Hyperadiponectinemia During Infliximab Induction Therapy in Pediatric Crohn Disease

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ABSTRACT

Objectives: The inflammatory process in Crohn disease (CD) involves the visceral fat, characterized by adipocyte hyperplasia and altered adipose tissue and serum concentrations of tumor necrosis factor (TNF), leptin, adiponectin and resistin. We investigated the effect of anti-TNF therapy with infliximab (IFX) on serum adipokine levels in pediatric CD.

Methods: Serum concentrations of resistin (ng/mL), leptin (ng/mL), and total adiponectin (μg/mL) were assessed by enzyme-linked immunosorbent assays (ELISA) in 18 pediatric CD patients (mean age 15.0 ± 1.5 years) before first, second, and fourth IFX infusion (weeks 0, 2, and 14) and compared with baseline values from sex- and BMI-matched healthy controls (HC, mean age 13.4 ± 1.6 years).

Results: At baseline, CD patients (mean age 15.0 ± 1.5 years, 10 of 18 boys) compared with HC (13.4 ± 1.6 years, 7 of 15 boys) had higher resistin levels (median 14.7 ng/mL, range 5.1–50.5 vs 7.3 ng/mL, 0.5–14.5); $P = 0.0002$). At weeks 2 and 14, resistin decreased to 6.9 ng/mL (2.9–16.8) ($P < 0.0001$) and 9.2 ng/mL (4.1–20.6; $P = 0.0011$), respectively. Leptin and adiponectin were comparable between patients and HC at baseline. Leptin increased in girls from 9.5 ng/mL (4.0–30.1) to 16.0 ng/mL (7.9–35.2; $P = 0.0156$) and 17.2 ng/mL (10.8- 26.8; $P = 0.1953$) at weeks 0, 2, and 14 respectively; with a trend in boys from 2 (0.6–12.9) to 2.8 (1.7–8.6; $P = 0.0840$) and 3.3 (1.3–4.6; $P = 0.1309$). Adiponectin peaked initially from 7.8 μg/mL (4.6–11.9) at week 0 to 9.2 μg/mL (4.1–20.7; $P = 0.0005$) at week 2 and thereafter fell to 6.5 μg/mL (3.0–12.7; $P = 0.0182$) at week 14.

Conclusions: TNF blockade is associated with changes in circulating adipokines. The marked early increase of the potent anti-inflammatory adiponectin may contribute to the rapid response to IFX in CD.

Key Words: adipokines, infliximab, pediatric Crohn disease

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What Is Known

- Mesenteric adipose tissue hyperplasia near the inflamed intestine is characteristic for Crohn disease, represents an important source of different pro- and anti-inflammatory mediators and is associated with altered serum adipokine concentrations.
- Resistin levels have been suggested as a biomarker of successful anti-tumor necrosis factor (anti-TNF) therapy, whereas leptin and adiponectin concentrations reflect body fat mass in opposite manner.

What Is New

- Tumor necrosis factor (TNF) blockade is associated with a rapid increase of the anti-inflammatory adiponectin in pediatric Crohn disease, which may contribute to effective induction therapy.
- Measurements of serum adipokines may serve as a biomarker for short- and long-term response to infliximab.

When Crohn et al (1) first described Crohn disease (CD) in the early 1930s, they noticed increased mesenteric adipose tissue attached to the inflamed intestine. The importance in the pathogenesis and course of the disease, however, caught only

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Dr Klara Frivolt, a young pediatrician in training at the University of Bratislava, died on August 5, 2017 in Hungary being pregnant with her second child. Klara had spent two research periods of 18 months each at the Division of Gastroenterology and Hepatology at the Dr von Hauner Children's Hospital, LMU Munich, Germany. She had received several research awards including the Nestle Nutrition Award from the European Crohn and Colitis Organization (ECCO) in 2014. On July 4, 2017 she successfully defended her PhD. Klara Frivolt was an extremely talented young physician scientist and a wonderful person. We are in deep grief.

