

Effect of Low dose Isotretinoin on Lipid Profile and Liver enzymes in Acne Patients: A Cross Sectional Study

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Abstract

Introduction: Oral isotretinoin remains the most clinically effective anti-acne therapy. However, a myriad of adverse effects are associated with isotretinoin use. Elevated liver enzymes and an altered lipid profile are well documented side effects of prolonged oral isotretinoin usage.

Objectives: To assess the alteration in liver enzymes and lipid profiles of acne patients on isotretinoin therapy.

Materials and Methods: The current prospective hospital based study, was carried out from September 2022 to December 2023, and included 150 patients with acne vulgaris on isotretinoin therapy. All consenting patients were then subjected to a detailed history and clinical examination. Subsequently, baseline Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Triglyceride (TG), Low density Lipoprotein (LDL), and High density Lipoprotein levels (HDL) levels were measured. Patients were then started on oral isotretinoin therapy at conventional dosages. Levels of ALT, AST, TG, LDL and HDL were repeated at 3- month and 6- month follow-up visits. A self-designed proforma was used to collect all relevant data. The collected data was analyzed as per standard statistical protocol. Repeated measures analysis of variance was used to compare means between 3 groups (baseline, 3-month, and 6-month values). Results with a $p < .05$ were considered statistically significant.

Results: The mean age of patients was 22.31(\pm SD 4.44) years. Females comprised the majority of our study subjects ($n = 95$; 63.33%). Levels of Alanine ($F_{2,226}=30.73$, $p < .0005$) and Aspartate transaminase ($F_{2,232}=13.13$, $p < .0005$) were increased significantly at 3 and 6 month follow up visits. Levels of TG were, also, increased significantly at follow up visits ($F_{2,239}=14.45$, $p < .0005$). Similarly, levels of low density lipoprotein increased significantly when compared to baseline levels ($F_{1,215}=38.43$, $p < .0005$). High density lipoprotein levels were decreased significantly when compared to baseline levels ($F_{1,209}=105.83$, $p < .0005$).

Conclusion: Our study has highlighted the significant alterations that occur in liver function tests and lipid profiles in patients on isotretinoin therapy.

Keywords: Isotretinoin; liver function tests; Lipid profile

Introduction

Since approval by the Food and Drug Administration (FDA) in 1982, oral isotretinoin (13-cis-retinoic acid) remains the most clinically effective anti-acne therapy. It results in decreased sebum production, influences comedogenesis, lowers Propionibacterium acnes concentration, and has anti-inflammatory properties. This multifaceted effect is achieved by influencing cell-cycle progression, cellular differentiation, cell survival, and apoptosis. Isotretinoin has a minimal ability to bind to cellular retinol-binding proteins or retinoic acid

nuclear receptors (RARs and RXRs). However, it may act as a pro-drug that is converted intracellularly to metabolites that are agonists for RAR and RXR nuclear receptors.¹

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A myriad of adverse effects are associated with the use of isotretinoin. Mucocutaneous, musculoskeletal, and teratogenic side effects are the most prominent adverse effects of isotretinoin administration. Elevated liver enzymes and altered lipid profiles are well documented in prolonged oral isotretinoin usage. Studies have shown that oral isotretinoin usage causes increased liver transaminase levels. This is coupled with an increase in the low density lipoprotein fraction and a reduction in high-density lipoprotein, together with an increase in triglyceride levels.^{2,3}

The need for monitoring liver function and lipid profiles has been a subject of debate. Changes in these functions occur in most patients and are reversible. However, regulatory bodies recommend the investigations to be performed at baseline and repeated at 3 monthly intervals throughout treatment.⁴ Hence, this prospective cross-sectional study was carried out to assess the alteration in liver enzymes and lipid profile of acne patients on isotretinoin therapy.

