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13-*cis*-Retinoic acid therapy induces insulin resistance, regulates inflammatory parameters, and paradoxically increases serum adiponectin concentration

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Abstract

13-*cis*-Retinoic acid treatment causes insulin resistance and disturbances in lipid and glucose metabolism. We studied how 13-*cis*-retinoic acid affects inflammatory factors and adiponectin. A total of 23 healthy patients (age, 24.9 ± 0.9 years; body mass index, 22.6 ± 0.7 kg/m^2) who received 13-*cis*-retinoic acid treatment of acne participated in the study. The patients were studied before the treatment, after 3 months of therapy, and 1 month after the treatment. Inflammatory parameters were measured, and a 4-hour oral glucose tolerance test was performed at each visit. Treatment with 13-*cis*-retinoic acid resulted in a significantly elevated serum adiponectin concentration (from 24.9 ± 2.5 to 29.4 ± 3.6 mg/L, $P < .05$), hemoglobin A_{1c} (from 5.27% ± 0.05% to 5.42% ± 0.06%, $P < .01$), C-peptide area under the curve (from 314.2 ± 16.6 to 350.0 ± 21.0 (nmol · min)/L, $P < .05$), and triglycerides (from 0.97 ± 0.06 to 1.29 ± 0.10 mmol/L, $P < .05$), whereas high-density lipoprotein cholesterol decreased (from 1.50 ± 0.07 to 1.38 ± 0.08 mmol/L, $P < .05$). The increase in adiponectin during 13-*cis*-retinoic acid therapy correlated with baseline triglycerides ($r = 0.51$, $P < .02$). Many inflammatory markers, which were nonsignificantly elevated during therapy, decreased significantly after cessation of treatment. These were C-reactive protein (median from 1.78 to 1.23 mg/L, $P < .05$), soluble intercellular adhesion molecule 1 (from 210 ± 10 to 204 ± 10 μg/L, $P < .02$), ceruloplasmin (256 ± 17 to 231 ± 17 μg/L, $P < .02$), and erythrocyte sedimentation rate (from 6.4 ± 1.3 to 4.7 ± 0.9 mm/h, $P < .02$). Interleukin 6 concentration was unaffected by the therapy, but decreased significantly after the treatment (from 2.18 ± 0.46 to 1.65 ± 0.43 ng/L, $P < .05$). In conclusion, although treatment with 13-*cis*-retinoic acid results in disturbances in glucose and lipid metabolism, paradoxically serum adiponectin concentration increases. 13-*cis*-Retinoic acid has profound effects on the regulation of inflammatory markers.

1. Introduction

Insulin resistance is a common disorder. It is most often found in the elderly population, and it is strongly associated with type 2 diabetes mellitus and cardiovascular disease. Atherosclerosis is clearly an inflammatory disease and does not result simply from the accumulation of lipids [1]. High baseline C-reactive protein (CRP) in healthy men is a risk factor for myocardial infarction and stroke [2]. Insulin resistance precedes type 2 diabetes mellitus [3]. Also, inflammation precedes type 2 diabetes mellitus. In patients with carotid atherosclerosis, high α-1-acid glycoprotein (A1GP) and sialic acid were associated with an increased risk for type 2 diabetes mellitus 4.9 years later [4]. High γ-globulin [5], CRP [6], and interleukin 6 (IL-6) [6] are risk factors for the development of type 2 diabetes mellitus. Already in healthy young normal-weight subjects, insulin sensitivity is inversely related to inflammatory factors, as we have previously shown for the cytokine IL-6 [7]. Lipid disturbances play a central role in the insulin resistance syndrome. Lipid levels were, in our study, associated with several acute-phase proteins [7].

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Hence, insulin resistance, inflammation, and lipid metabolism are closely interrelated. The production of acute-phase proteins is regulated by inflammatory cytokines [8]. Each acute-phase protein has its own pattern of stimulation. Therefore, a combination of different acute-phase proteins gives a better perception of the profile of the underlying inflammation than any acute-phase protein alone.

