamine		38 (77)		56 (100)	
Azathioprine		39 (80)		18 (32)	
Anti-TNF		13 (20)		0	

Notes: All values are represented as mean ± standard deviation, unless stated otherwise. ^a*p*-value between CD group and HC and ^b*p*-value between UC group and HC. Bold represents statistically significant values.

Abbreviations: CD, Crohn's disease; UC, ulcerative colitis; HC, healthy control; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TNF, tumor necrosis factor.

Table 2 Assessment of leptin, adiponectin, HOMA-IR index, and IR in the control group and patients with UC and CD

	HC	CD	UC	p-value
Leptin (ng/mL)	41±26	544±171	570±132	<0.001 ^a <0.001 ^b 0.54 ^c
Adiponectin (ng/mL)	26.49±24	23.98±20	21.26±36	<0.001 ^a <0.001 ^b <0.001 ^c
HOMA-IR	1.81±0.96	1.56±0.98	1.95±1.29	0.43 ^a 0.71 ^b 0.18 ^c
CRP (mg/dL)	0.45±0.32	0.82±1.13	0.63±0.89	0.04 ^a 0.42 ^b 0.50 ^c

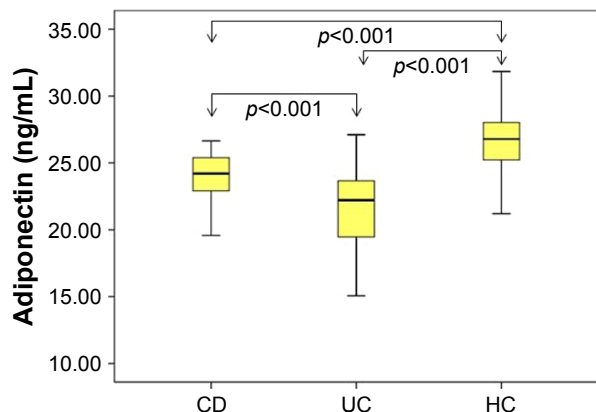
Notes: All values are represented as mean ± standard deviation. ^ap-value between CD group and HC group; ^bp-value between UC group and HC group; and ^cp-value between CD group and UC group.

Abbreviations: HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; IR, insulin resistance; UC, ulcerative colitis; CD, Crohn's disease; HC, healthy control; CRP, C-reactive protein.

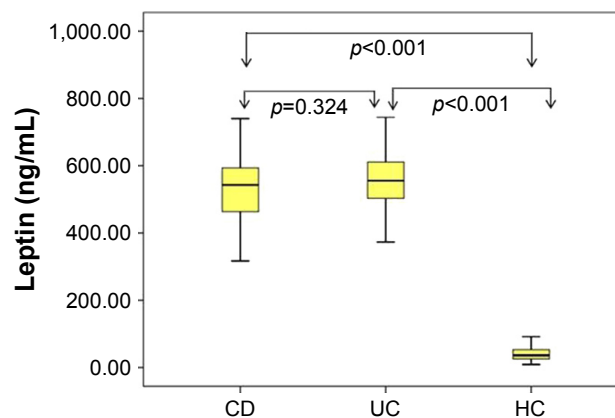
(21.57±36 vs 20.80±38; $p=0.53$), and the HOMA-IR index (1.93±1.02 vs 2.09±1.60; $p=0.85$) between the two groups (data not shown).

Similarly, when patients with CD were divided into two groups according to the involvement areas as ileal involvement ($n=21$) and ileocolonic involvement ($n=28$), no significant difference was found in terms of serum leptin (526±155 vs 570±180; $p=0.46$), adiponectin (24.31±16 vs 23.78±22; $p=0.46$), and the HOMA-IR index (1.49±1.10 vs 1.56±0.95; $p=0.82$; data not shown).

In both IBD and control groups, HOMA-IR was found to be significantly correlated with BMI ($r=0.43$, $p<0.001$ and $r=0.43$, $p<0.001$, respectively). However, the HOMA-IR score was not found to be associated with adipocytokine levels (data not shown).