Materials and Methods

After obtaining approval from the Institutional Review Committee (IRC Reference Number: 2079/80/78), the current prospective cross-sectional study was carried out from September 2022 to December 2023. The study was conducted in the outpatient department of the dermatology unit of KIST Medical College. Using the non probability purposive sampling method, 170 confirmed cases of acne vulgaris who warranted oral isotretinoin therapy, aged between 18 and 65 years, were initially recruited in the study. However, 20 patients were lost at subsequent follow-up visits and were excluded from the study. Patients with pre-existing liver or renal diseases, a history of active neoplasm, recent major surgical operations, alcohol use, other drug use, and pregnant women were excluded from our study. After a detailed history and clinical examination, venous blood was collected from each subject after 12 hours of overnight fasting. The enzymatic method was used for the measurement of Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Triglyceride (TG), low density lipoprotein (LDL), and high density lipoprotein levels. This constituted the baseline levels. Female patients in the childbearing age group were given advice regarding contraception, and urine pregnancy tests were conducted routinely. Patients were then started on oral isotretinoin therapy at conventional dosages ranging from 0.5 to 1 mg/kg daily.⁵ Levels of ALT, AST, TG, LDL and HDL were repeated at 3 and 6 month follow up visits. Levels of ALT and AST were classified as normal (<40 U/L) or high (≥ 40 U/L). Triglyceride levels were classified as normal (<150 mg/dL), borderline high (150-199 mg/dL), high (200-499 mg/dL), and very high (≥ 500 mg/dL). Low-density lipoprotein levels were classified as optimal (<100 mg/

dL), above optimal (100-129 mg/dL), borderline high (130-159 mg/dL), high (160-189 mg/dL), and very high (≥ 190 mg/dL). High-density lipoprotein levels were classified as low (<40 mg/dL), normal (40-59 mg/dL), and high (≥ 60 mg/dL).⁶ Data was recorded as per a pre-designed proforma. A self-designed proforma was used to collect all relevant data. The collected data was analyzed using Statistical Package of Social Sciences (SPSS) version 26 (SPSS Inc., Chicago, USA). All analysis was performed as per standard statistical protocol. Repeated measures analysis of variance (ANOVA, one way) was used to compare means between 3 groups (baseline, 3-month, and 6-month values). Results with a $p < .05$ were considered statistically significant.

Results

A total of 150 patients with acne vulgaris on isotretinoin therapy were our study participants. The mean age of patients was 22.31(\pm SD 4.44) years, with a range in age from 18 to 39 years. Females comprised a majority of our study subjects (n = 95; 63.33%). Whereas, males (n = 55; 36.66%) comprised the rest.

The effect of isotretinoin therapy on liver function was assessed by analyzing alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. Recorded levels were classified as normal and high, as per the previously mentioned criteria. At baseline, mean ALT levels were 26.81(\pm SD 10.95) U/L, with normal levels in 137 (91.33%) patients and high levels in 13 (8.66%) patients. At 3 month follow-up, mean ALT levels were 28.79(\pm SD 12.85) U/L, with normal levels in 129 (86%) patients and high levels in 21 (14%) patients. At 6 month follow-up mean ALT levels were 30.99(\pm SD 14.69) U/L, with normal levels in 124 (82.66%) patients and high levels in 26 (17.33%) patients. Levels of ALT were significantly increased at 3 and 6 months follow when compared to baseline levels ($F_{2,226} = 30.73$, $p < .0005$).

Similarly, at baseline, mean AST levels were 20.73 (\pm SD 7.76) U/L, with normal levels in 144 (96%) patients and high levels in six (4%) patients. At 3 month follow-up mean AST levels were 22.01(\pm SD 9.85) U/L, with normal levels in 142 (94.66%) patients and high levels in eight (5.33%) patients. At 6 month follow-up mean AST levels were 23.99 (\pm SD 12.91) U/L, with normal levels in 138 (92%) patients and high levels in 12 (8%) patients. Levels of AST were increased significantly at 3 and 6 month follow when compared to baseline levels ($F_{2,232} = 13.13$, $p < .0005$).

