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# Effect of systemic Retinoids on Lipid Profile in patients with dermatological diseases

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## Abstract

Many drugs besides lipid-lowering drugs affect serum lipid levels in either a potentially harmful or beneficial way, and may therefore increase or decrease the risk of vascular disease. Oral retinoids like isotretinoin and acitretin are among the drugs of choice for treating dermatological diseases and long term usage may cause common side effects such as serum lipid alterations, hepatotoxicity, pancreatitis, and skeletal deformities. In several cases of retinoid therapy, drug induced hypertriglyceridaemia have been reported. To investigate the effect of systemic retinoids usage and response in changes occur in the lipid profile after treatment, we conducted an open clinical intervention study on eighty dermatological patients admitted to our outpatient department. At the end of treatment at 12th week, 9 patients (11.25%) showed increase in Serum triglyceride levels, 5 patients (6.25%) with elevated serum cholesterol levels. 3 patients (3.75%) had decrease in HDL levels. Triglycerides were more often and elevated earlier than cholesterol 14 (17.5%) Vs 9 (11.25%). Our study concludes that alteration in lipid levels is not significant while on treatment with retinoid therapy. Only such people who had predisposing factors >3 should be carefully monitored with lipid levels and if drug use is expected to be long term, the existing guidelines for the management of dyslipidaemia has to be followed. In cases of extreme hyperlipidaemia, medication use should be reassessed.

## Introduction

Retinoids are synthetic and natural analogues of vitamin A involved in diverse biological activities and mediated by their ability to bind to complex groups of intra nuclear receptors- retinoic acid A receptors (RARs) and retinoic acid X receptors (RXRs).[1]

The introduction of retinoids has virtually revolutionized medical therapy in dermatology. Retinoids regulate various biologic functions, cell proliferation and differentiation, alter cell cohesiveness and possess antikeratinization properties. They exhibit anti-acne and

anti-seborrheic effects, have immunologic, anti-inflammatory and anti-proliferative functions and are involved in the induction of apoptosis, tumor prevention, and affect extracellular matrix.[2]

Systemic retinoids are classified into three generations. Tretinoin and Isotretinoin are considered as first generation retinoids; the aromatic retinoids Etretinate, and its active metabolite Acitretin as second generation retinoids. Bexarotene and Alitretinoin are the third generation retinoid.[3]

Isotretinoin inhibits sebaceous gland activity and promotes normalization of epidermal differentiation. Additionally it also has anti-inflammatory and antibacterial effects. It is FDA-approved, and considered as a gold standard in the treatment of severe nodular, recalcitrant acne and acne scarring.[4] The Indications for using isotretinoin in acne has expanded.[5] Therefore it can be concluded that the usage of isotretinoin will become more common in future.

The use of Acitretin in dermatology has been approved by FDA in conditions like Psoriasis vulgaris and Mycosis fungoides. Other off label indications includes Follicular disorders, Keratinization disorders, inflammatory disorders and chemoprevention of certain malignancies.

Retinoids are associated with a spectrum of idiosyncratic and dose dependent side effects.The most common laboratory abnormality observed in patients taking systemic retinoids is elevation in serum lipids, especially triglyceride levels. Alteration in lipid levels have been grouped as a very common side effect (occurring in >1/10 patients).[6]

Isotretinoin, Etretinate and Acitretin elevate triglycerides in 50% of patients and cholesterol in 30%. Bexarotene elevates these levels in 79% of patients.[7]

Hyperlipidemia is proportional to the dose of retinoids and usually reverses within 4–8 weeks after discontinuation. In addition, HDL levels have been found to be decreased in about 40% of patients taking Acitretin. The LDL /HDL ratio (atherogenic index) has been directly correlated to the risk of developing cardiovascular disease, and therefore fasting lipids should be regularly checked in all patients receiving treatment with Acitretin. These variations are more likely to occur in patients with predisposing factors such as Diabetes mellitus, Obesity, increased alcohol intake, or a family history of these conditions. Guidelines have been framed on the use of retinoids and to monitor for the lipid levels while on retinoids.[8,9]

There has been much debate as to whether Liver function tests and lipids should be monitored while on therapy. There is a paucity of literature especially involving the Indian population where the prevalence of hyperlipidemia and Metabolic Syndrome is significantly high in the general population. The objective of this study is to evaluate the Lipid profile changes in patients who are on treatment with Tab Isotretinoin and Tab Acitretin.