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attention in the last 2 decades. Initially, it was suggested that mesenteric adipose tissue inflammation precedes mucosal inflammation and represents a causative factor in the pathogenesis of CD (2,3). More recent findings conclude that the hyperplasia of the mesenteric adipose tissue is a protective mechanism to improve barrier function against bacterial translocation through the inflamed gut (4).

Visceral adipose tissue is a dynamic endocrine and paracrine organ, which participates in the regulation of metabolism and acts as an active innate immune organ (5). It was shown that not only the mesenteric adipose tissue attached to the inflamed intestine but also the omental adipose tissue more distant from the inflamed intestine is affected by inflammation in CD (6), and represents a source of pro- and anti-inflammatory cytokines and chemokines (3,4,7–10). Preadipocytes and adipocytes are immunologically active cells expressing pattern recognition receptors and secreting inflammatory mediators (11). Furthermore, pre-adipocytes have phagocytic and antimicrobial activity similar to macrophages (12). Two major players in the family of adipose tissue-derived cytokines, so called adipokines, are leptin and adiponectin. Although leptin is attributed a rather pro-inflammatory role, adiponectin has potent anti-inflammatory effects (13,14). In contrast to leptin, changes in body fat correlate inversely with adiponectin levels (15). Adiponectin is present in high amounts in the circulation and has several isoforms that bind specifically to 2 types of adiponectin receptors. The pro-inflammatory resistin increases during inflammation and is produced in humans not only in adipocytes but also in macrophages and peripheral blood mononuclear cells (16).

The mesenteric adipose tissue of CD patients is involved in the inflammatory process indicated by increased tissue concentrations of tumor necrosis factor (TNF) (3), C-reactive protein (CRP) (10), resistin and leptin (7,8) but also of various other anti-inflammatory cell mediators, including adiponectin (8,9). In vitro TNF inhibits leptin and adiponectin expression but stimulates the release of resistin (15,17,18). Alterations in serum adipokine levels have been reported in both pediatric and adult CD patients (19–24).

The monoclonal chimeric anti-TNF antibody infliximab (IFX) is a highly effective induction and maintenance treatment in patients with severe and complicated CD (25,26). The aim of this study was to investigate whether the TNF blockade by IFX modulates circulating adipokine levels in pediatric CD during the induction phase. Baseline adipokine levels were compared with concentrations found in sex- and body mass index (BMI)-matched healthy control children.

METHODS

This retrospective case control study was approved by the Ethics Committee of the Medical Faculty of the Ludwig-Maximilian University in Munich.

Patients and Controls

Patients with CD were eligible for inclusion if they were treated with IFX at Dr. von Hauner Children's Hospital in Munich and had frozen serum samples available taken before the first, second, and fourth IFX infusion (weeks 0, 2, and 14). Serum is routinely sampled before each infusion and directly stored at −20 °C to allow the measurement of IFX trough levels or antibodies against IFX, in case, the patient shows an allergic adverse reaction during or after the infusion or loss of response. Exclusion criteria were prior treatment with an anti-TNF antibody.

CD was diagnosed in all patients according to Porto criteria (27). The phenotype was assessed according to the Paris classification (28). IFX was given as intravenous induction therapy (5 mg/kg per dose) at 0, 2, and 6 weeks, followed by a maintenance treatment, every 8 weeks (29). Disease activity, laboratory, and anthropometric parameters before and during therapy were compared with adipokine levels. As serum levels of leptin and adiponectin are affected by sex and body composition, results were compared with adipokine concentrations measured in anonymized serum samples of 15 healthy sex- and BMI-matched adolescents obtained by Freudenberg et al (30).

Data Collection and Patient Evaluation

Electronic health care records and patient files were used to collect data before IFX initiation, at second and fourth IFX infusion (weeks 0, 2, and 14). Concomitant medications (eg 5-aminosalycilates, azathioprine, or corticosteroids) were recorded. At all visits, clinical, anthropometric, and laboratory parameters (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], serum albumin, and hematocrit) were assessed, which allowed calculation of the mathematically weighted Pediatric Crohn's Disease Activity Index (wPCDAI, range 0–125). Remission was defined as wPCDAI <12.5 points, mild disease as wPCDAI ≥ 12.5 points but <40 points, wPCDAI ≥ 40 points indicated moderate, and wPCDAI ≥ 57.5 points severe disease activity (31). Responders were defined as being in remission at week 14. Partial responders were patients with small (change in wPCDAI >17.5 points) or moderate improvement (change in wPCDAI >37.5 points) in disease activity but not achieving remission at week 14. Non-responders achieved neither improvement nor remission until week 14.

