

## Do Gender, Age and Drug Dosage Effect Liver Functions and Serum Lipids on Isotretinoin Therapy?

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### Abstract

**Background:** Isotretinoin is a synthetic vitamin A analogue that is used to treat severe acne and other dermatologic diseases. However there are some concerns about this drug regarding the adverse effects.

**Aim:** In this study we evaluated the adverse effects of isotretinoin on liver functions and serum lipids with focus on the gender, age and isotretinoin dosages.

**Material and Methods:** Medical records of patients from 2011 to 2013 to whom oral isotretinoin had been prescribed and maintained the treatment at least 3 months were retrospectively reviewed. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gama-glutamyltransferase (GGT), triglyceride (TG), low-density lipoprotein (LDL), very low density lipoprotein (VLDL), high-density lipoprotein (HDL), creatinine (Cre) levels were evaluated pretreatment and at the third month of the treatment, respectively.

**Results:** The levels of AST, ALT, GGT, Cre, TG, LDL, VLDL, HDL at the third month of treatment did not differ significantly between male and female patients. With regard to age, the levels of AST, ALT, GGT, LDL, VLDL were significantly higher in patients older than 25 years when compared to patients younger than 25 years. When the drug dosage was taken into account, it was found that the levels of AST, ALT, GGT, TG, LDL, VLDL were significantly higher in patients taking more than 0,5mg/kg/day compared to patients taking less than 0,5mg/kg/day.

**Conclusion:** The major factor that increases TG levels during isotretinoin treatment seems to be the drug dosage. The major factors that increase AST, ALT, GGT, LDL, VLDL levels on isotretinoin treatment seems to be the patients' age and drug dosage. Gender does not have a major role on serum lipids and liver functions associated with isotretinoin therapy.

### Introduction

Isotretinoin (13-cis-retinoic acid) is a synthetic vitamin A analogue that was approved by the Food and Drug Administration in 1982 in the US for the treatment of recalcitrant severe, and nodulocystic acne [1, 2]. By the time it is used to treat several dermatologic

diseases (rosacea, hidradenitis suppurativa, ichthyoses, Darier's disease) [3]. Though there are numerous reported adverse effects, only a few of them led to treatment cessation. The most common laboratory abnormality seen in patients on oral isotretinoin therapy is hypertriglyceridemia [3, 4, 5, 6]. Elevations to the level of 500 mg/dL or more, warrant dose

**Table 1.** Alterations of AST, ALT, GGT, Creatinin, TG, LDL, VLDL, HDL Levels On Isotretinoin at The Third Month of The Treatment

		Mean± SD	Med (min-max)	P
AST	Pretreatment level	18,9±6,3	18 8-40	
(U/L)	3rd month level	24,3±14,3	20 9-78	<b>0,000</b>
ALT	Pretreatment level	17,1±8,7	14 6-46	
(U/L)	3rd month level	22,2±16,2	15 6-80	<b>0,001</b>
GGT	Pretreatment level	15,7±6,0	15 6-47	
(U/L)	3rd month level	19,7±10,4	17 7-50	<b>0,000</b>
Creatinin	Pretreatment level	0,82±0,11	0,8 0,5-1,2	
(mg/dL)	3rd month level	0,83±0,11	0,8 0,5-1,1	0,191
TG	Pretreatment level	72,5±26,1	67 29-165	
(mg/dL)	3rd month level	98,3±45,2	81 34-240	<b>0,000</b>
LDL	Pretreatment level	85,9±20,8	86 45-153	
(mg/dL)	3rd month level	102,0±33,6	100 48-190	<b>0,000</b>
VLDL	Pretreatment level	19,8±8,4	17 10-50	
(mg/dL)	3rd month level	24,5±13,2	20 12-70	<b>0,000</b>
HDL	Pretreatment level	49,7±11,1	50 29-90	
(mg/dL)	3rd month level	46,9±11,2	49 13-93	<b>0,000</b>

reduction/cessation of therapy, and patients who reach 800 mg/dL are at risk of developing pancreatitis. Liver function test abnormalities, most commonly involving the transaminases, occur in 11% of patients during isotretinoin therapy [3]. Elevations in transaminases greater than three times the upper-normal range warrant cessation of the therapy [1, 2, 3].

