

Effects of isotretinoin on body mass index, serum adiponectin, leptin, and ghrelin levels in acne vulgaris patients

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Abstract

Introduction: Isotretinoin has been successfully used for the treatment of acne vulgaris.

Aim: To investigate the effects of isotretinoin on body mass index (BMI), to determine whether isotretinoin causes any changes in serum adiponectin, leptin, and ghrelin levels in acne vulgaris patients, and to correlate variables.

Material and methods: Thirty-two patients were included in this study. Oral isotretinoin was begun at a dose of 0.5–0.6 mg/kg and raised to 0.6–0.75 mg/kg. Pretreatment and posttreatment third-month BMI and adiponectin, leptin, and ghrelin serum levels were measured.

Results: The pre- and posttreatment BMI values were not significantly different. In addition, serum adiponectin and leptin levels were significantly increased following isotretinoin therapy while serum ghrelin levels were not different.

Conclusions: Isotretinoin may exert its anti-inflammatory activity by increasing leptin and adiponectin levels.

Key words: acne vulgaris, adipocytokines, body mass index, ghrelin, isotretinoin.

Introduction

Acne is a chronic inflammatory disorder of the pilosebaceous units in the skin. Although it commonly affects the majority of the adolescent population [1], it is also prevalent in adults [2]. The pathogenesis of acne is multifactorial and includes hormonal, inflammatory, and immunologic mechanisms [3, 4]. There are four processes that play a pivotal role in the formation of acne lesions as follows: inflammatory mediators released into the skin, alteration of the keratinization process leading to comedones, increased and altered sebum production under androgen control (or increased androgen receptor sensitivity), and follicular colonization by *Propionibacterium acnes*. The sequence of and the interactions between these events remain unclear [5]. Harrison *et al.* reported that the pathways of differentiation in sebaceous glands and adipocytes may be similar; therefore, further understanding of sebaceous gland differentiation and lipogenesis as well as potential therapies for sebaceous gland

disorders may be gleaned from what is known about adipocyte differentiation [6]. The expression of galectin-12, resistin, sterol response element binding protein-1, and stearoyl-CoA desaturase (SCD), all of which are involved in adipocyte differentiation, has also been reported in sebaceous glands. The fact that these adipogenic factors have also been detected in human sebaceous glands suggests that they may play a similar role in sebocyte differentiation as in adipocyte differentiation [6]. Because adipokines affect sebocytes, adipokines may also play a role in the pathogenesis of acne vulgaris.

Isotretinoin (13-*cis* retinoic acid) is widely used to treat severe cystic or recalcitrant acne. Isotretinoin is the most potent pharmacological inhibitor of sebum secretion; it causes a reduction in the size of sebaceous glands, it causes sebocytes to appear undifferentiated, and it leads to a decrease in lipid accumulation. However, the exact mechanisms behind the effects of isotretinoin are not yet known [7].

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Adipose tissue is a major site for storage of vitamin A derivatives (collectively named retinoids); therefore, it plays an active role in their homeostasis and metabolism [8]. Moreover, adipose tissue is a known target organ for retinoic acid as retinoid and retinoid X receptors are expressed in adipose tissue [9]. In addition, white adipose tissue acts as an endocrine organ and produces a variety of hormones (adipocytokines), including leptin, adiponectin, tumor necrosis factor α (TNF- α) and angiotensin II (Ang II), all of which influence lipid metabolism, systemic insulin sensitivity and inflammation [10]. *In vitro* and *in vivo* studies have shown that retinoids affect adipocyte-derived leptin levels, and that this effect is primary (i.e. not a consequence of the reduction in adipose tissue mass) [8].

To our knowledge, few studies have focused on changes in body mass index (BMI) in humans treated with isotretinoin [11–15], and only one reported associations between adipocytokines and isotretinoin treatment [13]. In addition, investigation of correlations between global acne grading system (GAGS) and adipocytokines, and pre-post treatment levels of adipocytokines has not been evaluated previously. Therefore, this study aimed to determine the effects of isotretinoin therapy on BMI, leptin, adiponectin, and ghrelin levels in patients with acne vulgaris.

Aim

The aim of this study was to investigate the effects of isotretinoin on BMI, to determine whether isotretinoin causes any changes in serum adiponectin, leptin, and ghrelin levels in acne vulgaris patients, and to correlate variables.