Immunoassays

All serum samples of patients and controls were stored at −20 °C until measurement. Resistin, leptin (Human Leptin and Resistin Quantikine ELISA Kits, R&D Systems, Minneapolis, MN) and total adiponectin (Total Adiponectin ELISA Kit, ALPCO Diagnostics, Salem, NH) serum levels were assessed with commercially available enzyme-linked immunosorbent assays (ELISA) according to the manufacturer's instructions.

Statistical Analysis

Continuous variables are expressed as medians (range) or means ± standard deviation. Wilcoxon matched-pairs signed rank test was applied to analyze differences between changes in non-parametric data between IFX patients and healthy controls (HC). For comparison of parametric data paired *t*-test and for sex differences Mann-Whitney *U* test was applied. Spearman correlation analysis was used to determine correlation significance between adipokines and disease activity, inflammatory and anthropometric parameters. Results are expressed as correlation coefficient (r) and exact P value. Statistical analyses were performed using GraphPad Prism version 6.00 for Mac OS X (GraphPad Software Inc., La Jolla, CA). P values below 0.05 were considered statistically significant.

RESULTS

Baseline patient characteristics are provided in Table 1. Eighteen patients (10 boys) were eligible, with a mean age at diagnosis of 12.0 ± 2.2 years and a mean age at IFX initiation of 15.0 ± 1.5 years. Four patients had stricturing and 1 stricturing and penetrating disease behavior, whereas 7 of 18 presented with perianal involvement. Indications for biological therapy were complicated or perianal disease (n = 10), relapse or persistent inflammation despite immunomodulatory therapy (n = 8). All 18 patients

TABLE 1. Baseline patient characteristics

	Infliximab patients
Gender (male/female)	10/8
Mean age (±SD) at therapy initiation	15.0 ± 1.5 years
Mean age (±SD) at diagnosis	12.0 ± 2.2 years
Extraintestinal manifestation	2/18
Disease location	
L1 Terminal ileum	7/18
L2 Colon	3/18
L3 Ileocolonic	8/18
+ L4 (upper GI tract)	10/18
Disease behavior	
B1 nonstricturing-nonpenetrating	13/18
B2 stricturing	4/18
B3 penetrating	0/18
B2B3 penetrating and structuring	1/18
Perianal involvement	7/18
Associated medical therapy	
5-aminosalycilic acid	15/18
Azathioprine	18/18
Systemic corticosteroids	2/18
Budesonide	3/18

GI = gastrointestinal; SD = standard deviation.

were treated with azathioprine on a stable dose for at least 3 months, 2 received systemic steroids, and 3 budesonide before or during IFX-induction therapy.

The 15 sex- and BMI-matched HC were younger compared with CD patients with a mean age of 13.4 ± 1.6 years ($P = 0.0033$). Table 2 depicts anthropometric characteristics of HC and patients.

Disease Activity and Inflammatory Parameters Under Infliximab

According to wPCDAI, 1 of 18 patients had severe and 7 of 18 had moderate disease activity. Indication for IFX in 5 of 10 patients with mild disease was perianal involvement with severe fistula and in 1 patient, presence of internal fistulas. IFX decreased overall disease activity, normalized inflammatory parameters after 2 and 14 weeks, respectively (Table 2) and induced remission in 13 of 18 patients. We detected partial response with moderate improvement in disease activity in 3 patients with stricturing disease. Two patients with complex perianal fistulas did not respond to treatment.