**Figure 1** Distribution of serum adiponectin concentration.

Abbreviations: CD, Crohn's disease; UC, ulcerative colitis; HC, healthy control.

**Figure 2** Distribution of serum leptin concentration.

Abbreviations: CD, Crohn's disease; UC, ulcerative colitis; HC, healthy control.

Discussion

In this study, it was shown that serum adiponectin levels in adult patients with IBD were significantly lower than those in the HC group. Adiponectin levels in patients with UC were also significantly lower than those in patients with CD. As another important adipocytokine, serum leptin levels were found significantly higher in both the UC and CD groups than in the HC group. When patients with IBD were evaluated for serum leptin levels, adiponectin levels, and HOMA-IR index, no significant correlation was found between disease localization and disease activity.

Capristo et al²² first reported that entire body glucose uptake and oxidation were similar in patients with IBD, irrespective of disease activity. In the study by Nagahori et al,²³ MS prevalence in Japanese patients with IBD was found to be considerably higher in patients with UC compared with patients with CD. In the study by Yorulmaz et al,²⁴ the incidence of MS was found to be higher in patients with UC than in patients with CD. In our study, the incidence of IR in patients with UC was 21% and in those with CD was 18%. There were no significant differences between the IBD subgroups and control group.

In a study by Chouliaras et al¹⁷ in which glucose metabolism and adipocytokines were assessed for pediatric patients with UC and CD, it was reported that IR was considerably higher in patients with both UC and CD. Bregenger et al²⁵ assessed IR and β -cell activity using the HOMA-IR test in 17 patients with CD, and IR was detected higher in the patient group compared with the control group. It was thought that IR could be correlated with chronic inflammation.

Dagli et al²⁶ assessed risk factors in IBD regarding atherosclerotic diseases and included 40 patients with IBD and 40 controls in their study. In patients with IBD, carotid

Table 3 Comparison of serum leptin, adiponectin, and HOMA-IR index in groups with normal and high CRP levels, in terms of disease activity indexes and in terms of BMI in patients with IBD

UC patients	CRP <0.5	CRP ≥0.5	p-value	Mild TW index	Moderate TW index	p-value	BMI <25 kg/m ²	BMI ≥25 kg/m ²	p-value
Leptin	567±1	579±1	0.80	581±1	519±7	0.23	605±1	548±1	0.21
Adiponectin	21.4±3	21±52	0.81	21.3±3	21.5±4	0.87	22.7±2	20.5±4	0.04*
HOMA-IR	1.9±1	2.2±2	0.92	2.05±1	1.7±1	0.30	2±1	2.1±1	0.75
CD patients	CRP <0.5	CRP ≥0.5	p-value	CDAI <150	CDAI ≥150	p-value	BMI <25 kg/m ²	BMI ≥25 kg/m ²	p-value
Leptin	487±1	572±2	0.18	539±2	550±2	0.84	558±2	515±2	0.53
Adiponectin	24.3±2	23.8±2	0.49	24.5±2	23.4±2	0.14	23.8±2	24.3±3	0.54
HOMA-IR	1.5±1	1.6±1	0.53	1.5±1	1.6±1	0.94	1.3±1	2.04±1	0.03*

Notes: All values are represented as mean ± standard deviation. * $p < 0.05$. Bold represents statistically significant values.

Abbreviations: HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; CRP, C-reactive protein; BMI, body mass index; IBD, inflammatory bowel disease; UC, ulcerative colitis; TW, Truelove–Witts; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index.

artery stiffness, CRP, HOMA-IR, and homocysteine were found to be considerably higher compared with the control group. In our study, the HOMA-IR index was found to be significantly higher in patients with BMI ≥ 25 kg/m² in both groups and the control group. In the UC group, serum adiponectin levels were higher in patients with BMI < 25 kg/m² compared with patients who had BMI ≥ 25 kg/m². Higher IR and lower serum adiponectin levels were the expected findings in patients who were overweight–obese. However, in our study, the absence of significant elevations in the IR index may be due to the absence of patients with severe active disease.

