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Original Article

Serum lipid profile in adolescents and adults with acne vulgaris receiving isotretinoin

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Abstract

Background: Acne vulgaris is a chronic, inflammatory disease and one of the most common skin diseases. Isotretinoin is the best treatment for severe nodulocystic acne compared to other systemic medicine. Although serum lipids elevation is one of the side effects of this medicine; recent studies have shown controversial results. This study aimed to assess the serum lipid profile in adolescents and adults with acne vulgaris receiving isotretinoin.

Methods: This is a cross-sectional study on 65 adolescents and adults older than 16 years old (55 females and 10 males) with moderate to severe degrees of acne vulgaris under a fixed low dose of 20 mg/day Isotretinoin treatment for 120 days. We analyzed the data using the SPSS software Version 16 using paired sample t-test, Wilcoxon, and ANCOVA test.

Results: In this study, 65 records of patients with a mean age of 22.21±6.25 years were assessed. There was a significant elevation in Cholesterol and LDL levels, but in HDL and triglyceride levels no significant change occurred. A significant change in cholesterol levels was noticed in the adolescent age group, the female sex, and the normal weight group. Triglyceride had a significant change in the female sex and normal weight group and HDL significantly increased in male patients.

Conclusion: Although a low dose of isotretinoin can be used with minimal concern for changes in lipid profile in acne vulgaris patients, in the long-term follow-up and treatment, it seems that we have to administer it cautiously.

Keywords: Acne vulgaris, Body mass index, Isotretinoin, Lipids.

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Acne vulgaris is a multifactorial chronic inflammatory disease of pilosebaceous units affecting 80% of young people (1). It is the tenth leading cause of disability-adjusted life years (DALYs) in the late adolescent period (15-19 years old) worldwide (2). Its psychological complications include vulnerability to depression, anxiety, embarrassment, social withdrawal, and anger (3). Follicular hyperkeratinization, increased sebum production, propionibacterium acnes colonization, and inflammatory response are the pathogenic mechanisms involved in the development of acne (2). There are several different treatment options available for acne vulgaris. The topical treatments for acne which are used frequently include benzoyl peroxide, antibiotics, and topical retinoids. Clinicians usually administer systemic treatment, such as systemic antibiotics or oral retinoids, as a combination therapy with topical treatments. These systemic treatments are the last choice for severe acne (4, 5). Isotretinoin or 13-cis-retinoic acid affects the four pathogenic mechanisms, involved in the development of acne at the same time. As a result, compared to the other systemic treatment options, it is considered superior. In 95% of patients who complete the treatment period ranging from 16-20 weeks, isotretinoin produces complete or near-complete clearing of acne (6).

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It is a recommended medicine for the treatment of severe inflammatory acne of the nodulocystic or conglobate types. It can also be used for patients with acne vulgaris who are resistant to previous treatments with antibiotics or topical medications (7).

The standard regimen of oral isotretinoin is 0.5–1.0 mg/kg/day for 16–32 weeks which causes some dose-dependent mucocutaneous and systemic adverse effects. It has been shown that lower doses could also be effective in terms of response, adverse effects, and cost. Therefore, they recommended a low-dose regimen, 20 mg daily, as a preferred choice for severe acne in terms of response (8).

Although it is a common method of treating acne, it may cause various side effects such as; cheilitis, dry skin, photosensitivity, photophobia, paronychia, arthralgia, myalgia, headache, etc. It also can cause potentially serious side effects like teratogenicity, pancreatitis, hepatic dysfunction, and depression (9). Besides, it has been reported that it can increase serum levels of liver aminotransferases and cause changes in lipid profile (10-13). However; many studies in recent decades have shown uncertainty about the frequent laboratory monitoring and various healthcare institutes have established and utilized different protocols for laboratory monitoring during isotretinoin therapy (12, 14-19).

As there is a shortage of evidence on the effect of oral isotretinoin on lipid profiles based on demographic characteristics, we aimed to assess the laboratory changes of lipid profile in patients with acne vulgaris referred to the Dermatology Clinics of Guilan University of Medical Sciences. We hypothesized that these treatments should be administered cautiously, due to their probable adverse effects.

Methods

This is a cross-sectional study that was conducted on the records of outpatients referred to Dermatology Clinics of Guilan University of Medical Sciences from April to September 2021. The present study included the records of 65 patients (55 females and 10 males) with moderate to severe degrees of acne vulgaris under a fixed low dose of 20 mg/day oral Isotretinoin (Roaaccutane, Zahravi company, Tabriz) treatment for 120 days. The patients older than 16 years old who did not have satisfactory responses to topical therapies and systemic antibiotics and had received 20 milligrams daily isotretinoin for 120 days were included.

