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Original Research

Effects of Oral Isotretinoin on Skin and Serum Levels of FoxO3, TRAIL and p53 and Metabolic Parameters

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Abstract

Objectives: Isotretinoin-mediated apoptosis is considered the main cause of anti-acne side effects of isotretinoin. The aim of this study is to investigate the effects of oral isotretinoin therapy on the skin and serum levels of forkhead box transcription factor (FoxO)-3, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), p53 and metabolic parameters and examine the relationship between these parameters.

Methods: Sixteen acne vulgaris patients who were administered the appropriate cumulative dose of oral isotretinoin were enrolled in this prospective study.

Results: The decreases in the values of body mass index, waist circumference, systolic blood pressure (BP), CRP, and ferritin from the baseline to the end of the treatment were statistically significant (p=0.028, p=0.029, p=0.008, p=0.046, and p=0.003, respectively). The increases in the levels of serum low-density lipoprotein-cholesterol (LDL-C), triglyceride (TG), total cholesterol, gamma-glutamyl transferase (GGT), and FoxO3 from the baseline to the end of the treatment were statistically significant (p=0.001, p=0.004, p<0.001, p=0.010, p=0.007, respectively). In terms of changes from the baseline to the end of the treatment, serum FoxO3 levels were positively correlated with the changes in serum TRAIL levels (r=0.674, p=0.004). The changes in serum FoxO3 levels were positively correlated with the changes in fasting blood glucose levels (r=0.540, p=0.031). The changes in serum TRAIL levels were positively correlated with the changes in the values of systolic BP (r=0.552, p=0.027) and diastolic BP (r=0.511, p=0.043). The changes in serum p53 levels and serum LDL-C levels were also positively correlated (r=0.499, p=0.049).

Conclusion: Isotretinoin therapy caused an increase in skin and serum levels of FoxO3 and TRAIL and a decrease in serum and skin p53 values. However, only the increase in serum FoxO3 levels was statistically significant. The observed reduction in p53 levels implies that the isotretinoin-related side effects may not rely on p53-mediated apoptosis, and it may be considered that its safety profile is better than expected. The correlations between the changes during isotretinoin therapy in metabolic parameters and TRAIL, p53, and FoxO3 values suggest that isotretinoin's metabolic side effects may involve these molecules.

Keywords: Acne vulgaris, forkhead box transcription factor (FoxO3), isotretinoin, p53, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)

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Acne vulgaris (AV) is defined as a mechanistic target of rapamycin complex 1 (mTORC1)-mediated condition, affecting the pilosebaceous structure.[1,2] Elevated insulin/insulin-like growth factor-1 (IGF-1) signaling and reduced mTORC1 activity are observed due to failure in the forkhead box transcription factor (FoxO)/sestrin-3/AMP-activated protein kinase (AMPK) pathway.[3]

Isotretinoin (13-cis retinoic acid), an efficient anti-acne agent,[4] strongly inhibits sebum formation, is known to have many side effects.[5] Isotretinoin-mediated apoptosis is considered the main cause of its anti-acne side effects.[6] The enhanced nuclear function of FoxO regulator proteins has been proposed as the main contributor to isotretinoin-mediated apoptosis.[7] FoxO proteins, particularly FoxO1 and FoxO3, play roles in combating oxidative stress, promoting cell-cycle inhibition, and inducing apoptosis. Taken together with p53, FoxOs act as a key group of tumor suppressors.[3] Additionally, both FoxO1 and FoxO3 promote the expression of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), one of the key pro-apoptotic proteins.[5]

The purpose of this study is to evaluate the effects of oral isotretinoin therapy on the skin and serum levels of FoxO3, TRAIL, and p53. Additionally, insulin resistance and the criteria of metabolic syndrome (MS) in patients with AV are also studied.

Methods

The local ethics committee evaluated and authorized the research (approval number: E-48670771-514.99; date of approval: 02/03/2021), and all subjects signed written consent forms. The research was performed in alignment with the principles outlined in the Declaration of Helsinki.

The effects of oral isotretinoin therapy on insulin resistance; the criteria of MS; the values of FoxO3, TRAIL and p53 in the skin and serum; and the potential links between the studied parameters and disease characteristics were evaluated in this prospective study.