Adiponectin is a recently found anti-inflammatory plasma protein with many associations to glucose and lipid metabolism. Also known as ACRP30, AdipoQ, or apM1, it is produced exclusively in adipose tissue [9]. Adiponectin inhibits tumor necrosis factor α–induced inflammation [10]. Adiponectin is found at a high concentration in human plasma. Paradoxically, its concentrations are significantly lower in obese than in nonobese subjects [11]. Plasma adiponectin was significantly lower in patients with coronary artery disease (CAD) than in age- and body mass index (BMI)–adjusted control subjects [10]. Plasma levels of adiponectin in diabetic subjects without CAD were lower than in nondiabetic subjects and lowest in patients with diabetes and CAD [12].

Recent data suggest that retinoid metabolism, especially serum retinoid binding protein 4, is associated with insulin resistance [13]. Severe acne is treated with the inhibitor of sebum production, 13-*cis*-retinoic acid [14]. It increases serum levels of total cholesterol, triglycerides, and reduces high-density lipoprotein cholesterol (HDL-C) [15,16] and causes insulin resistance [16]. However, it is generally considered anti-inflammatory. It has effects through the retinoic acid receptor [17]. Therefore, we wanted to study the effects of 13-*cis*-retinoic acid on the relationship of glucose and lipid metabolism to inflammatory parameters.

2. Patients and methods

A total of 23 (11 females, 12 males; age, 24.9 ± 0.9 years, BMI, 22.6 ± 0.7 kg/m^2) patients with acne participated in this study. The study consisted of patients attending the dermatologic policlinics of the Helsinki University Central Hospital (Helsinki, Finland) and chosen by the clinician to receive 13-*cis*-retinoic acid for treatment of their acne. The patients were otherwise healthy. Five of the female patients were using contraceptive pills, 1 progesterone intrauterine device, and 1 progesterone subcutaneous capsules. The study was approved by the ethics committee of the Helsinki University Hospital. Each patient gave his or her written informed consent, and the study was conducted according to the rules of good clinical practice.

The patients were examined 3 times during the study. The first visit was before the start of 13-*cis*-retinoic acid treatment (Roaccutane, F Hoffmann-La Roche, Basel, Switzerland) and the second visit was when the patient had been on treatment for at least 3 months. The third visit was 1 month after the end of the therapy. At all visits, special attention was focused on anamnestic and clinical signs of recent inflammation. If the patient had inflammation the visit was postponed until 10 days after the end of the inflammation. Oral glucose tolerance test was done at each visit with 75 g glucose after an overnight fast. Blood samples were taken at 30- to 60-minute intervals for 4 hours. All blood samples were taken at the research laboratory of the Helsinki University Hospital. For clinical evaluation the patients were seen before treatment, after 1 month of treatment, and then every second month.

2.1. Methods

Hemoglobin A_{1c} (reference range, 4.0%-6.0%) was determined with a DCA 2000 analyzer (Bayer Diagnostics, Dublin, Ireland). Serum free insulin was measured by a double-antibody radioimmunoassay (Pharmacia, Uppsala, Sweden). Plasma glucose was determined with a glucose oxidase method using the Beckman glucose analyzer (Beckman Instruments, Fullerton, CA). Serum cortisol (reference range, 150-650 nmol/L) was measured by an enzyme immunoassay (Tecnicon Immuno 1 System, Bayer, Tarrytown, NY). Serum growth hormone (reference range, 0-11 mU/L) was determined with a fluoroimmunoassay (AutoDELFIA, Wallac Oy, Turku, Finland). Serum haptoglobin (reference range, 0.29-2.00 g/L), A1GP (reference range, 500-1200 mg/L), α-1-antitrypsin (reference range, 0.98-1.78 g/L), ceruloplasmin (reference range, 200-550 mg/L), and complement C3 protein (C3) (reference range, 0.7-1.6 g/L) concentrations were determined with automated immunoturbidimetric methods (Hitachi 911).

