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Full Length Research Paper

Effects of oral isotretinoin on serum lipids and gamma glutamyl transpeptidase activity in acne vulgaris patients

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The aim of the present study was the evaluation of serum level of lipids and gamma glutamyl transpeptidase (GGT) activities in patients with acne vulgaris undergoing isotretinoin treatment. Forty-four patients, with severe acne or moderate acne (age mean 23.6±6.0 year) who were resistant to conventional treatment were supplemented with 0.5 mg/kg/day of oral isotretinoin for 120 days. This study revealed a significant increase in serum level of cholesterol, triglyceride and GGT activity. The findings of this work showed a number of negative effects of isotretinoin on disturbances in lipid profile and antioxidant status, in acne patients. Therefore, to control abnormalities in lipid profiles and oxidative stress, we recommend further studies to use antioxidant such as vitamin E supplementation in patients using isotertinoin.

Key words: Acne vulgaris, isotertinoin, serum lipid, gamma glutamyl transpeptidase (GGT).

INTRODUCTION

Acne vulgaris is a chronic, inflammatory disease of the pilosebaceous unit, which affects seborrhoeic areas like face, chest, and back; it is characterized by comedones, papules, nodules and scars (Piskin and Uzunali, 2007). Acne is a major psychosocial problem for many patients with acne vulgaris (Rubin et al., 2008). The exact mechanisms of the acne process are not completely understood, however it is known to be characterized by sebum overproduction, follicular hyperkeratinization, inflammation and oxidative stress. Androgens, microbes and other pathogenetic influences are also in the development of acne (Amichai et al., 2006). For many patients, acne poses a heavy psychosocial burden, negatively impacting mood, self-esteem, body image, and perceived levels of social isolation. Successful treatment of acne significantly reduces symptoms of anxiety and depression and improves acne patients' quality of life (Simić et al., 2009; Thomas, 2004; Tan, 2004). The treatment of acne vulgaris has changed over the years. Agents containing resorcinol or sulphur were used in especially first part of 20th century. Salicylic acid and retinoids were used some time (Piskin and Uzunali, 2007; Amichai et al., 2006). Isotretinoin, a systemic retinoid, was approved for use in acne vulgaris in 1982. It is arguably the most effective acne medication available, offering a durable clearing of acne lesions in 85% of its users (Cheetham et al., 2006). Isotretinoin administered to patients with severe cystic acne, has marked effects on sebum production and composition in the sebaceous glands (Al Hallak and Zouain, 2009). Oral isotretinoin is clearly more effective than oral antibiotics in acne of all grades of severity (Dréno et al., 2006; Perera et al., 2009). There is strong evidence to show that isotretinoin significantly reduces the psychological problems associated with acne (Misery, 2011). A small number of patients with mild acne have psychological problems disproportionate to their degree of acne. These patients may have body dysmorphophobic syndrome (Simić et al., 2009). There is evidence to suggest these patients respond to isotretinoin but withdrawing the drug may be difficult (Brito et al., 2010). Isotretinoin is chemically similar to the retinoid vitamin A, a fat-soluble vitamin stored in high concentrations in the liver (Monga, 1997).

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Table 1. Characteristics of the patient.

Parameter	Mean	S.D
Age (years)	23.75	5.49
Weight (kg)	64.82	15.12
Hight (cm)	167.14	9.96
Body mass index (kg/m^2)	22.09	2.11

Therefore, effective treatments that have minimal side effects are still needed. The exact mechanism of action of isotretinoin is still unknown. It is unclear why treatment results are maintained in many individuals after discontinuation of the drug. A greater understanding of the mechanism of action of isotretinoin in acne will help us to design new drugs and procedures that are as effective as isotretinoin but avoid the unwanted side effects and associated risks (Amichai et al., 2006; Lammer et al., 1985).

Acne vulgaris is an inflammatory disease that could create oxidative stress (Arican et al., 2005; Leopold and Loscalzo, 2009). Because the possible link between isotretinoin intake oxidative stress, and dyslipidemic profile and gamma glutamyl transpeptidase (GGT) activity, it would be of interest to examine the effects of isotretinoin intake on lipid profile and GGT activity in acne vulgaris patients. Hypercholesterolemia is a risk factor for the development of many diseases including atherosclerosis, myocardial infarction, heart attacks (Pesic et al., 2006; Ahmadvand et al., 2010). The reduction of serum levels of low-density lipoprotein or total cholesterol through diet therapy or drug administration in hypercholesterolemia patients have been shown to decrease the incidence of coronary heart disease (Ani et al., 2008; Berlin and Colditz, 1990). Also, recent studies have suggested that serum GGT can also be considered a marker of oxidative stress (Ceyssens et al., 2004). Thus, agents such as some drugs, oxidative stress and inflammation that interfere with lipid metabolism may increase the susceptibility to atherosclerosis and are the subjects of widespread investigations (Lamon-Fava et al., 2009; Pushpavalli et al., 2010).