Sixteen AV patients who were eligible to start oral isotretinoin treatment according to the guidelines were enrolled in the study. All patients received the recommended total dose of oral isotretinoin and did not receive any other systemic or topical treatment. Patients with back involvement were included in the study, and skin samples of the patients were taken from the skin of the back.

The demographic data and clinical findings of the patients were recorded. Patients with any systemic diseases (e.g., infections, inflammatory or any endocrinologic conditions), those who had received any systemic treatment in the six months prior to the study or topical treatment within last two months and smokers were excluded.

All clinical assessments and laboratory tests were analyzed at the start and upon completion of the treatment. Measurements of height, weight, waist circumference (WC), body mass index (BMI) and blood pressure (BP) were performed as described by Centers for Disease Control and Prevention[8] and the severity of acne was evaluated according to the Global Acne Grading System.[9]

Isotretinoin is recommended for the therapy of moderate to severe acne and also for patients who don't respond to other therapies.[10] In this study, isotretinoin doses of approximately 0.5 mg/kg per day were given over a 24-week period to achieve the cumulative dose of 120–150 mg/kg.[11]

Laboratory Analyses

The levels of serum fasting glucose, insulin, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), FoxO3, TRAIL, and p53 were assessed from fasting venous blood samples of the participants. The skin samples were also studied to evaluate the values of FoxO3, TRAIL, and p53. The skin specimens were taken from the lesional skin on the backs of the patients using a 2.00 mm punch biopsy. The specimens were washed in PBS (pH 7.4) to thoroughly remove excess blood. The tissues were finely chopped and blended in PBS (pH 7.4) using a glass homogenizer on ice. After centrifuging at 2000–3000 RPM for approximately 20 minutes, they were kept at -80°C until the time the examples were studied.

The serum glucose, LDL-C, HDL-C, and TG levels were measured by an enzymatic method. The insulin concentrations were assessed with an electrochemiluminescence immunoassay. The FoxO3, TRAIL, and p53 levels were assessed by ELISA with commercially available ELISA kits (Human Forkhead Box Protein O3 [FoxO3] ELISA Kit, catalog no. E0626Hu, BioAssay Technology Laboratory, Shangai, China; Human sTRAIL ELISA kit, catalog no: SG-13924, Sinogeneclon Co., Ltd, Hang Zhou, China; Human p53 ELISA kit, catalog no: SG-10350, Sinogeneclon Co., Ltd, Hang Zhou, China). The measures of FoxO3, TRAIL, and p53 were defined as ng/mL, pg/mL, and µg/mL, respectively.

The formula that was used to calculate the HOMA-IR was: fasting insulin (mU/L) x fasting glucose (mmol/L)/22.5.[12]

Statistical Analysis

The R Core Team (2013) version 2.15.3 (Vienna, Austria: The R Foundation for Statistical Computing) was used for statistical analyses. The descriptive data are presented as mean ± standard deviation, along with numeric variables, frequencies, and percentages. To analyze normally distributed variables, the Shapiro-Wilk test was conducted to as-

sess the differences between the two groups. The Wilcoxon signed-ranks test was employed to evaluate changes in variables over time. For comparing two independent groups with non-normally distributed variables, the non-parametric Mann-Whitney U test was utilized, and the Kruskal-Wallis test was applied when more than two groups were involved. A Spearman correlation test was performed to assess the relationship between quantitative variables. $p<0.05$ was defined as statistically significant.

Results

Table 1 displays the features of the patients.

A total of 16 AV patients who were given the total dose of oral isotretinoin were included. The mean age of the patients was 19.00±4.26 years. The mean disease duration was 43.88±27.60 months. Ten patients (62.5%) had moderate disease, and 6 (37.5%) had severe disease. Face and back were the involvement sites in all patients (n=16, 100%), while 5 (31.25%) of the patients additionally had chest involvement.

The changes in the levels of parameters and the association between the parameters at the end of the treatment

The changes in the clinical findings, biochemical parameters serum, and the levels of FoxO3, TRAIL, and p53 in the skin were evaluated (Table 2).