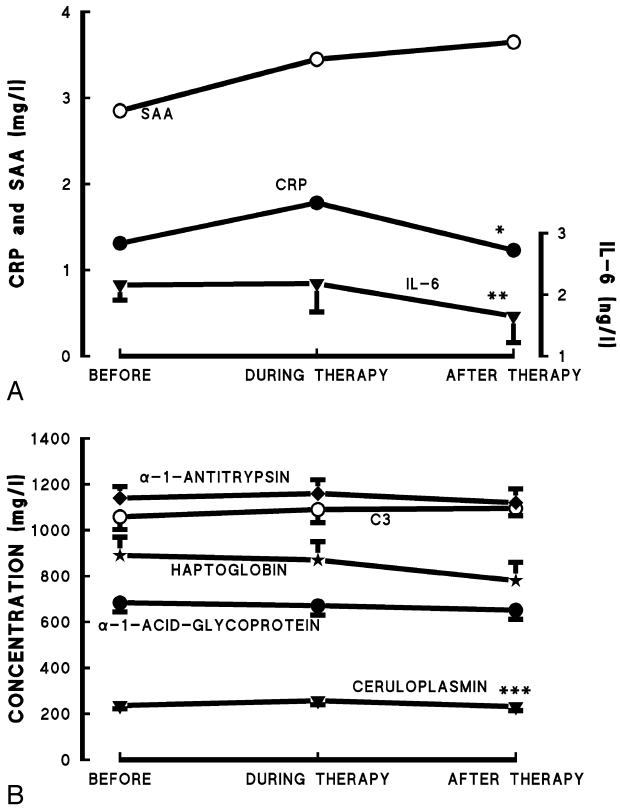

Fig. 1. The effects of 13-*cis*-retinoic acid treatment. Panel A, The changes in the serum concentrations of SAA (median), CRP (median), and IL-6. Panel B, The variations in the serum concentrations of α-1-antitrypsin, C3, haptoglobin, A1GP, and ceruloplasmin. *$P < .05$ vs during therapy; ** $P < .05$ vs baseline and during therapy; ***$P < .02$ vs during therapy.

Table 1
The concentrations of metabolic parameters and inflammatory factors before, during, and after treatment with 13-*cis*-retinoic acid

	Baseline	Treatment	After treatment
BMI (kg/m^2)	22.51 ± 0,69	22.58 ± 0.72	22.95 ± 0.82
Glucose (mg/dL)	85.70 ± 1.62	86.17 ± 1.44	81.67 ± 1.76[d,e]
Glucose AUC ([mg · min]/dL)	22169.3 ± 635.8	22818.3 ± 618.6	22542.8 ± 715.2
C-peptide (nmol/L)	0.503 ± 0.032	0.540 ± 0.043	0.618 ± 0.080
Insulin (mU/L)	6.48 ± 0.48	6.44 ± 0.74	5.91 ± 0.65
Insulin AUC ([mU · min]/L)	5445.7 ± 362.8	5906.1 ± 470.8	6307.5 ± 580.4
HbA_{1c} (%)	5.27 ± 0.05	5.42 ± 0.06[b]	5.26 ± 0.07[d]
FFA (μmol/L)	0.61 ± 0,04	0.58 ± 0.04	0.62 ± 0.07
Cholesterol (mmol/L)	4.20 ± 0.13	4.60 ± 0.14[b]	4.45 ± 0.13
HDL-C (mmol/L)	1.50 ± 0.07	1.38 ± 0.08[a]	1.59 ± 0.09[d]
LDL-C (mmol/L)	2.27 ± 0.12	2.62 ± 0.16[b]	2.44 ± 0.15[d]
Triglycerides (mmol/L)	0.97 ± 0.06	1.29 ± 0.10[a]	1.04 ± 0.08[c]
Triglyceride AUC ([mmol · min]/L)	184.9 ± 12.2	257.6 ± 20.9[b]	209.9 ± 16.9[d]
Growth hormone (mU/L)[1]	0.90 (0.09-19.60)	0.30 (0.09-40.90)[a]	0.60 (0.09-16.60)
Cortisol (nmol/L)	515.5 ± 46.9	601.4 ± 49.6	552.4 ± 52.9
ALT (U/L)	20.9 ± 2.1	25.7 ± 3.7	20.9 ± 1.5
Sedimentation rate (mm/h)	4.5 ± 0.5	6.4 ± 1.3	4.7 ± 0.9[c]
ASP (μg/L)	129.6 ± 24.8	114.9 ± 13.4	116.6 ± 11.4
sE-selectin (μg/L)	50.5 ± 3.9	49.2 ± 4.5	49.0 ± 4.2
Fibrinogen (g/L)[1]	2.5 (2.1-4.1)	2.6 (1.8-5.2)	2.6 (1.8-4.9)
s-ICAM-1 (μg/L)	202.8 ± 8.9	210.7 ± 10.5	204.0 ± 9.8[c]
s-VCAM-1 (μg/L)	418.5 ± 22.2	426.6 ± 28.4	390.9 ± 29.8
IL-1RA (ng/L)	168.8 ± 14.2	238.0 ± 42.0	174.6 ± 19.1