Material and methods

This study consisted of patients who were admitted to the dermatology outpatient clinic between December 2013 and May 2014. A total of 32 patients (out of 48) suffering from acne vulgaris met the inclusion criteria in this study (12/20 females/males; mean age: 18.9 \pm 2.57 years). Sixteen patients were excluded from the study because they did not complete a minimum treatment period of three months or because they did not undergo the required tests needed to monitor their treatment. The study group was selected from a group of male and non-pregnant female patients who did not want to become pregnant and who had moderate to severe nodulocystic acne. The GAGS was used to evaluate acne severity. Briefly, each of six locations (forehead, right cheek, left cheek, nose, chin, chest and upper back) was given a score between 0 and 4 and was assigned a factor on the basis of size. A score of 19–30 indicates moderate acne while a score of 31–38 indicates severe acne [16]. Patients were excluded from the study if they met any of the following criteria: previously diagnosed diabetes mellitus, hyperthyroidism, pituitary disease, hypogonadism,

polycystic ovary syndrome, chronic liver disease, chronic renal disease, and other inflammatory or infectious disease, or a recent history of psychiatric, mood or depressive disorders. The protocol for this study was approved by the Diskapi Yildirim Beyazit Educational and Research Hospital ethics committee, and informed consent was obtained from all of the patients or their parents.

At recruitment and after 3 months of isotretinoin treatment, the weight and height of all subjects were recorded, and the BMI was calculated (weight (kg) divided by height (m) squared). Isotretinoin therapy was initiated at a dose of 0.5–0.6 mg/kg/day body weight, and after 1 month, the dose was adjusted to 0.6–0.75 mg/kg/day as a maintenance dosage. Biochemical parameters (total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), leptin, adiponectin, and ghrelin) were screened immediately prior to initiation (pretreatment) and after 3 months of isotretinoin treatment (posttreatment). Blood samples were obtained after 12 h of fasting. Blood samples were centrifuged at 2500 \times g for 15 min at 4°C within 30 min of collection, and serum samples were stored at –70°C until further analysis. Measurements of total cholesterol (reference range: 0–200 mg/dl), HDL-C (reference range: 40–60 mg/dl), LDL cholesterol (reference range: 0–100 mg/dl) and triglycerides (reference range: 0–250 mg/dl) were performed using a Siemens Advia 2400 with commercially available kits (Siemens Healthcare Diagnostics Inc., Tarrytown, USA). Measurements of ghrelin (Phoenix Pharmaceuticals, California, USA), leptin (DRG Diagnostic International, Inc., USA) and adiponectin (eBioscience Inc. USA) were performed using an EPOCH system (BioTek Instruments, Inc, USA) with commercially available enzyme-linked immunosorbent assay (ELISA) kits. Ghrelin and leptin levels were expressed as nanograms/milliliter (ng/ml) and adiponectin levels were expressed as micrograms/liter (μ g/l). All of the samples were evaluated for the above biochemical parameters at the same time.

Statistical analysis

SPSS (Statistical Package for the Social Sciences version 16.0) software was used to analyze the data. Descriptive statistics for variables were expressed as means \pm standard deviations. The Wilcoxon signed rank test was used to compare pretreatment and posttreatment data. To compare male and female patients' data, Mann-Whitney *U* test was used. Pearson correlation was used to analyze the correlation between the variables. Values of $p < 0.05$ were considered statistically significant for all analyses.

Results

Thirty two patients (62.5% – males and 37.5% – females) were included in this study, and their mean age was 18.0 \pm 2.57 years (range: 16–25 years). The main clini-

Table 1. Main clinical characteristics

Parameter	Result
Age, mean \pm SD [years]	18.9 \pm 2.57
Gender (male/female)	20/12
BMI, mean \pm SD [kg/m ²]	21.86 \pm 3.56
Acne duration, mean \pm SD [years]	4.03 \pm 2.36
Positive family history (%)	84.4
Acne severity score (%):	
Moderate (19–30)	71.9
Severe (31–38)	28.1

cal characteristics of the patients are presented in Table 1. Following isotretinoin treatment, BMI was increased in 15 patients, decreased in 14 patients, and unchanged in 2 patients ($p > 0.05$). Blood lipid and hormonal parameters before and after isotretinoin treatment are summarized in Table 2. Serum levels of total cholesterol, LDL-C, and triglycerides ($p < 0.05$) were significantly increased following isotretinoin treatment, while HDL-C levels did not differ ($p > 0.05$). Adiponectin and leptin levels were significantly increased following isotretinoin treatment ($p < 0.05$). There were no significant changes in the levels of ghrelin after isotretinoin treatment. When adiponectin, leptin, and ghrelin levels are evaluated separately in men and women before and after isotretinoin treatment, a significant difference was shown for leptin values between male and female patients ($p < 0.05$). Higher leptin levels were found in women patients than male patients. Both adiponectin and ghrelin values did not reveal any significant difference between male and female patients ($p > 0.05$). In addition, we found that leptin and adiponectin levels increased significantly in patients who had significantly increased BMI after isotretinoin treatment; however, these patients did not have any significant changes in ghrelin levels. Patients who had a decrease

in BMI after isotretinoin treatment showed a significant increment in adiponectin levels ($p < 0.05$); but there were no changes in leptin and ghrelin levels ($p > 0.05$). The insufficient number of samples for both groups may be the reason of non-significant difference. We did not observe any correlation between GAGS and variables studied.