Isotretinoin's effect on the lipid profile was assessed by analyzing triglyceride (TG), low density lipoprotein (LDL) and high density lipoprotein (HDL) levels. Triglyceride levels were classified as normal, borderline high, high, and very high. At baseline, mean TG levels were 90.16 (\pm SD 45.23) mg/dl, with normal levels in 135 (90%) patients, borderline high in 12 (8%) patients, high in three (2%) patients, and very high in none of

the patients. At 3 month follow-up, mean TG levels were 99.13(±SD 51.38) mg/dl, with normal levels in 124 (82.66%) patients, borderline high in 17 (11.33%) patients, high in nine (6%) patients, and very high in none of the patients. At 6 month follow up, mean TG levels were 102.15(±SD 59.17) mg/dl, with normal levels in 115 (76.66%) patients, borderline high in 22 (14.66%) patients, high in 13 (8.66%) patients, and very high in none of the patients. Levels of TG were increased significantly at 3 and 6 month follow when compared to baseline levels ($F_{2,239}=14.45, p<.0005$). Low-density lipoprotein (LDL) levels were classified as optimal, above optimal, borderline high, high, and very high. At baseline, mean LDL levels were 83.60 (±SD 27.33) mg/dl, with optimal levels in 117 (78%) patients, above optimal in 23 (15.33%) patients, borderline high in nine (6%) patients, high in one (.67%) patient, and very high in none of the patients. At 3 months follow-up, mean LDL levels were 85.49 (±SD 28.22) mg/dl, with optimal levels in 117 (78%) patients, above optimal in 20 (13.33%) patients, borderline high in nine (6%) patients, high in four (2.66%) patients, and

very high in none of the patients. At 6 month follow up, mean LDL levels were 94.26(±SD 32.57) mg/dl, with optimal levels in 101 (67.33%) patients, above optimal in 22 (14.66%) patients, borderline high in 18 (12%) patients, high in seven (4.66%) patients, and very high in two (1.33%) patients. Levels of LDL were increased significantly at 3 and 6 month follow when compared to baseline levels ($F_{1,215}=38.43, p<.0005$). High-density lipoprotein (HDL) levels were classified as low, normal, and high. At baseline, mean HDL levels were 51.91(±SD 15.68) mg/dl, with low levels in 21 (14%) patients, normal in 96 (64%) patients, and high in 33 (22%) patients. At 3 months of follow-up, mean HDL levels were 47.40 (±SD 13.12) mg/dl, with low levels in 37 (24.66%) patients, normal in 93 (62%), and high in 20 (13.33%) patients. At 6 months follow-up, mean HDL levels were 43.68 (±SD 11.81) mg/dl, with low levels in 64 (42.66%) patients, normal in 74 (49.33%) patients, and high in 12 (8%) patients. Levels of HDL decreased significantly at 3 and 6 months follow-up when compared to baseline levels ($F_{1,209}=105.83, p<.0005$). Laboratory findings are summarized in **Table 1**.