**Materials and Method**

This study was carried out in the OPD of Dermatology department at Vydehi Hospital, B'lore between January 2016 to December 2017. The ethical clearance was obtained by the IEC. Such patients with various dermatological disorders who were planned to be treated with systemic retinoids were included in the study. A written informed consent was taken from all the participants. 80 patients (M: F; 54:26) aged between 15 to 61 years were included in the study. Of these, 32 (M: F; 22:10) of them were treated with Acitretin and 48 (M: F:: 30:18) were treated with Isotretinoin.

All these patients were drug free before starting the treatment with retinoids and none of them received medication other than oral retinoids during the study period.

The following patients were excluded from the study:

- Men and women with moderate to severe hyperlipidemia.
- Patients with features of metabolic syndrome
- Women in reproductive age group not yet completing the family life.
- Children below 15 years or people above 65 years of age.
- Patients with pre-existing liver, kidney, cardiovascular or any other organ illness
- Patients with past history of skin and or other malignancies.
- Patients with past history of eye or skeletal abnormalities.
- Patients with past history of psychiatric disorders like anxiety, depression or history of attempted suicide.
- Patients with uncontrolled or complicated diabetes mellitus.
- Patients who are on concomitant drugs which are metabolized in liver or by p450 metabolism.

5 mL of venous blood samples was collected from median cubital vein by venepuncture avoiding haemolysis into vacutainer, after overnight fasting. Samples were centrifuged at 3000 rpm for 10 minutes. The samples were aliquoted and kept at -20° C until analysis was done. All the analysis was carried on serum samples. Serum triacylglecerol, cholesterol, high density lipoproteine and low density lipoprotein were assessed on auto analyzer Beckman Coulter. The patients included in the study were serially monitored with lipid profile and other necessary results at monthly intervals for the first 3 months. Later lipid profiles were done only if required. The results were referred to physician for further management.Moderate levels of elevations in triglycerides (>300-500 mg/dl) were managed with weight reduction, increased physical activity and low-fat, low-carbohydrate, low-alcohol diet. For triglycerides >500 mg.dl an LLA use and monitoring lipid levels more frequently was recommended. Because elevations in triglycerides > 800-1000 mg/dl can cause pancreatitis, drug discontinuation was recommended. Statistical analysis is done by Paired‘t’ test to compare at the time of admission and end of treatment.

**Results**

**Table1:Age profile of the patients**

| Age group (Years) | Acitretin | isotretinoin |
|---|---|---|
| 15 – 20 | 02 | 06 |
| 21 – 30 | 06 | 15 |
| 31 - 40 | 08 | 20 |
| 41 - 50 | 10 | 04 |
| 50 - 65 | 06 | 03 |

**Table 2: Dermatological conditions for using retinoids**

| **Acitretin: (N=32)** | | **Isotretinoin (N=48)** | |
|---|---|---|---|
| PPP | 10 | Acne vulgaris Gr III | 20 |
| Psoriasis Vulgaris | 08 | Acne vulgaris Gr IV | 16 |
| Ichthyosis | 04 | Post adolescent acne >35 | 07 |
| Pustular Psoriasis | 03 | Seborrheic dermatitis | 02 |
| Pityriasis Rubra Pilaris | 01 | Hidranetis Suppurativa | 02 |
| Epidermolysis Dysplasia Verruciformis | 01 | Rosacea | 01 |
| Darrier’s disease | 01 | | |

**Table 3: Patients whose lipid levels showed abnormalities during the study period. Acitretin/isotretinoin A/I**

| | W0 | W4 | W8 | W12 |
|---|---|---|---|---|
| S-Cholesterol | -- | 01/00 | 03/02 | 05/04 |
| S-Triglyceride | -- | 03/02 | 05/04 | 09/05 |
| S-LDL | -- | -- | -- | -- |
| S-VLDL | -- | -- | -- | -- |
| S-HDL | -- | -- | 01/00 | 03/00 |
| LDL/HDL ratio | -- | -- | -- | -- |

**Table 4: Patient characteristics whose lipid levels increased during treatment with retinoids**

| | A/I |
|---|---|
| Increased BMR – Obesity etc. | 5/4 |
| Diabetes Mellitus | 3/3 |
| Sex: Males | 3/3 |
| F/h of metabolic syndrome features | 3/4 |
| Alcohol/smoking | 2/5 |