In the presented study we evaluated the adverse effect of isotretinoin on liver functions and serum lipids with focus on the gender, age and isotretinoin dosages.

### Materials and Methods

Data from the medical records of patients from 2011 to 2013 to whom oral isotretinoin had been prescribed and maintained the treatment for at least 3 months were retrospectively reviewed. Pretreatment and third month of the treatment serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gama-glutamyltransferase (GGT), triglyceride (TG), low-density lipoprotein (LDL), very low density lipoprotein (VLDL), high-density lipoprotein (HDL), creatinine (Cre) measurements were evaluated.

Statistical analysis was performed using the SPSS software program, version 21. Wilcoxon test and Mann-Whitney U test was used. To establish cor-

relations between variables, Kolmogorov-simirnov test was calculated. Results with  $p < 0.005$  were considered statistically significant.

### Results

Totally 121 patients were prescribed isotretinoin; 2 patients with hidradenitis suppurativa, one patient with Darier disease and 118 patients with acne. 100 patients maintained on isotretinoin therapy at least for 3 months. One patient stopped the treatment because of high TG level (300mg/dl) at the first month, this patient's baseline TG level was 180mg/dl. Two patients were diagnosed as anal fissure at the sixth and eight weeks of the treatment and interrupted the isotretinoin treatment. One patient stopped the treatment because of severe muscle ache, and one patient for severe headache. Five patients did not want to maintain the treatment after investigation of the drug from internet and refused to use isotretinoin because of bad reputation. Ten patients did not come for follow up in our hospital. Of these 100 patients who maintained the treatment at least 3 months; 48 were female, 52 were men. Age ranged between 15 to 47 years, with a mean of 22,5±6,3. Isotretinoin dosage was 0,2 to 0,7 mg/kg/day, with a mean of 0,47±0,14 mg/kg/day. Forty-two patients used less than 0.5mg/kg/day isotretinoin, 58 patients used 0.5 mg/kg/day and higher dosages of isotretinoin. The levels of AST, ALT, GGT, TG, LDL, VLDL at the third month were significantly increased compared to pretreatment levels (Table 1).

**Table 2.** Alterations of AST, ALT, GGT, Creatinin, TG, LDL, VLDL, HDL Levels On Isotretinoin Treatment Based On The Gender

		Female	Male	P (difference between gender)
AST (U/L)	Pretreatment level	17,9±5,4	19,9±6,9	
	3rd month level	20,9±10,7	27,5±16,4	
	3rd month difference p	0,021	0,000	0,128
ALT (U/L)	Pretreatment level	16,1±8,2	18,0±9,0	
	3rd month level	19,4±12,7	24,7±18,7	
	3rd month difference p	0,000	0,007	0,584
GGT (U/L)	Pretreatment level	15,5±6,5	15,8±5,5	
	3rd month level	18,3±8,5	21,1±11,8	
	3rd month difference p	0,005	0,000	0,711
CRE (mg/dL)	Pretreatment level	0,79±0,09	0,85±0,12	
	3rd month level	0,80±0,07	0,86±0,13	
	3rd month difference p	0,050	0,805	0,117
TG (mg/dL)	Pretreatment level	75,4±30,1	69,8±21,7	
	3rd month level	95,6±43,4	100,8±47,0	
	3rd month difference p	0,000	0,000	0,176
LDL (mg/dL)	Pretreatment level	83,2±21,8	88,3±19,8	
	3rd month level	98,1±32,8	105,6±34,1	
	3rd month difference p	0,000	0,000	0,609
VLDL (mg/dL)	Pretreatment level	19,6±7,7	20,0±9,0	
	3rd month level	23,3±9,9	25,6±15,7	
	3rd month difference p	0,000	0,000	0,950
HDL (mg/dL)	Pretreatment level	53,3±12,6	46,4±8,4	
	3rd month level	49,9±11,7	44,1±10,0	
	3rd month difference p	0,003	0,007	0,543