There have not been clear studies about the effects of isotretinoin on lipid profile and GGT activity in acne vulgaris patients, hence this work is undertaken to investigate the effect of isotretinoin on serum levels of lipid profile and GGT activity in acne vulgaris patients.

MATERIALS AND METHODS

All experiments were performed with analytical reagent grade chemicals. Forty-four patients (20 males and 24 females), with severe acne or moderate acne and resistant to conventional treatment were supplemented with 0.5 mg/kg/day of oral isotertinoin for 120 days. They were instructed not to use any other drug or change their diet. The study protocol was approved by the Lorestan University of Medicine of Ethics Committee, and all subjects of the study provided informed consent for participation. Following an overnight fasting period, blood samples were obtained during 8 to 10 a.m. venous blood sample was taken from each patient after an overnight fast. Blood samples were immediately centrifuged at 2000 rpm for separation of serum. Samples were used directly, or stored in deep freeze at -20°C until analyses. The serum levels of fast blood sugar (FBS), cholesterol and triglyceride and alanine transaminase (ALT), aspartate transaminase (AST) and GGT activity were measured at the baseline and also at the end of the treatment period. Serum fast blood sugar (FBS), cholesterol and triglyceride concentrations and ALT, AST and GGT activity were measured by biochemical analyzer using commercial kits (Olympus AU-600, Tokyo, Japan). The data obtained were evaluated and compared by parried T-test. A *P*-value of less than 0.05 was considered as significant point.

RESULTS

The characteristics of the patient are shown in Table 1. Serum levels of fast blood sugar (FBS), cholesterol and triglyceride; and ALT, AST and GGT activity at the baseline and after 120 days of isotretinoin supplementation are shown in Table 2.

The mean levels of cholesterol were 156.23±32.43 and 175.02±32.44 mg/dl, respectively at the baseline and after 120 days of isotretinoin supplementation. This showed a significant increase in serum cholesterol level (P = 0.0001). Also, the mean levels of triglyceride were 96.256±38.13 and 152±89.62 mg/dl, respectively at the baseline and after 120 days of isotretinoin supplementation. This showed a significant increase in serum triglyceride level and GGT activity (P = 0.0001), while FBS, ALT and AST activity were unaltered.

DISCUSSION

This study showed that isotretinoin increased cholesterol, triglyceride, and GGT activity (P<0/005). The exact mechanisms of action of isotretinoin on increasing cholesterol and triglyceride are still unknown. It is possible that isotretinoin interacts with some essential groups in the active site of the important proteins or enzymes at lipid metabolism such as HMG (hydroxyl metyl glutaryl) redutase, a key regulatory enzyme that plays an important role in cholesterol metabolism (Lamon-Fava et al., 2009; Pushpavalli et al., 2010). However, the exact mechanisms of isotretinoin action on increasing GGT activity are still unknown. It is possible

Table 2. Serum levels of fast blood sugar (FBS), cholesterol and triglyceride and GGT, ALT and AST activity at the baseline and at the end of the treatment period.

Parameter	Baseline	Treatment	P Value
FBS (mg/dl)	89.95±15.67	92.23±12.89	0.2950
TG (mg/dl)	96.256±38.13	152.00±89.62	0.0001*
Cholesterol (mg/dl)	156.23±32.43	175.02±32.44	0.0001*
GGT (U/L)	13.44±7.25	17.95±6.94	0.0001*
ALT (U/L)	19.41±8.98	22.33±13.69	0.1350
AST (U/L)	20.67±12.23	23.81±10.57	0.2060

*Statistically significant (P<0.005).

that GGT enzyme induction may be associated with the generation of reactive oxygen species (ROS) (Holt and Ju, 2010). Also isotretinoin similar to xenobiotic and others drugs may lead to an increase in risk of liver problems (Holt and Ju, 2010; Drozdz et al., 1998). It is observed in patients with acne vulgaris, the incidence of laboratory abnormalities that occurred after management with oral isotretinoin. These abnormalities were observed in serum levels and GGT activity after the treatment period, compared with the baseline. Also, our results indicated no alteration serum level of FBS, ALT and AST activity.

Clear studies have not been done to examine the incidence of abnormalities in serum lipid levels among patients at baseline. Others studies have reported that isotretinoin decreased hematological parameters in acne vulgaris patients (Moeller and Touma, 2003; Johnson and Rapini, 1987; Brito et al., 2010). Considering present data, it can be concluded that the systemic changes in serum lipid parameters and GGT, at the cellular level, may induce changes in cell membrane and metabolism, then it can be the start of metabolic disorders in patients who are under isotretinoin therapy for a long period of time. Also, changes in these parameters at the cellular level may be related to oxidative stress (Holt and Ju, 2010; Cho, 2010; Yolaç Yarpuz et al., 2008); all these may cause an increase in risk of liver problems and increase cholesterol and triglyceride in patients who are under isotretinoin therapy for a long period of time. Concerning the important role of antioxidants in reduction of oxidative stress, we recommend further studies to assess the effect of longer periods of isotretinoin and antioxidants in oxidative stress markers in acne vulgaris patients.

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