Table 1. The demographic data and clinical characteristics of the patients

(n=16)	Min-Max (Median)	Median±SD
Age	14-30 (18)	19.00±4.26
Disease duration (months)	6-120 (39)	43.88±27.60
Acne score	3-4 (3)	3.38±0.50
	n	**%**
Gender		
Female	10	62.5
Male	6	37.5
Smoking	1	6.2
Family history of acne	11	68.8
Scarring	7	43.7
Localization		
Face+Back	11	68.8
Face+Back+Chest	5	31.2
Previous Treatments		
None	3	18.8
Systemic Azitromycin	5	31.2
Systemic Tetracylin	7	43.7
Topical treatment	13	81.2

SD: Standard deviation.

The decreases in the values of BMI, WC, systolic BP, CRP, and ferritin between the initiation and completion of the treatment were statistically significant (p=0.028, p=0.029, p=0.008, p=0.046, and p=0.003, respectively).

The increases in the levels of serum LDL-C, HDL-C, TG, total cholesterol, GGT, and FoxO3 from the start to the completion of the treatment were statistically significant (p=0.001, p=0.018, p=0.004, p<0.001, p=0.010, and p=0.007, respectively).

Increase in TRAIL levels was statistically significantly higher in patients with scarring acne (p=0.030).

The association between the parameters at the baseline and at the end of the treatment

At the baseline, positive correlation was noted between the skin levels of p53 and both the serum TRAIL (r=0.568, p=0.022) and the serum p53 levels (r=0.669, p=0.005) (Table 3).

By the conclusion of the treatment, there was a positive correlation between serum FoxO3 levels and serum TRAIL (r=0.903, p<0.001) and serum p53 levels (r=0.579, p=0.019). After completion of the treatment, the serum TRAIL levels also showed positive correlation with the serum p53 levels (r=0.579, p=0.019) (Table 3).

The correlation between the changes in parameters from the baseline to the end of the treatment

The correlation between the changes in parameters from the baseline to the end of the treatment is shown in Table 4.

The changes in serum FoxO3 levels were positively correlated with the changes in fasting blood glucose levels (r=0.540, p=0.031). The changes in serum TRAIL levels were positively correlated with the changes in the values of systolic BP (r=0.552, p=0.027) and diastolic BP (r=0.511, p=0.043). The changes in serum p53 levels and serum LDL-C levels were also positively correlated (r=0.499, p=0.049).

As the values at the initiation and completion of therapy were evaluated, a positive correlation was observed between the serum FoxO3 levels and the changes in the serum TRAIL levels (r=0.674, p=0.004).

The alteration in serum and skin p53 levels from baseline to the end of treatment showed a statistically significant correlation between each other (r=0.603, p=0.013), while no such correlation was observed from the baseline to the end of the treatment between the skin and serum levels of FoxO3 (p>0.05) or TRAIL (p>0.05) (Table 3).

Table 2. The changes in the clinical findings, biochemical parameters serum and skin levels of FoxO3, TRAIL and p53