[a] $P < .05$ and [b] $P < .01$, between baseline and 3 months of treatment. [c] $P < .02$ and [d] $P < .01$, between 3 months of therapy and 1 month after treatment. [e] $P < .05$, between baseline and 1 month after the therapy. HbA_{1c} indicates hemoglobin $_{1c}$; FFA, free fatty acids; s-VCAM-1, soluble vascular cell adhesion molecule 1; IL-1RA, IL-1 receptor antagonist.

[1] Nonparametric distribution; median and range are given.

Serum amyloid A (SAA) protein was measured by an immunoassay (Cytoscreen, Biosource International, Camarillo, CA) and CRP by an radioimmunoassay as described [18]. The detection limit for SAA is 0.005 mg/L and for CRP is 0.01 mg/L. Plasma acylation-stimulating protein (reference range, 26-146 μg/L) was measured by an enzyme immunoassay (QUINDEL C3a, Quindel, San Diego, CA). Intercellular cell adhesion molecule 1 (ICAM-1) (reference range, 115-306 μg/L), vascular cell adhesion molecule 1 (reference range, 395-714 μg/L), and E-selectin (reference range, 29.1-63.4 μg/L) were measured using a solid-phase enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN). Free fatty acids were determined with an enzymatic colorimetric method (NEFA C, Wako Chemicals, Neuss, Germany). Interleukin 1 receptor antagonist (reference range, 48-1168 ng/L) and IL-6 (reference range, not determined to 11.5 ng/mL) were measured using a solid-phase enzyme-linked immunosorbent assay (R&D Systems). Serum adiponectin was determined with a radioimmunoassay (Linco Research, St Charles, MO). Blood pressure was measured using Omron M4 (Omron Healthcare, Hamburg, Germany) after the patients rested for least 5 minutes in lying position.

2.2. Statistical analysis

The statistical differences between baseline, during, and after the 13-*cis*-retinoic acid therapy were calculated using Wilcoxon signed rank test .The correlation analysis was done using Spearman test. A P value of less than .05 was considered statistically significant. The results are given as mean ± SEM, except those for CRP, SAA, fibrinogen, and growth hormone where medians are reported.

3. Results

Before therapy the patients had a mean age of 24.9 ± 0.9 years, mean BMI of 22.6 ± 0.7 kg/m^2, and a normal systolic (121.1 ± 2.7 mm Hg) and diastolic (72.5 ± 1.7 mm Hg) blood pressure. Serum baseline adiponectin correlated with baseline cholesterol ($r = 0.61$, $P < .001$), HDL-C ($r = 0.45$, $P < .05$), and s-ICAM-1 ($r = 0.69$, $P < .001$). Basal adiponectin was inversely associated with CRP ($r = -0.52$, $P < .02$).

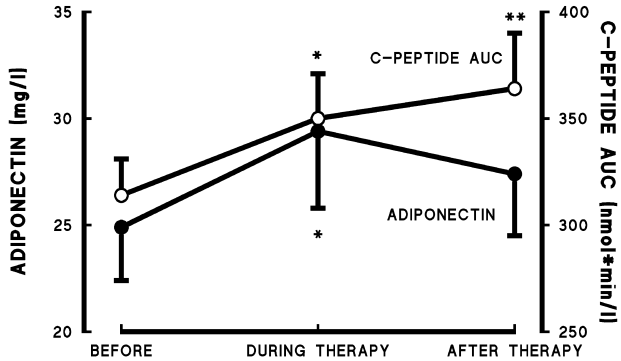

Fig. 2. Serum adiponectin concentration and the AUC for C-peptide during oral glucose tolerance test before 13-*cis*-retinoic acid treatment, during the treatment, and after the treatment. *$P = .02$ and **$P < .01$ vs baseline.