In experimental models, a decrease in adiponectin levels was demonstrated to be associated with the development of IR and diabetes.²⁷ Serum adiponectin was also regarded as a biomarker of MS, and it was shown that a decrease in serum adiponectin level led to an increase in IR and was an independent predictor for the development of diabetes.^{28–31}

In the study by Valentini et al, 44 patients with UC and 49 patients with CD were examined and IR and adiponectin levels were evaluated. In their study, serum adiponectin levels were found to be significantly lower in the patient group compared with the HC group and hyperinsulinemia was detected.¹⁴

Adiponectin has been demonstrated in experimental animal studies in relation to intestinal inflammation. In an experimental colitis model, it was shown that the severity of colitis was significantly increased in adiponectin-deficient mice and that adiponectin had protective effects against colitis.^{13,32} In contrast, another study showed that the experimental colitis model regulates inflammatory cytokines but does not affect disease severity.³³

Yamamoto et al³⁴ found that adiponectin expression in mesenteric fat tissues increased in patients with CD. On the

other hand, Rodrigues et al¹⁵ showed that adiponectin levels significantly decreased in patients with active CD, but adiponectin levels did not change in those in remission. Weigert et al³⁵ found higher adiponectin levels in patients with UC than in those with CD and HC. Adiponectin levels were found to be similar for all three groups (UC, CD, and HC) in the studies of Karmiris et al¹⁸ and Waluga et al.¹⁶ In our study, serum adiponectin levels were detected to be significantly lower in patients with CD and UC compared with those in the control group. Although serum adiponectin levels decreased in the entire IBD group, the decrease was more notable in patients with UC than in patients with CD. As mentioned in the earlier studies, serum adiponectin levels are variable in patients with IBD and their role in the pathogenesis of the disease is still unclear.

Leptin has metabolic, endocrinologic, and also immunologic effects. Leptin stimulates T lymphocytes by regulating the release of various cytokines. The direct role assumed by leptin in intestinal inflammation was indicated in experimental models.¹⁰ Leptin mRNA overexpression in mesenteric adipose tissue was found in patients with IBD.³⁶ Leptin receptors were detected in inflamed colonic epithelium of patients with IBD, and leptin levels were found to be considerably high.³⁷ It was indicated in another study that colonic lavage leptin concentrations were 15 times higher in patients with UC and CD compared with the control group. It has also been demonstrated that the increase in leptin level was correlated with severity of disease and inversely correlated with the number of T regulator cells.⁹ Tuzun et al³⁸ showed that leptin levels were substantially higher in patients with active UC. On the other hand, Waluga et al¹⁶ found that leptin levels were very high in patients with CD during the posttreatment period. In our study, leptin levels were also detected to be higher both in patients with UC and CD. It was found to be

high in both mild-to-moderate active patients, independent of disease activity. However, leptin levels were reported to be lower in the study by Karmiris et al.¹⁸ In the study of Nishi et al,³⁹ there was no significant difference in leptin levels in patients with CD compared with those in the control group. Similarly, in the study by Rodrigues et al,¹⁵ leptin levels in patients with CD did not change. In a recently published study by Ghomraoui et al,⁴⁰ leptin levels were found to be lower in patients with IBD compared with those in the control group, but no significant difference in leptin levels was found between the control group and patients with IBD. These conflicting results regarding leptin levels merit further studies on this issue.

Conclusion

A significant increase in leptin levels and a decrease in adiponectin levels were found in patients with IBD. These findings suggest that adipocytokines may play a role in inflammatory and metabolic processes in patients with IBD. Further studies are needed to investigate the possible effects of adipocytokines on inflammatory and metabolic processes in patients with IBD.

Disclosure

The authors report no conflicts of interest in this work.

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