Mann-Whitney u test / Wilcoxon test

HDL levels were significantly decreased compared to pretreatment levels (**Table 1**). Creatinin levels were not significantly different compared to baseline levels (**Table 1**). The levels of AST, ALT, GGT, Cre, TG, LDL, VLDL, HDL at the third month of treatment did not differ significantly between male and female patients (**Table 2**). With regard to age, the levels of AST, ALT, GGT, LDL, VLDL were significantly higher in patients older than 25 years when compared to patients younger than 25 years (**Table 3**). When the drug dosage was taken into account, it was found that the levels of AST, ALT, GGT, TG, LDL, VLDL were significantly higher in patients taking more than 0,5mg/kg/day compared to patients taking less than 0,5mg/kg/day (**Table 4**).

## Discussion

As shown by previous studies [7, 8, 9, 10, 11], current study also revealed that oral

isotretinoin therapy alters liver functions and serum lipids, but kidney functions do not alter. In this study only one patient had to interrupt the treatment because of abnormal lipid or liver function tests. That patient also had abnormal pretreatment TG level and familial hypercholesterolemia history. In our study, although the lipid and liver test levels increased significantly at the third month, none of the abnormal levels were more than two fold of the pretreatment levels. This result may be due to patients consciousness about this drug, that most patients restrict their diet, alcohol consumption and unnecessary drugs as we advised. These results show that by restricting the diet and making life style changes we can minimize the adverse effects on serum lipids and liver functions.

**Table 3.** Alterations of AST, ALT, GGT, Creatinin, TG, LDL, VLDL, HDL Levels On Isotretinoin Treatment Based On The Age

		Age<25	Age≥25	P (difference between age)
AST (U/L)	Pretreatment level	18,5±5,9	20,1±7,1	
	3rd month level	21,5±10,2	32,5±20,2	
	3rd month difference p	0,002	0,001	<b>0,004</b>
ALT (U/L)	Pretreatment level	15,8±7,5	20,7±10,7	
	3rd month level	18,6±12	32,4±21,9	
	3rd month difference p	0,071	0,003	<b>0,006</b>
GGT (U/L)	Pretreatment level	15,5±5,9	16,1±6,2	
	3rd month level	18,3±9,5	23,8±11,8	
	3rd month difference p	0,001	0,001	0,060
CRE (mg/dL)	Pretreatment level	0,83±0,11	0,81±0,10	
	3rd month level	0,83±0,11	0,82±0,10	
	3rd month difference p	0,437	0,200	0,513
TG (mg/dL)	Pretreatment level	72,1±25,7	73,5±27,6	
	3rd month level	94,0±43,1	110,7±49,4	
	3rd month difference p	0,000	0,000	0,054
LDL (mg/dL)	Pretreatment level	82,5±20,3	95,4±19,6	
	3rd month level	95,5±30,3	120,5±36,2	
	3rd month difference p	0,000	0,000	<b>0,025</b>
VLDL (mg/dL)	Pretreatment level	18,6±7,0	23,2±11,0	
	3rd month level	22,2±10,5	31,1±17,5	
	3rd month difference p	0,000	0,000	<b>0,002</b>
HDL (mg/dL)	Pretreatment level	49,1±10,9	51,3±11,7	
	3rd month level	46,5±11,2	48,0±11,4	
	3rd month difference p	0,000	0,054	0,850

Mann-Whitney u test / Wilcoxon test

Our results show that the alterations on the lipids and liver tests depend on the drug dosage and the age of patient but not gender.

There is no significant difference with regard to AST, ALT, GGT levels between pretreatment and posttreatment levels in patients on isotretinoin less than 0.5mg/kg/day; while there is a significant difference with regard to TG, LDL, VLDL levels between pretreatment and posttreatment levels in patients taking isotretinoin less than 0,5mg/kg/day. On the other hand, the difference rates of TG, LDL, VLDL levels in patients using isotretinoin less than 0,5mg/kg/day were lower than the difference rates TG, LDL, VLDL levels in patients using isotretinoin more than 0,5mg/kg/day. It shows that lipid levels can also alter on low isotretinoin dosage, but not so severe as high isotretinoin dosages. So we should also ad-

vise diet restriction to the patients taking low isotretinoin dosages.