Exclusion criteria were: pregnancy, breastfeeding, major depression, patients of reproductive age who were unable to use contraceptives, allergy to the drug components, pretreatment abnormal serum lipids, poor compliance, and consumption of other medications which affect lipid profile such as statins, androgen and estrogen hormones, and corticosteroids.

Data were gathered by a checklist consisting of demographic characteristics including sex, age, and body mass index (BMI) as well as a lipid profile. BMI was calculated by dividing weight in kilograms by height in squared meters. BMI in adult patients (≥20 years old) was categorized into four groups: less than 18.5 Kg/m^2 (underweight), 18.5 to 24.9 Kg/m^2 (normal weight), 25 to 29.9 Kg/m^2 (overweight), and ≥30 Kg/m^2 (obese). Besides, in adolescent patients (<20 years old), we used the BMI percentile. BMI percentile was classified as below: <5 as underweight, ≥5 and <85 as normal weight, ≥85 and <95 as overweight, and ≥95 as obese (20).

The data of baseline and after 120 days levels of fasting cholesterol, triglyceride, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were recorded regarding lipid profile. Triglyceride, cholesterol, and HDL were measured by SL-TRIGLYCERIDES, SL-CHOLESTEROL, and SL-CHOLESTEROL HDL Direct kit, respectively (Man company, Iran).

A total cholesterol level of less than 200 mg/dL is normal. Normal triglycerides range is less than 150 mg/dL. Levels of HDL cholesterol less than 40 mg/dL in women and less than 50 mg/dL in men are considered lower than desirable. Healthy LDL cholesterol level is considered to be below 130 mg/dL.

Statistical analysis: Data were reported by descriptive statistics (number, percent, mean, standard deviation). The normality of quantitative data was assessed by Kolmogrov-Smirnov. We analyzed the data using the SPSS software Version 16 (SPSS, Inc, IL, Chicago, USA) using paired sample T-test, Wilcoxon, and ANCOVA test based on whether or not the variables are normally distributed. A p-value<0.05 indicated statistical significance.

Results

In this study, 65 records of patients with a mean age of 22.21±6.25 years were assessed. Results showed that most of the patients (84.6%) were females with a mean BMI of 22.51±3.69. Also, 28 patients were adolescents, and according to their BMI percentile, 7.1%, 82.1%, 3.6%, and 7.1% were underweight, normal weight, overweight, and obese, respectively. In addition, 37 patients were adults, and 16.2%, 51.4%, 29.7%, and 2.7% of patients were underweight, normal weight, overweight, and obese patients, respectively.

At the baseline and after 120 days of isotretinoin treatment, the mean levels of cholesterol were 154.97±26.67 and 167.57±32.01 mg/dL, respectively. This showed a significant increase in serum cholesterol level (P<0.001). However, the result showed no significant change in the serum triglyceride level (P=0.259). Although the levels of LDL increased significantly (P=0.04), HDL did not have significant changes (P=0.626) (table 1).

Table 1. Lipid changes before and after 120 days of oral isotretinoin

Lipids	Before treatment (mg/dL)	After 120 days of treatment (mg/dL)	P-Value
TC Mean (SD)	154.97 (26.67)	167.57 (32.01)	<0.001*
TG Median (IQR)	91 (69.5_134)	100 (81.5_132.5)	0.259 †
LDL Median (IQR)	91 (73_100)	97 (72_111.75)	0.040 †
HDL Mean (SD)	46.86 (12.81)	47.48 (11.45)	0.626*

SD: standard deviation, LDL: low-density lipoprotein, IQR: interquartile range, HDL: high-density lipoprotein, TC: Total cholesterol, TG: Triglyceride. *: paired sample T-test. †: Wilcoxon test.

Analysis in different BMI groups showed that triglyceride had a significant rise in the normal weight group (P=0.014), but there was no significant change in other BMI groups. Cholesterol had also a significant increase in the normal weight group (P=0.006). LDL and HDL did not have a significant change in the BMI groups. As BMI did not have a significant relation with lipid levels, we could not use a ROC curve to report a specific cut-off for BMI (table2). Results showed that cholesterol (P=0.001) and triglyceride (P=0.033) had a significant increase in female patients. On the other hand, HDL increased significantly in male patients (P=0.032) (table 3). Comparing serum lipids based on age groups showed that cholesterol had a significant rise in adolescents (P= 0.003) and a slight increase in adults (P=0.051). Also, LDL had a mild increase in this group of patients (P=0.054).