Serum Adipokine Levels in Health and Disease

Serum adipokine levels are listed in Table 2. At baseline, resistin levels were significantly elevated in patients compared with HC. Resistin significantly decreased under IFX (Fig. 1A). There was no difference in resistin concentrations between boys and girls. Baseline resistin concentrations correlated with CRP ($r = 0.549$, $P = 0.018$) and the decrease after 2 and 14 weeks correlated with improvement in CRP ($r = 0.614$, $P = 0.007$ and $r = 0.665$, $P = 0.003$, respectively). Similarly, resistin correlated with wPCDAI. This correlation was significant but weak ($r = 0.316$, $P = 0.02$). Leptin levels in boys were significantly lower compared with girls (at 0, 2, and 14 weeks). Before IFX, leptin did not differ between patients and HC but increased in CD patients under IFX (Fig. 1B). Baseline adiponectin levels were similar in CD patients and HC and tended to be lower in boys. Adiponectin significantly increased after the first IFX infusion but decreased after 14 weeks to levels lower than at week 2, at baseline or in HC (Fig. 1C).

DISCUSSION

Using magnetic resonance imaging studies in pediatric CD patients, we could recently show that intra-abdominal adipose tissue is increased compared with non-CD children and correlates with disease duration (32). During IFX treatment, a homogenous increase in both subcutaneous- and intra-abdominal adipose tissue was observed in adults (33). In this retrospective study, we show that induction therapy with IFX induced early changes in circulating adipokines in pediatric CD with a significant increase of adiponectin, a potent anti-inflammatory compound, after the first infusion.

Resistin is a pro-inflammatory adipokine expressed mainly in peripheral blood mononuclear cells (PBMCs) and partially in

TABLE 2. Serum adipokines, disease activity, inflammatory and anthropometric parameters under infliximab therapy

	HC	*P* (HC vs w0)	Week 0	*P* (w0 vs w2)	Week 2	*P* (w2 vs w14)	Week 14	*P* (w0 vs w14)
Resistin, ng/mL	7.3 (0.5; 14.5)	**0.0002**	14.7 (5.1; 50.5)	**<0.0001**	6.9 (2.9; 16.8)	0.0665	9.2 (4.1; 20.6)	**0.0011**
Adiponectin, μg/mL	8.7 (5.0; 10.8)	0.6705	7.8 (4.6; 11.9)	**0.0005**	9.2 (4.1; 20.7)	**0.0001**	6.5 (3.0; 12.7)	**0.0182**
Adiponectin, girls, μg/mL	8.8 (5.0; 10.8)	0.9453	8.2 (6.0; 11.1)	**0.0078**	11.7 (8.0; 17.5)	**0.0078**	7.0 (4.9; 12.7)	0.9999
Adiponectin, boys, μg/mL	8.5 (5.6; 9.4)	0.4922	7.0 (4.6; 11.9)	0.0645	8.1 (4.1; 20.7)	**0.0098**	4.7 (3.0; 7.7)	**0.0098**
Leptin, ng/mL	3.6 (1.2; 15.7)	0.8986	3.2 (0.6; 30.1)	**0.0047**	6.4 (1.7; 35.2)	0.8986	4.3 (1.3; 26.8)	**0.0208**
Leptin, girls, ng/mL	10.1 (3.2; 15.7)	0.9999	9.5 (4.0; 30.1)	**0.0156**	16.0 (7.9; 35.2)	0.7422	17.2 (10.8; 26.8)	0.1953
Leptin, boys, ng/mL	2.1 (1.2; 4.1)	0.6250	2.0 (0.6; 12.9)	0.0840	2.8 (1.7; 8.6)	0.5566	3.3 (1.3; 4.6)	0.1309
BMI, kg/m^2	18.4 (2.0)	0.0979	18.0 (2.2)	**0.0077**	18.2 (2.1)	**0.0046**	19.1 (2.2)	**0.0009**
Height, cm	156.5 (15.0)	0.1428	161.0 (9.9)	**0.0067**	161.4 (9.8)	**<0.0001**	162.8 (9.8)	**<0.0001**
wPCDAI			26.3 (7.5; 72.5)	**<0.0001**	15.0 (0; 35.0)	0.0837	8.8 (0; 45.0)	**0.0003**
CRP, mg/dL			1.4 (0; 6.3)	**<0.0001**	0.1 (0; 1.4)	0.1514	0.1 (0; 1.7)	**0.0009**
ESR, mm/h			40 (8; 67)	**0.0037**	21 (2; 44)	0.3968	18 (2; 40)	**0.0004**
Albumin, g/dL			4 (3.2; 4.9)	**0.0002**	4.2 (3.4; 5)	0.1642	4.4 (3.9; 4.8)	**0.0035**
Hematocrit, %			36 (32; 43)	**<0.001**	38 (33; 46)	0.1108	38 (29; 44)	0.3519