	Baseline Median (Q1, Q3)	End of the treatment Median (Q1, Q3)	Change Median (Q1, Q3)	p
BMI	22.35 (20.85, 24.05)	21.6 (19.7, 24.25)	-1.05 (-1.65, 0.05)	**0.028***
WC	76.5 (70.5, 84.5)	73.5 (67.5, 86.5)	-2 (-4.5, 1)	**0.029***
SBP	142 (125, 147)	124.5 (120.5, 139)	-10 (-19.5, -3)	**0.008***
DBP	95 (85.5, 107.5)	83.5 (80.5, 94.5)	-5 (-14, 4)	0.133
LDL-C	79 (60.5, 88)	93 (76.5, 103)	13.5 (10.5, 31.5)	**0.001***
HDL-C	45.5 (38.5, 56.5)	46 (33, 50.5)	-4.5 (-9, -1)	**0.018***
TG	83 (67, 118)	122 (75.5, 159)	18 (9, 50)	**0.004***
TC	143 (119, 158.5)	162 (144.5, 181)	28.5 (8.5, 41.5)	**<0.001***
AST	17.5 (14.5, 24)	19.5 (17.5, 23.5)	2 (-4.5, 7)	0.659
ALT	12.5 (9.5, 19)	12.5 (9, 18.5)	0.5 (-5.5, 4)	0.842
GGT	10 (10, 16.5)	14 (12, 20.5)	4 (-0.5, 7)	**0.010***
CK	73 (62, 116.5)	76 (65.5, 126.5)	-2 (-15, 24.5)	0.877
CRP	2.02 (0.86, 3.66)	1.17 (0.38, 2.53)	-0.42 (-1.72, 0.2)	**0.046***
ESR	5.5 (4, 10)	4 (3, 9.5)	-1 (-3, 2)	0.732
NLR	2.02 (1.69, 2.38)	1.95 (1.49, 2.62)	-0.02 (-0.45, 0.56)	0.979
Ferritin	30.55 (18.85, 65.6)	26.25 (16.95, 52.15)	-5.25 (-14.2, -0.65)	**0.003***
Vitamine B12	256 (216, 377.5)	279.5 (217.5, 377)	-6 (-33, 23.5)	0.737
Folate	5.31 (3.78, 6.2)	5.63 (4.68, 6.99)	0.21 (-0.44, 1.66)	0.605
FBG	86.5 (81.5, 89)	87.5 (84, 90)	1.5 (-6, 3.5)	0.909
Insulin	12.6 (10.6, 17.15)	13.6 (11.75, 15.6)	0.7 (-2, 2.55)	0.796
HOMA-IR	2.95 (2.25, 3.85)	2.8 (2.45, 3.15)	-0.05 (-0.75, 0.35)	0.659
FoxO3	30.83 (24.68, 49.01)	47.04 (28.26, 86.25)	10.17 (5.31, 31.21)	**0.007***
Skin FoxO3	57.44 (53.04, 68.04)	66.95 (57.6, 72.48)	10.23 (-7.72, 20.88)	0.127
TRAIL	572.73 (392.31, 665.51)	647.97 (508.7, 789.49)	150.93 (-68.09, 276.52)	0.088
Skin TRAIL	468.11 (391.34, 599.48)	548.66 (496.26, 624.69)	57.47 (-100.99, 204.92)	0.196
P53	1425.41 (998.74, 1669.83)	1335 (1081.53, 1616.9)	-241.63 (-488.89, 444.85)	0.756
Skin P53	1316.15 (1011.78, 1449.41)	1044.1 (848.52, 1427.22)	-159.77 (-619.88, 234.32)	0.408

Wilcoxon signed-ranks test, represented as median (first quarter, third quarter). *p<0.05. BMI: Body mass index; WC: Waist circumference; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TG: Triglyceride; TC: Total cholesterol; AST: Aspartate transaminase; ALT: Alanine transaminase; GGT: Gamma-glutamyl transferase; CK: Creatinine kinase; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; NLR: Neutrophil-lymphocyte ratio; FBG: Fasting blood glucose; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; FoxO3: Forkhead box transcription factor 3; TRAIL: Tumour necrosis factor-related apoptosis-inducing ligand.

Discussion

In AV, increased insulin/IGF-1 signaling activates the Phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway, which results in sebaceous lipogenesis and increased mTORC1 activity, decreased nuclear FoxO levels in sebaceous glands. Nuclear FoxO transcription factors, particularly FoxO3a, stimulate the expression of apoptotic signaling molecules, including TRAIL.[13]

Isotretinoin is a very effective anti-acne agent due to its several effects, such as inhibition of sebaceous gland activity, improving the keratinization within the follicle, anti-inflammatory effects, decreasing the colonization of Propionibacterium acnes, and the regulation of tissue matrix metalloproteinases. Isotretinoin may also cause undesirable effects on many tissues of the body other than sebaceous follicles. It has several effects on the organism including cell cycle, sebum synthesis, oxidative and inflammatory processes; still its precise mechanism of action remains unclear.[7] Beyond its physical effects, AV significantly impacts the psychological well-being of patients, underscoring the need for effective treatments and a deeper understanding of therapeutic agents.[14]

Isotretinoin binds to retinoic acid receptors (RARs) after transformation to all-trans retinoic acid (ATRA) in sebocytes.[15] ATRA/RAR signaling triggers a cascade of gene expressions, enhancing nuclear FoxO1, FoxO3, and p53 levels.[16-20] These factors promote apoptosis through pro-apoptotic molecules like Fas ligand (FasL) and TRAIL.[21-24] TRAIL, an important apoptotic signal for human sebocytes,