The changes in SAA, CRP, IL-6, α-1-antitrypsin, C3, haptoglobin, A1GP, and ceruloplasmin are given in Fig. 1. The concentrations of metabolic parameters and the remaining inflammatory factors at the 3 study visits are shown in Table 1. The changes in adiponectin and C-peptide area under the curve (AUC) are shown in Fig. 2. The change in adiponectin between visits 1 and 2 correlated with baseline triglycerides ($r = 0.51$, $P < .02$) and triglyceride AUC ($r = 0.43$, $P < .05$), whereas there was an inverse correlation to baseline acylation-stimulating protein ($r = -0.44$, $P < .05$). The change in adiponectin between visits 1 and 2 correlated also with the change in triglycerides ($r = 0.45$, $P < .05$) and triglyceride AUC ($r = 0.42$, $P < .05$) between visits 1 and 2.

The complement C3 protein correlated with A1GP ($r \geq 0.52$ for all, $P < .05$ for all) and CRP ($r \geq 0.49$ for all, $P < .02$) at all 3 visits regardless of treatment. C-reactive protein correlated also with SAA ($r \geq 0.57$ for all, $P < .01$ for all). Also, α-1-antitrypsin correlated with cortisol ($r \geq 0.55$ for all, $P < .02$ for all) and fibrinogen with erythrocyte sedimentation rate (ESR, $r \geq 0.42$ for all, $P < .05$ for all). Glucose correlated with soluble E selectin (sE-selectin) ($r \geq 0.44$ for all, $P < .05$ for all) and insulin ($r \geq 0.42$ for all, $P < .05$ for all).

Erythrocyte sedimentation rate correlated with alanine aminotransferase (ALT) at visit 1 ($r = 0.43$, $P < .05$) and visit 3 ($r = 0.50$, $P < .05$); the correlation disappeared at visit 2. The same phenomenon was seen in the correlation of growth hormone with low-density lipoprotein cholesterol (LDL-C) (visit 1: $r = -0.52$, $P < .05$; visit 2: not significant [NS]; visit 3: $r = -0.57$, $P < .01$). Likewise, C3 correlated with triglycerides (visit 1: $r = 0.45$, $P < .01$; visit 2: NS; visit 3: $r = 0.51$, $P < .05$) and triglyceride AUC (visit 1: $r = 0.50$, $P < .02$; visit 2: NS; visit 3: $r = 0.51$, $P < .05$). Haptoglobin correlated with IL-6 (visit 1: $r = 0.42$, $P < .05$; visit 2: NS; visit 3: $r = 0.60$, $P < .01$).

4. Discussion

As expected, the 13-*cis*-retinoic acid therapy induced disturbances in glucose and lipid metabolism. The treatment was also associated with many profound hitherto unknown effects. Firstly, it led to a reversible increase in serum adiponectin concentration (Fig. 2), although the lipid parameters and glucose tolerance test indicated simultaneous unfavorable effects. Secondly, the treatment affected the concentrations of various acute-phase reactants in different ways (Fig. 1). Some were unaffected, whereas others experienced changes, especially after cessation of the treatment. Thirdly, the treatment had varying effect on the interrelationship between different inflammatory parameters.

The increase in serum adiponectin concentration during the 13-*cis*-retinoic acid treatment seems to be in discordance with the generally accepted association of high adiponectin with insulin sensitivity. This treatment causes insulin resistance as we have previously shown [16] and also increases serum levels of total cholesterol and triglycerides, and reduces HDL-C [15,16]. These effects are seen in the current study, too. Despite these changes, serum adiponectin concentration increased. This corroborates our recent finding [19]. However, in that study we did not investigate the inflammatory factors. The regulation of adiponectin is complicated. Although produced exclusively in adipose tissue [9], plasma adiponectin concentration is reduced in obesity [11]. Plasma adiponectin concentration is also significantly lower in patients with CAD than in age- and BMI-adjusted control subjects [10]. Plasma levels of adiponectin in diabetic subjects without CAD are lower than in nondiabetic subjects and lowest in patients with diabetes and CAD [12]. Serum adiponectin concentration is increased by thiazolidinediones, such as pioglitazone [20]. Also, moderate alcohol consumption results in increased circulating adiponectin concentration [21]. Although acromegaly is an insulin-resistant state, adiponectin levels are elevated in acromegalic subjects [22]. In mice, adiponectin per se reverses insulin resistance associated with both lipoatrophy and obesity [23]. In humans, serum adiponectin concentration predicts subsequent changes in insulin resistance [24]. One possible explanation for this phenomenon may be the fact that adiponectin is anti-inflammatory as demonstrated by the inhibition of endothelial nuclear factor κB signaling [25]. The reason for increased adiponectin serum concentration during 13-*cis*-retinoic acid treatment may be the inherent anti-inflammatory effect of retinoids [26]. Thus, 13-*cis* retinoic acid, by binding solely to retinoic acid receptor and not to retinoid X receptor (RXR) [27], gives us an opportunity to study insulin sensitivity, lipid disturbances, and inflammation in a reversible situation, when they are not concertedly regulated. When considering factors associated with the magnitude of adiponectin increase during 13-*cis*-retinoic acid therapy, triglycerides attain a central role. The higher the baseline triglyceride concentration, the greater the increase in adiponectin concentration during treatment. This finding is further corroborated by the correlation between the increments in adiponectin and triglycerides during the 13-*cis*-retinoic acid therapy. The mechanisms of this interrelationship are not clear. However, adipose tissue is a common nominator for the regulation of adiponectin and triglycerides. Likewise, lipid metabolism is the main target of therapy in the retinoid treatment of acne.