Serum adipokines, disease activity, inflammatory and anthropometric parameters in healthy controls (HC) and in patients under infliximab therapy: values at baseline (week 0, w0), at second infliximab infusion (week 2, w2), and at fourth infliximab infusion (week 14, w14). Adipokines, disease activity, and inflammatory parameters expressed as median (range), differences were analyzed with Wilcoxon matched-pairs signed rank test. Anthropometric parameters expressed as mean (standard deviation), differences were analyzed with paired *t*-test. BMI = body mass index, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, N = number of patients, wPCDAI = mathematically weighted Pediatric Crohn's Disease Activity Index.

Bold values were used for significant effects.

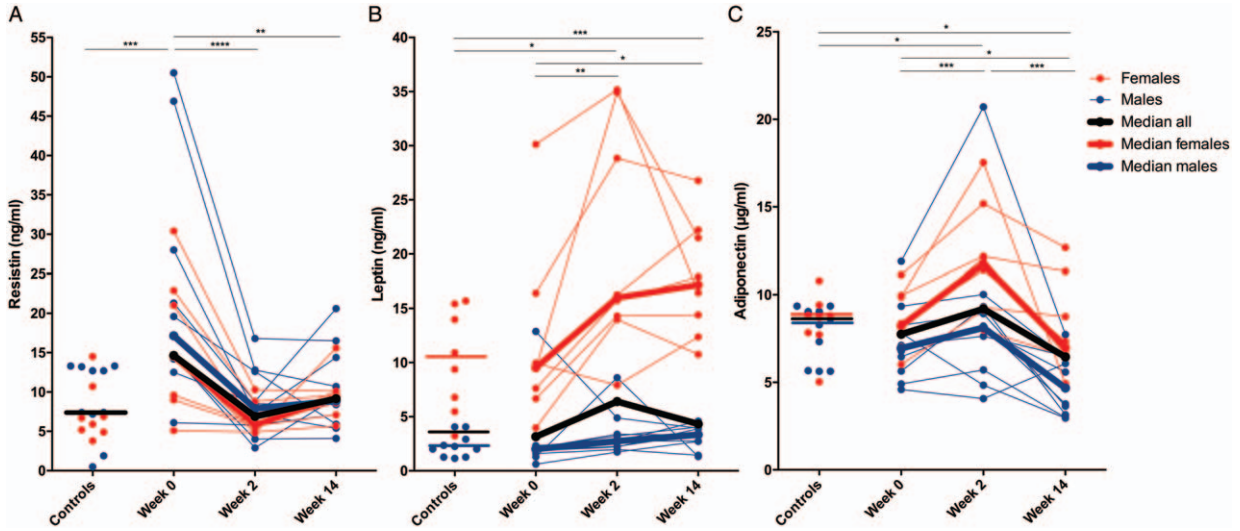

FIGURE 1. Serum adipokine levels according to sex in healthy controls and in CD patients at baseline (week 0) and under infliximab therapy (weeks 2 and 14) displaying each patient individually and the median lines (n = 18). (A) Resistin levels were higher in CD at baseline, decreased under therapy and showed no sex differences. (B) Leptin was significantly higher in girls at all time points and increased under IFX. (C) Adiponectin tended to be higher in girls, peaked 2 weeks after first IFX infusion and thereafter decreased. Differences were analyzed with Wilcoxon matched-pairs signed rank test. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$. CD = Crohn disease, HC = healthy controls, IFX = infliximab.

adipocytes in humans. TNF and lipopolysaccharide stimulate resistin release in human PBMCs, whereas resistin upregulates TNF, IL-6 and IL-1β mRNA expression, and protein release (18). Increased resistin expression in the mesenteric adipose tissue in CD indicates unspecific inflammation (8). A decrease in resistin was suggested as a biomarker of successful IFX treatment in adults (34). In agreement with previous studies (22,34), we found high resistin serum levels in active CD compared with control children and observed a decrease under IFX induction therapy. In our cohort, resistin levels correlated with the inflammatory parameter CRP as previously reported in patients with rheumatoid arthritis (35).