Table 3. Association between the parameters at baseline and at the end of treatment

Baseline	**Serum FoxO3**	**Serum Trail**	**Serum P53**	**Skin FoxO3**	**Skin Trail**	**Skin P53**
Serum FoxO3						
r	1.000					
p	-					
Serum TRAIL						
r	0.462	1.000				
p	0.072	-				
Serum P53						
r	0.216	0.487	1.000			
p	0.422	0.055	-			
Skin FoxO3						
r	0.130	0.403	-0.290	1.000		
p	0.633	0.122	0.276	-		
Skin Trail						
r	0.243	0.288	-0.166	0.091	1.000	
p	0.365	0.279	0.538	0.737	-	
Skin P53						
r	0.166	0.568	0.669	0.094	-0.035	1.000
p	0.538	0.022*	0.005*	0.729	0.897	-
End of treatment	**Serum FOXO3**	**Serum Trail**	**Serum P53**	**Skin FOXO3**	**Skin Trail**	**Skin P53**
Serum FoxO3						
r	1.000					
p	-					
Serum TRAIL						
r	0.903	1.000				
p	<0.001*	-				
Serum P53						
r	0.579	0.579	1.000			
p	0.019*	0.019*	-			
Skin FoxO3						
r	0.168	0.079	-0.209	1.000		
p	0.535	0.770	0.438	-		
Skin TRAIL						
r	-0.153	-0.091	0.212	-0.124	1.000	
p	0.572	0.737	0.431	0.649	-	
Skin P53						
r	-0.156	-0.206	0.044	0.276	0.415	1.000
p	0.564	0.444	0.871	0.300	0.110	-
Change	**Serum FOXO3**	**Serum Trail**	**Serum P53**	**Skin FOXO3**	**Skin Trail**	**Skin P53**
Serum FoxO3						
r	1.000					
p	-					
Serum TRAIL						
r	0.674	1.000				
p	0.004*	-				
Serum P53						
r	0.221	0.262	1.000			
p	0.412	0.327	-			

Table 3. Association between the parameters at baseline and at the end of treatment (Cont.)

Change	Serum FOXO3	Serum Trail	Serum P53	Skin FOXO3	Skin Trail	Skin P53
Skin FoxO3						
r	0.082	0.132	-0.250	1.000		
p	0.762	0.625	0.350	-		
Skin Trail						
r	-0.368	-0.085	0.003	-0.050	1.000	
p	0.161	0.753	0.991	0.854	-	
Skin P53						
r	0.103	0.241	0.603	0.059	0.141	1.000
p	0.704	0.368	0.013*	0.829	0.602	-

r=Spearman's correlation coefficient. *p<0.05. FoxO3: Forkhead box transcription factor 3; TRAIL: Tumour necrosis factor-related apoptosis-inducing ligand.

Table 4. Correlation between the changes in parameters from baseline to the end of treatment

	HOMA-IR		FoxO3		TRAIL		P53	
	r	p	r	p	r	p	r	p
BMI	-0.030	0.912	0.178	0.509	-0.054	0.841	0.216	0.421
WC	-0.113	0.676	0.349	0.185	0.330	0.212	0.109	0.687
SBP	-0.127	0.639	0.391	0.134	0.552	0.027*	0.154	0.570
DBP	-0.002	0.994	0.233	0.385	0.511	0.043*	0.382	0.145
LDL-C	0.194	0.472	0.138	0.609	0.330	0.212	0.499	0.049*
HDL-C	-0.025	0.927	-0.063	0.816	-0.068	0.803	-0.277	0.299
TG 0.359	0.172	-0.172	0.524	-0.152	0.575	0.128	0.637	
TC 0.070	0.797	-0.079	0.770	0.286	0.284	0.337	0.202	
AST	0.406	0.119	-0.114	0.674	0.065	0.810	0.110	0.686
ALT	0.038	0.890	0.184	0.495	0.405	0.120	0.013	0.961
GGT	0.473	0.065	0.101	0.710	-0.110	0.686	0.084	0.756
CK -0.074	0.786	0.411	0.114	0.412	0.112	0.327	0.216	
CRP	0.365	0.164	-0.474	0.064	-0.235	0.380	-0.165	0.542
ESR	0.266	0.319	-0.265	0.321	-0.041	0.879	-0.120	0.658
NLR	0.074	0.786	-0.226	0.399	0.018	0.948	0.391	0.134
Ferritin	0.122	0.652	0.103	0.704	0.321	0.226	0.103	0.704
Vitamine B12	-0.343	0.193	-0.085	0.753	0.285	0.284	0.244	0.362
Folate	-0.141	0.601	0.000	0.999	0.082	0.762	0.206	0.444
FBG	0.451	0.080	0.540	0.031*	0.214	0.427	0.123	0.649
Insulin	0.652	0.006*	-0.015	0.957	-0.379	0.147	-0.029	0.914