The results of the patients who showed abnormalities in lipid levels are shown in the table 3. At the end of week 12, 9 patients (11.25%) showed increase in S-triglyceride levels, 5 patients (6.25%) with S-cholesterol levels. 3 patients (3.75%) had decrease in HDL levels.Triglycerides were more often and earlier elevated than cholesterol 14 (17.5%) Vs 9 (11.25%). Clinical trials have shown a similar finding of increased triglycerides, followed by increased cholesterol and decrease in HDL occurring following retinoid therapy.[10] Of the 9 patients 4 returned to normal levels even after continuing retinoids and with diet modifications advised; whereas the rest 5 continued to have persistent levels. Only 4 patients had moderate to severe elevation which made us to stop retinoids treatment. Their levels returned to normalcy slowly after starting lipid lowering agents and dietary adjustments.None of the patient had altered lipid levels after stopping retinoids treatment.

Two patients who were treated with an increased dose of Acrotac to 50 mg had mildly increased triglyceride levels. However 4 patients who had increased dosage of isotretinoin to 20 mg did not show any increase in lipid levels.

HDL which is a cardio protective lipid was mildly decreased in 1 patient at the 8$^{th}$ week and in 3 patients at 12 weeks.

3 patients with psoriatic arthritis, 2 with pustular psoriasis and one each with psoriasis vulgaris and with EDV had elevated lipid levels.

The alterations were more seen in Acitretin than in isotretinoin. 14 (17.5%) with Acitretin and 9 (11.25%) patients with isotretinoin had abnormalities in lipid levels. The alterations were noted in the third follow up visit. Not much elevation was seen either in the first visit or after stopping retinoids.

**Discussion**

Dermatological diseases are chronic inflammatory disease of the skin with world wide prevalence and can occur at any age. In recent years, retinoids has gained wide range of clinical use. Administration of oral vitamin A and the synthetic retinoids, like isotretinoin and Acitretin, to humans and experimental animals results in changes of serum lipid metabolism. [11, 12] However, retinoid therapy is usually complicated by dose related side effects. Side effects like mucocutaneous toxicity and laboratory abnormalities can compromise patient compliance and necessitate dose reduction or discontinuation of therapy. The most apparent side effect is on lipid metabolism causing hypertriglyceridaemia due to increased serum triglycerides in the very-lowdensity lipoprotein (VLDL) fraction. [13, 14, 15, 16] All lipid studies on isotretinoin and Acitretin consistently revealed significant increases of

LDL-cholesterol and decrements of HDL cholesterol levels. During isotretinoin treatment, the mean ratio of total cholesterol and HDL-cholesterol and indicates an average high risk for cardiovascular disease.

The main objective of our study is to evaluate the changes in lipid profile at each interval in patients on intermittent low dose isotretinoin and Acetretin. The study showed that there is increase in cholesterol, triglycerides at all the intervals when compared with the baseline. But the increase is within the normal limits. The exact mechanism of action of isotretinoin and Acetretin on increasing cholesterol and triglycerides are still unknown. Isotretinoin possibly could interact with some essential groups in the active site of the proteins or enzymes in lipid metabolism. [17, 18] Other studies have reported that isotretinoin and Acetretin increases cholesterol and triglycerides [19], similar to our study. The laboratory abnormalities have been observed in the serum levels during and after the treatment period when compared with the baseline. The HDL levels are observed to be decreased at all the intervals when compared with baseline but within normal limits. Clear studies have not been done to know the incidence of abnormalities in serum lipid levels among patients at baseline. The effectiveness of isotretinoin and Acetretin in treating acne has been well documented. [20,21,22,23] Our study demonstrated that the laboratory parameters (lipid profile) are not affected much with the intermittent isotretinoin therapy and the adverse effects were not serious and could be treated by conservative methods. Limitations such as the small sample size could affect the results validity.

**Conclusion**

The study concludes that alteration in lipid levels is not significant while on treatment with retinoid therapy. Only such people who had predisposing factors >3 should be carefully monitored with lipid levels. Replacement of the dyslipidaemia-inducing drug by an equivalent alternative therapy is preferred. However, such alternatives are often difficult to find. If there is no equivalent alternative and treatment with the dyslipidaemia-inducing drug must be initiated, monitoring of serum lipid levels is important. If drug use is expected to be long term, the existing guidelines for the management of dyslipidaemia in the general population can be applied to drug-induced dyslipidaemia. In cases of extreme hyperlipidaemia, medication use should be reassessed.

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