Table 1: Summary of laboratory findings

Laboratory Value	Baseline n (%)	3 months n (%)	6 months n (%)	F score, P value
ALT Normal (<40U/L) High (≥40U/L)	137 (91.33%) 13 (8.66%)	129 (86%) 21 (14%)	124 (82.66%) 26 (17.33%)	$F_{2,226}=30.73,$ $p<.0005^*$
AST Normal (<40U/L) High (≥40U/L)	144 (96%) 6 (4%)	142 (94.66%) 8 (5.33%)	138 (92%) 12 (8%)	$F_{2,232}=13.13,$ $p<.0005^*$
TG Normal (<150mg/dl) Borderline High (150-199 mg/dl) High (200-499 mg/dl) Very High (≥500mg/dl)	135 (90%) 12 (8%) 3 (2%) -	124 (82.66%) 17 (11.33%) 9 (6%) -	115 (76.66%) 22 (14.66%) 13 (8.66%) -	$F_{2,239}=14.45,$ $p<.0005^*$
LDL Optimal (<100 mg/dl) Above optimal (100-129 mg/dl) Borderline High (130-159 mg/dl) High (160-189 mg/dl) Very High (≥190mg/dl)	117 (78%) 23 (15.33%) 9 (6%) 1 (.67%) -	117 (78%) 20 (13.33%) 9 (6%) 4 (2.66%) -	101 (67.33%) 22 (14.66%) 18 (12%) 7 (4.66%) 2 (1.33%)	$F_{1,215}=38.43,$ $p<.0005^*$
HDL Low (<40 mg/dl) Normal (40-59 mg/dl) High (≥60mg/dl)	21 (14%) 96 (64%) 33 (22%)	37 (24.66%) 93 (62%) 20 (13.33%)	64 (42.66%) 74 (49.33%) 12 (8%)	$F_{1,209}=105.83,$ $p<.0005^*$
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein *significant p value				

Discussion

Isotretinoin is currently considered the treatment of choice for moderate and severe acne, and early initiation has been advocated to prevent psychosocial impact and scars.⁷ However, potential laboratory alterations, have served as a barrier to widespread adoption by patients and caregivers. Liver test abnormalities, of varying degrees, can occur in isotretinoin therapy. The exact mechanisms of isotretinoin induced serum aminotransferase level alterations are not exactly known. It may occur via a direct toxic effect, in that it appears to be more frequent with higher dose therapy.⁸ Our study also demonstrated significantly increased levels of ALT ($F_{2,226}=30.73$, $p<.0005$) and AST ($F_{2,232}=13.13$, $p<.0005$) at 3 and 6 months follow-up when compared to baseline levels. Our results are in concordance with several studies.^{2,9} No drug discontinuation was warranted in our study. Marked elevations above three times the upper limit of normal or those requiring drug discontinuation are rare. A clinically apparent liver injury due to isotretinoin is exceedingly rare. The majority of reported cases of isotretinoin induced liver injury have been anicteric with no or minimal symptoms. Nevertheless, the lack of reports of more severe hepatitis with jaundice may be due to the close monitoring and early discontinuation of isotretinoin, which is required in the use of this agent for acne.¹⁰

Several studies have demonstrated an alteration in the lipid plasma levels in isotretinoin therapy. They are usually characterized by increased triglycerides

(TG) and low-density lipoprotein (LDL), and decreased high - density lipoprotein (HDL) levels.^{2,11} Our study demonstrated a similar pattern of alteration, characterized by significant increase in TG ($F_{2,239}=14.45$, $p<.0005$) and LDL levels ($F_{1,215}=38.43$, $p<.0005$), and a significant decrease in HDL levels ($F_{1,209}=105.83$, $p<.0005$). Similar observations have been made in other studies. Lipid alterations are dependent on the dose and duration of therapy. In some cases, they can be transient, possibly due to the hepatic adaptation to drug metabolism. However, in the majority of cases, the lipid profile is restored to normal only with treatment withdrawal.¹² Laboratorial alterations may have a genetic background. A study has investigated the presence of the rs7799039 gene polymorphism, which encodes leptin involved in sebum lipid metabolism. They evaluated 200 patients before and after the use of oral isotretinoin and concluded that there was an association between the presence of the rs7799039 CC genotype and lower LDL and triglyceride percentage changes after oral isotretinoin therapy.¹³

Conclusion

Our study has highlighted the significant alterations that occur in AST, ALT, TG, LDL, and HDL levels, in patients on isotretinoin therapy. Hence, monitoring patients on isotretinoin therapy is advisable. However, the mild and reversible nature of these alterations seldom warrants drug discontinuation or pharmacological intervention. Caution should be adopted when treating patients with pre-existing abnormalities.

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