Discussion

Sebaceous glands are present all over the human body, except on the palms of the hands and soles of the feet. They are usually found in association with hair follicles [17]. The sebaceous gland is a holocrine gland, meaning that the glandular secretion consists of cells from the gland itself. The sebaceous gland contains two kinds of sebocytes: peripheral cells and central cells. The peripheral cells are immature cells that are cuboidal or flattened and do not contain lipids [18]. The central cells are larger than the peripheral cells, and the majority of this size increase is due to the elevated amount of cytoplasmic lipids. Adipocytes are most like sebocytes. Both cell types have a similar physiology, which is the accumulation of lipids. Sebocytes release lipids that eventually make their way to the skin surface, while adipocyte lipids have energy-storing functions. Both adipocytes and sebocytes have similar receptors and express enzymes important for lipid production (e.g., LDL, liver X receptor (LXR), diacylglycerol acyltransferase, and SCD1). Treatment of adipocytes and sebocytes with LXR agonists causes a decrease in lipogenesis [18].

Oral isotretinoin is generally reserved for severe, recalcitrant, nodular acne that is unresponsive to topical therapy. Its mechanism of action and side effect profile is not yet completely understood [19]. Isotretinoin significantly decreases sebum production [20] and growth of *P. acnes* [21]; in addition, it reverses hyperkeratinization and reduces inflammation. Although it is an effective therapy for acne, isotretinoin is associated with significant adverse effects, including cheilitis, dry skin and mucous membranes [22], epistaxis, increased risk of cu-

Table 2. Comparisons of blood lipid and hormonal parameters before and after isotretinoin treatment

Parameter	Pretreatment Mean \pm SD	Posttreatment Mean \pm SD	P-value
Total cholesterol [mg/dl]	143.31 \pm 23.49	165.91 \pm 29.46	< 0.05
Triglycerides [mg/dl]	74.66 \pm 27.70	91.03 \pm 42.04	< 0.05
LDL cholesterol [mg/dl]	79.38 \pm 24.09	93.38 \pm 23.97	< 0.05
HDL cholesterol [mg/dl]	44.94 \pm 9.25	42.63 \pm 6.98	> 0.05
BMI [kg/m ²]	21.86 \pm 3.56	21.85 \pm 3.59	> 0.05
Adiponectin [μ g/l]	93.59 \pm 230.96	409.18 \pm 409.09	< 0.05
Leptin [ng/ml]	5.70 \pm 6.38	7.19 \pm 6.95	< 0.05
Ghrelin [ng/ml]	80.99 \pm 32.26	80.89 \pm 33.99	> 0.05

taneous *Staphylococcus aureus* infections [23], myalgias, and pseudotumor cerebri [24]. Frequently reported blood chemistry abnormalities in isotretinoin users include elevated levels of triglycerides and cholesterol [25], elevated LDL concentrations and decreased HDL concentrations [26]. In our current study, isotretinoin treatment often caused significant elevations in cholesterol, LDL-C, and triglycerides, which are comparable with results seen in the literature. However, we found no differences in HDL-C levels after isotretinoin treatment.

There are very few clinical studies that investigated the effect of retinoic acids on BMI [11–15]. The results of previous clinical studies conflict with those of experimental studies [10, 27]. In animal studies, retinoic acid induced decreases in body weight and fat loss despite unchanged or increased energy intake [27]. In contrast, clinical studies reported that BMI was unchanged [13] or increased [15] following retinoic acid. In the current study, we found no significant difference in pre- and posttreatment BMI values, which is comparable with the results of previous clinical studies.

Adiponectin is an adipocyte-derived hormone that plays a role in insulin function and energy homeostasis [28]. Early studies indicated that adiponectin has an anti-inflammatory effect on endothelial cells by inhibiting the following: nuclear factor κ B activation [29], TNF-induced adhesion-molecule expression, vascular cell adhesion molecule-1, endothelial-leukocyte adhesion molecule-1 (E-selectin), and intracellular adhesion molecule-1 [30]. Adiponectin induces the secretion of some anti-inflammatory cytokines (e.g. interleukin (IL)-10 and IL-1 receptor antagonist) by human monocytes, macrophages and dendritic cells. Adiponectin can also suppress the production of interferon- γ [31], while pro-inflammatory mediators, such as TNF- α and IL-6, inhibit adiponectin gene expression [30, 32]. To our knowledge, there are only 3 published studies relating isotretinoin treatment and adiponectin blood level [11–13]. All of these reports indicate that isotretinoin treatment leads to elevated levels of adiponectin. In the present study, patients had significantly elevated adiponectin levels after isotretinoin treatment, which is comparable with results of the literature. Increased adiponectin levels following isotretinoin treatment may contribute to the anti-inflammatory effects of isotretinoin.