Leptin reflects body fat mass and has several metabolic functions. In patients with acute inflammation, like sepsis, leptin concentrations are increased (36). On the other hand, under conditions of chronic inflammation and in in vitro models of human adipose tissue, leptin release is inhibited by TNF (15). As serum levels of leptin are affected by sex and body composition, we selected sex- and BMI-matched HC. At baseline, we found similar leptin levels compared with BMI-matched HC, which is consistent with previous observations (19,22,24). Whenever children with IBD, however, were compared with age and sex, but not BMI-matched controls, leptin levels were lower, reflecting reduced total body fat (20). In line with others (19) we found leptin levels significantly higher in girls. In agreement with previous studies, leptin levels increased in the first weeks after starting IFX therapy (34,37). Franchimont et al (37) suggested that the chronic inhibitory effect of TNF on leptin release is blocked by IFX and resulted in increased leptin levels in a fat mass-independent manner. Serum TNF levels, however, were not measured in this study. Contrary to their results, in our cohort, IFX therapy led to a significant improvement in BMI. Increased appetite and weight gain following TNF blockade might be an additional mechanism explaining elevation of leptin levels under IFX induction therapy.

In vitro studies with human adipocytes and adipocyte cell lines demonstrated that TNF inhibits adiponectin secretion (15,38,39). Results on adiponectin in IBD patients are controversial with one study reporting slightly elevated (21), others decreased serum adiponectin levels (22,23,40). In our CD patients, adiponectin at baseline was similar to sex- and BMI-matched children. The marked increase of the adiponectin levels in our cohort after the first IFX infusion was surprising. This early hyperadiponectinemia could reflect adiponectin release through TNF blockade considering that the IFX drug levels are almost 10 times higher before second infusion after 2 weeks compared with the trough levels before the fourth infusion at week 14 (41). These higher IFX concentrations at week 2 compared with week 14 may explain that the changes in resistin and adiponectin concentrations from week 2 to baseline are stronger compared with the changes from week 14 to baseline. Our findings are supported by a similar hyperadiponectinemia reported in patients with rheumatoid arthritis during the induction phase of anti-TNF therapy (42). Adiponectin significantly decreased in our cohort at week 14. Similarly, Karmiris et al (34) reported a trend to lower adiponectin levels in adult IBD patients (17 with CD and 3 with ulcerative colitis) 4 months after starting IFX. No earlier measurements were performed in their patients.

We report an interesting observation in patients receiving IFX therapy. Due to the lack of, however, a comparator group we cannot answer whether this is an IFX-specific effect or an effect associated with successful induction treatment in pediatric CD in general. Limitations of our study include the number of patients with a spectrum of disease activity, disease behaviour, and treatment response, which precludes subgroup analysis. The retrospective character did only allow assessment of improved body composition according to changes in anthropometric parameters but not of objective data on changes in abdominal adipose tissue volumes measurable by MRI. A further limitation is the measurement of steady state, circulating leptin, resistin, and total adiponectin levels. The analysis of different serum adiponectin isoforms and adipokine expression in the intra-abdominal adipose tissue might have provided additional information.

In conclusion, anti-TNF therapy is associated with early changes in adipokine levels in pediatric CD. Although serum resistin decreased and leptin increased, serum adiponectin peaked after first IFX infusion. We speculate that the early hyperadiponectinemia induced by IFX may contribute to the successful and rapid anti-inflammatory response. Further investigations on larger cohorts are needed to evaluate the role of early serum adiponectin

measurements as a biomarker for short- and long-term response to IFX.

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