When we evaluate the patients younger than 25 years; the differences were significant between pretreatment and posttreatment AST, ALT, GGT, TG, LDL, VLDL, HDL levels. Similarly when we evaluate patients 25 years and older; the differences were significant between pretreatment and posttreatment AST, ALT, GGT, TG, LDL, VLDL, HDL levels. But the difference rate in older group was significantly higher than the difference rate of younger group but not TG and HDL levels; suggesting that TG and HDL levels alterations do not depend on the age and we should follow the young patients closely as well as older patients and advise to restrict the diet.

We interpret our results as following;

**Table 4.** Alterations of AST, ALT, GGT, creatinin, TG, LDL, VLDL, HDL Levels On Isotretinoin Treatment Based On The Drug Dosage

		Dosage<0,5 (mg/kg/day)	Dosage≥0,5 (mg/kg/day)	P (difference between gender)
AST (U/L)	Pretreatment level	18,0±5,5	19,6±6,8	
	3rd month level	18,1±6,6	28,9±16,5	
	3rd month difference p	0,856	0,000	<b>0,000</b>
ALT (U/L)	Pretreatment level	17,3±8,9	16,9±8,6	
	3rd month level	17,5±9,6	25,5±19,1	
	3rd month difference p	0,803	0,000	<b>0,000</b>
GGT (U/L)	Pretreatment level	15,8±4,9	15,6±6,7	
	3rd month level	16,0±6,0	22,5± 11,9	
	3rd month difference p	0,645	0,000	<b>0,000</b>
CRE (mg/dL)	Pretreatment level	0,81±0,10	0,83±0,12	
	3rd month level	0,81±0,10	0,85±0,11	
	3rd month difference p	0,880	0,065	0,206
TG (mg/dL)	Pretreatment level	73,8±22,8	71,5±28,4	
	3rd month level	84,7±32,1	108,2±50,7	
	3rd month difference p	0,000	0,000	<b>0,000</b>
LDL (mg/dL)	Pretreatment level	82,2±21,8	88,5±19,9	
	3rd month level	91,3±32,9	109,7±32,1	
	3rd month difference p	0,000	0,000	<b>0,000</b>
VLDL (mg/dL)	Pretreatment level	19,8±8,9	19,8±8,0	
	3rd month level	21,7±11,0	26,5±14,3	
	3rd month difference p	0,003	0,000	<b>0,000</b>
HDL (mg/dL)	Pretreatment level	49,7±12,6	49,7±10,0	
	3rd month level	47,6±13,1	46,4±9,6	
	3rd month difference p	0,030	0,001	0,315

Mann-Whitney u test / Wilcoxon test

1) The major factor that increases TG levels on isotretinoin treatment seems to be the drug dosage. Age and gender do not effect TG levels significantly. We should monitore TG levels in teenage patients as closely as adults if the drug dosage is over 0.5mg/kg/day.

2) The major factors that increase AST, ALT, GGT, LDL, VLDL levels on isotretinoin treatment seems to be the patients' age and drug dosage. Gender does not effect AST, ALT, GGT, LDL, VLDL levels significantly. We should monitore AST, ALT, GGT, VLDL, LDL levels more closely in adult patients taking isotretinoin 0.5mg/kg/day.

3) Although the liver functions and serum lipids alter on isotretinoin therapy, these alterations are not so severe to interrupt the treatment in the case of patients who has normal pretreatment levels.

However previous studies [12, 13] had shown that low-dose isotretinoin dosage regimens

have less side effects on serum lipids and liver functions, but we could not reach a study evaluating gender, age and drug dosage in the same study. *Schmitt et al* [14] reviewed 90 patients who used isotretinoin and revealed that female patients lipid levels increase more than male patients. But we found no effect of gender on serum lipids and transaminases on isotreatment therapy. Future studies will help to clear this confliction.

In conclusion isotretinoin alters serum lipids and liver functions, but in the case of normal baseline levels and restriction of diet and alcohol consumption the change is not life-threatening. Drug dosage and patients' age effect the alteration but gender does not.

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