Leptin is a 167 amino acid protein with a molecular weight of 16 kDa; it is mainly produced by the adipocytes that stem from the obese gene. Leptin levels are directly proportional to fat mass [33]. It is involved in the regulation of appetite and energy expenditure via hypothalamic-mediated effects [34]. In addition, it plays a role in carbohydrate and lipid metabolism [35]. Published data indicate that leptin levels are increased following acute infection and in chronic inflammation, which suggests that leptin may actively participate in the immune network and host defense [36]. In innate and adaptive

immune systems, leptin can induce chemotaxis of neutrophils, increase the number of cluster of differentiation CD4+/CD8+ T lymphocytes, facilitate the development of natural killer cells, and promote T helper 1 (Th1) cell differentiation [37]. However, it has been reported that the paracrine/autocrine actions of leptin can be both pro- or anti-inflammatory in the adipose tissue. In addition, it has been found that leptin has a stimulatory effect on the expression of adiponectin, which is an anti-inflammatory cytokine [38]. Further, it has been shown that leptin may suppress the regulation of TNF- α expression in the adipose tissue [38]. Recently, Agak *et al.* reported that Th17 cells may play a role in acne pathogenesis [39]. Moraes-Vieira *et al.* investigated whether leptin mediates its activity on T cells by influencing dendritic cells to promote Th17 and Treg-cell immune responses in mice. They reported that local leptin increases dendritic cells and Th1 cells *in vivo*, but inhibits Th17 cells and Tregs cells [40]. To our knowledge, there is only one published study investigating the effect of isotretinoin treatment on insulin resistance and adipokines in patients with acne vulgaris [13]. Karadag *et al.* reported that basal leptin levels were significantly lower in the group with acne when compared to the control group, while basal adiponectin levels were significantly higher in the acne group. In our current study, we found that leptin was increased after isotretinoin treatment, which is not compatible with the results of Karadag *et al.* Our results indicate that the effects of isotretinoin may be due to the increase in leptin, which may act through the suppression of TNF- α expression, inhibition of Th17 cells and Tregs cells. Finally, all of these changes may generate anti-inflammatory responses. Further studies with greater numbers of patients are needed in order to determine whether changes in leptin levels are related with isotretinoin treatment, and further, whether the efficacy of isotretinoin treatment correlates with leptin levels.

Ghrelin is a recently-discovered orexigenic hormone that is primarily secreted by the stomach and duodenum; it has been implicated in both mealtime hunger and the long-term regulation of body weight [41]. Ghrelin is currently recognized as the main endogenous ligand for growth hormone secretagogue receptors as well as other regulatory factors in growth hormone secretion and energy balance [42]. The levels of circulating ghrelin increase under conditions of starvation and in anorexia nervosa, but decrease under conditions of feeding and in obesity [43]. Ghrelin and leptin may have opposite actions in the regulation of body weight [44, 45]. Recently, it was reported that ghrelin exerts anti-inflammatory and immunoregulatory actions by inhibiting Ang II-induced expression of IL-8, TNF- α and monocyte chemoattractant protein-1 (MCP-1) [46]. Previously, ghrelin blood levels have not been evaluated in patients with acne vulgaris and in patients who were treated with isotretinoin. In the current study, we did not find any statistically significant

difference in ghrelin levels as they relate to isotretinoin treatment. Therefore, our data suggest that isotretinoin has no effect on ghrelin levels.

Conclusions

This study revealed that isotretinoin treatment does not affect BMI. Additionally, adiponectin and leptin serum levels were significantly increased with isotretinoin treatment. Prior to the current study, serum leptin and adiponectin levels in acne patients were investigated in only one study, which reported that leptin levels decreased, while adiponectin levels increased with isotretinoin treatment [13]. In our current study, adiponectin levels were similarly increased after isotretinoin treatment. However, we found that leptin levels were increased with treatment, which is in contrast with previously published data. Further, we found that ghrelin levels were not changed with isotretinoin treatment. Isotretinoin may exert its anti-inflammatory properties by increasing levels of leptin and adiponectin. New studies are required to discover the mechanism of action of those molecules in the pathogenesis of acne and in isotretinoin treatment.

Conflict of interest

The authors declare no conflict of interest.

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