The varying effect of 13-*cis*-retinoic acid on inflammatory factors (Fig. 1) is in good agreement with the known individual regulation of each of these parameters. They are generally elevated by the network of inflammatory signals during an inflammation, but the magnitude of elevation depends on the profile of inflammatory cytokines. This study describes a more restricted way to affect inflammatory parameters, through the retinoic acid receptor. Many inflammatory parameters were nonsignificantly increased from baseline during the treatment, but were significantly reduced from treatment values after cessation of therapy. These included CRP, s-ICAM-1, ceruloplasmin, and ESR. Others,

comprising interleukin 1 receptor antagonist, cortisol, and ALT, were nonsignificantly higher during the treatment than at baseline and after treatment. These variations could indicate that 13-*cis*-retinoic acid gives a common inflammatory stimulus for all these acute-phase proteins. However, on the contrary, many acute-phase proteins were not at all affected by 13-*cis*-retinoic acid. These were A1GP, α-1-antitrypsin, C3, SAA, sE-selectin, fibrinogen, and haptoglobin. These apparently conflicting results could indicate either that the unaffected acute-phase proteins were not sensitive enough to perceive the inflammatory stimulus or that the given stimulus is not inflammatory but somehow raises the concentration of some acute-phase proteins without affecting inflammation. Of these acute-phase proteins, SAA is probably the most sensitive. It is a more sensitive indicator of inflammation than CRP [28], the other major acute-phase protein [29]. Most circulating acute-phase proteins are produced mainly in the liver and IL-6 is their most important inducer [8]. The concentration of IL-6 remained unchanged during the 13-*cis*-retinoic acid treatment. This indicates that the retinoid did not have a proinflammatory effect but more likely intensified the production of acute-phase proteins in the liver despite unchanged inflammatory state as demonstrated by unchanged IL-6. After the treatment, IL-6 was reduced to a significantly lower level. This diverging regulation of CRP and its main inducer IL-6 [8] has been demonstrated also in other situations. Statins reduce serum CRP concentration without affecting the serum concentrations of IL-6 or its soluble receptor sIL-6R [30]. Statins are anti-inflammatory. Estrogens on the contrary increase serum CRP concentration [31] and reduce the level of IL-6 [32]. Also, sE-selectin is reduced by estrogens [31].

Many acute-phase proteins correlated with each other at all time points during the study. This indicates a strong common background for their regulation. The complement C3 protein had associations to A1GP and CRP. C-reactive protein also had a correlation to SAA. Fibrinogen had association to ESR and α-1-antitrypsin to cortisol. 13-*cis*-Retinoic acid temporarily disrupted the interrelationship between several inflammatory parameters such as the association of ESR to ALT, GH to LDL-C, C3 to triglycerides, and haptoglobin to IL-6. This suggests that they have common regulatory factors, but 13-*cis*-retinoic acid changes this regulation. No inflammatory factors were correlated with each other solely during the treatment.

Taken together, despite disturbances in lipid and glucose metabolism, 13-*cis*-retinoic acid increases serum adiponectin concentration. It has also profound selective effects on inflammatory parameters. The results of our study shed light to the complicated regulation of inflammatory parameters and lipid metabolism.

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