Table 2. Lipid changes before and after 120 days of oral isotretinoin in different BMI groups

Lipids BMI	underweight	Normal weight	Overweight	Obesity	P-value ‡
Cholesterol1 Mean (SD)	135.75 (23.81)	156.93 (24.69)	158.83 (33.70)	163.33 (17.21)	0.690
Cholesterol2 Mean (SD)	147.87 (25.27)	170.91 (30.99)	165.33 (38.81)	182.33 (20.53)	
P-value*	0.08	0.006	0.303	0.066	
Triglyceride1 Median (IQR)	86.50 (67.75_90.00)	96.00 (69.00_124.75)	112.50 (67.00_222.50)	137.00 (72.00_202.00)	0.198
Triglyceride2 Median (IQR)	82.50 (61.25_102.00)	140.25 (84.25_140.25)	97.50 (79.25_139.00)	100.00 (85.00_179.00)	
P-value †	0.779	0.014	0.272	0.593	

Lipids BMI	underweight	Normal weight	Overweight	Obesity	P-value ‡
HDL1 Mean (SD)	45.87 (10.56)	49.14 (13.14)	42 (12.86)	37 (3)	0.329
HDL2 Mean (SD)	51.37 (13.44)	48.02 (11.69)	45.58 (9.57)	37 (2.64)	
P-value*	0.98	0.515	0.127	1.000	
LDL1 Median (IQR)	65.00 (61.00_82.00)	92.00 (77.50_99.2)	88.00 (67.50_104.75)	102.00 (88.00_124.00)	0.776
LDL2 Median (IQR)	70.50 (62.25_95.00)	100.00 (78.00_113.50)	89.5 (68.50_134.50)	100 (97.00_136.00)	
P-value †	0.401	0.101	0.637	0.285	

SD: standard deviation, LDL: low-density lipoprotein, IQR: interquartile range, HDL: high-density lipoprotein. *: paired sample T-test. †: Wilcoxon test. ‡: ANCOVA.

Table 3. Lipid changes before and after 120 days of oral isotretinoin regarding sex

lipid	Sex	female	male
Cholesterol Mean (SD)	Before treatment Mean (SD)	153.76 (25.06)	161.60 (35.12)
	After 120 days of treatment Mean (SD)	167.38 (31.57)	168.60 (36.07)
	P-value*	0.001	0.240
Triglyceride Median (IQR)	Before treatment Median (IQR)	89.00 (68.00_121.00)	128.50 (108.00_189.00)
	After 120 days of treatment Median (IQR)	99.00 (78.00_125.00)	119.00 (86.00_160.00)
	P-value †	0.033	0.114
HDL Mean (SD)	Before treatment Mean (SD)	48.20 (13.31)	39.50 (5.64)
	After 120 days of treatment Mean (SD)	48.24 (11.98)	43.30 (7.04)
	P-value*	0.980	0.032
LDL Median (IQR)	Before treatment Median (IQR)	91.00 (74.00_100.00)	90.50 (66.25_105.50)
	After 120 days of treatment Median (IQR)	97.00 (75.75_110.25)	95.00 (70.00_131.50)
	P-value †	0.068	0.359

SD: standard deviation, LDL: low-density lipoprotein, IQR: interquartile range, HDL: high-density lipoprotein. *: paired sample T-test. †: Wilcoxon test.

Discussion

Serum lipid changes are the most common laboratory abnormality in patients under oral isotretinoin therapy (21). Isotretinoin may interact with some essential groups in the active site of proteins or enzymes that are involved with lipid metabolism like hydroxymethyl glutaryl reductase as an essential regulatory enzyme that plays an important role in cholesterol metabolism (22, 23). The results showed that the use of oral isotretinoin in acne vulgaris patients led to no significant change in LDL and HDL levels. Significant changes in triglyceride and cholesterol levels were within normal laboratory range, and these alterations did not cause discontinuation of treatment. Besides, 20 milligrams daily isotretinoin was a safe dose in overweight and obese patients because triglyceride and cholesterol increase only happened in patients with normal weight.

In the present study, cholesterol increased significantly (P<0.001). Consistent with our study, a cross-sectional study in Egypt showed that 21% of 285 patients on isotretinoin for more than one month and less than 6 months had a significant increase in cholesterol levels (24). A cohort study by Hansen et al. evaluated 515 patients with acne undergoing 574 courses of isotretinoin from March 2003 to July 2011 in the United States, and they also reported a significant rise in cholesterol levels (16). However, a cohort study on patients receiving isotretinoin for acne by Barbieri et al. in the United States, showed that most of the patients had cholesterol <300 mg/dL after oral isotretinoin treatment (25). These controversial results may be due to different sample sizes and methodologies. It is noteworthy that increased cholesterol was noted in most of the previous investigations and clinicians should consider it in long-term treatment and follow-up. In our study, triglyceride did not change significantly after treatment (P=0.259). likewise, Zanganeh et al. reported no significant increase in triglyceride in patients with acne under isotretinoin therapy (26), while another study in the United States (2016) showed a significant rise in triglyceride levels (16). These controversial results may occur since Zanganeh et al. excluded patients with baseline hyperlipidemia, while in the other study, baseline abnormalities were frequent. We followed the same protocol as Zanganeh et al. (16, 26). In our study, triglyceride and cholesterol had a significant rise in normal-weight patients, while in other BMI groups significant change was not seen. In previous studies, more dramatic increases in the triglyceride level were observed in patients who were obese, consumed excessive amounts of alcohol, and had a family history of hyperlipidemia, or other risk factors (27, 28). It is claimed that patients undergoing isotretinoin therapy who are overweight (>89 kg for male patients and >73 kg for female patients) are at a higher risk of hypertriglyceridemia (29). This result may be because our patients received a fixed low dose of (20 milligrams daily) isotretinoin treatment, which is a non-weight-dependent dose. It seems that administering fixed low doses is appropriate for obese patients. In the current study, LDL increased significantly, whereas, no meaningful change was detected in HDL level. In the study by Sarkar et al. in India in 2021, no change in HDL and a significant increase in LDL level was reported in patients receiving 20 mg daily isotretinoin (30).

In contrast, a recent study in Jordan by Khabour et al. has shown that the levels of HDL significantly decreased after 40 mg/day isotretinoin therapy (P=0.05) (31). On the other hand, Kutlu et al. who assessed 120 patients with severe/very severe acne vulgaris who received at least 3 months of isotretinoin treatment (0.5-1 mg/day) detected a meaningful increase in both LDL and HDL (32). In Zanganeh's study in Iran in 2021 in the group of patients who received 40 mg/day isotretinoin (the same dose used in Khabour's study) mild reduction in HDL level happened, while no significant change was observed in the group of patients who received 20 mg/day isotretinoin (26). Therefore, it seems that the low dose of oral isotretinoin is a safer protocol. In our analysis of serum lipid changes considering the sex of the patients, cholesterol and triglyceride had meaningful rises (P=0.001 and 0.033, respectively) in female patients. However, HDL increased significantly in male patients (P=0.032), and LDL levels did not differ significantly regarding sex. In a study in India by Sarkar et al. (2018), there was no statistically significant relation between hyperlipidemia and sex (P = 0.6869) (30), while a study in Brazil by Schmitt et al. (2011) reported that patients who developed alterations in triglyceride and cholesterol levels during isotretinoin treatment were more likely to be females (33).

Hypertriglyceridemia is reported to be due, at least partially, to the retinoid X receptor-mediated increase in expression apo C-III a known molecule that acts as an antagonist of plasma triglyceride catabolism (34). Retinoid X receptors (RXR) are reported to be involved in metabolic syndrome and in triggering polycystic ovary syndrome (35, 36). Rodondi et al. recognized a tendency to develop metabolic syndrome in patients who had a significant elevation in triglyceride levels during the use of oral isotretinoin, concluding that genetic factors play a part (37). Hence the tendency of women to develop high triglyceride levels can be explained. As only 15.3% of our patients were males, the significant elevation of HDL may be due to the small population of this group.

In our study, cholesterol had a significant rise in adolescents (P= 0.003). Also, LDL had a mild increase in this group of patients (P=0.054). Consistent with our study, Güngor et al. observed that concerning age, the levels of LDL were significantly higher in patients older than 25 years when compared to patients younger than 25 years, while they concluded that triglyceride and HDL levels alterations did not depend on the age. The rise in cholesterol levels in adolescents in our study may be due to the higher frequency of normal weight in this group (38) .

This study had some limitations. As we assessed the records of patients, we did not have an access to some variables such as BMI after treatment. In addition, we had a few patients in some specific BMI groups, especially obese ones. Although we checked all records, there were only ten male patients in this study. Regarding the above-mentioned limitations, it is better to perform further clinical trials assessing different doses of isotretinoin with a larger sample size.

Despite significant changes in some of the serum lipids, most of them were still in normal laboratory ranges. According to the results, it seems that a low dose of isotretinoin can be used with minimal concern for changes in lipid profile in acne vulgaris patients, however, we monitored the patients for 120 days. Nevertheless, in the long-term follow-up and treatment, it seems that we have to administer it cautiously.

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Authors' contribution: Study concept and design (KGH, AD, NA, HE, RR, SD), acquisition of data (STH), analysis and interpretation of data (STH, AHR, EK, SD), drafting of the manuscript (KGH, STH, AHR, RGH, SD), critical revision of the manuscript for important intellectual content (AD, NA, EK), administrative, technical, or material support (KGH, STH, RGH, SD), and study supervision (KGH, AD, NA, SD). All authors have made a significant contribution to this study and have approved the final manuscript.

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