r=Spearman's correlation coefficient. *p<0.05. BMI: Body mass index; WC: Waist circumference; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TG: Triglyceride; TC: Total cholesterol; AST: Aspartate transaminase; ALT: Alanine transaminase; GGT: Gamma-glutamyl transferase; CK: Creatinine kinase; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; NLR: Neutrophil-lymphocyte ratio; FBG: Fasting blood glucose; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; FoxO3: Forkhead box transcription factor 3; TRAIL: Tumour necrosis factor-related apoptosis-inducing ligand.

is upregulated by oral isotretinoin treatment.[5] Recent evidence suggests that isotretinoin/ATRA-mediated activation of p53, FoxO1, and FoxO3 all inhibit mTORC1 signaling and trigger apoptosis of sebocytes.[6] Agamia et al.[3] demonstrated that isotretionoin caused an elevation in the nucleo-cytoplasmic ratio of FoxO1 and FoxO3. Isotretinoin was reported to increase the synthesis of FoxO1, p53, and p21 in human keratinocytes, promoting apoptosis and treatment efficacy.[25] Isotretinoin also enhances p53 and FoxO1 production while suppressing IGF-1 and androgen receptor activity, disrupting IGF-1/mTORC1 and androgen signaling.[6,26]

However, the above-mentioned studies were in vitro, or cell culture studies. In our study, skin and serum levels of

FoxO3, TRAIL, and p53 were investigated and a statistically significant increase in the serum levels of FoxO3 at the end of isotretinoin therapy was observed, which suggests that isotretinoin may act on FoxO3 not only in keratinocytes but also systemically. Previous research proposed that isotretinoin exerts its anti-acne effects by inducing apoptosis via p53 expression. However, the observed decreases in skin and serum p53 levels in our study suggest that isotretinoin may not exert systemic apoptotic effects through p53. This finding implies that isotretinoin might have a lower risk of p53-related side effects, potentially enhancing its safety profile.

Our findings demonstrated decreases in BMI, WC, systolic BP, CRP, and ferritin levels. Reductions in BMI, WC, and BP may indicate improved metabolic health and potential cardioprotective effects, while lower CRP and ferritin levels may reflect isotretinoin's anti-inflammatory properties. On the other hand, isotretinoin's well-known reversible effects on lipid parameters (increased LDL-C and TG) were also observed. Changes in LDL-C levels were positively correlated with serum p53 levels, while changes in systolic/diastolic BP with serum TRAIL levels, and changes in fasting glucose levels were positively correlated with serum FoxO3 levels. Changes during the treatment were positively correlated between the serum FoxO3 and TRAIL levels. All these findings may suggest that common metabolic side effects of isotretinoin may be related to TRAIL, p53, FoxO3 molecules.

The study's small sample size limits generalizability, and its observational design prevents establishing causal relationships between isotretinoin therapy and metabolic or inflammatory changes.

Conclusion

Isotretinoin treatment increased FoxO3 and TRAIL levels in skin and serum while reducing p53 levels, with a significant increase only in serum FoxO3 levels. These findings suggest isotretinoin's systemic effects may be linked to increased serum FoxO3 levels, rather than p53-mediated apoptosis, potentially reducing p53-related side effects and improving its safety profile. Cardioprotective effects were also observed, represented as reductions in BMI, WC, systolic BP, CRP, and ferritin levels. Correlations were noted between post-treatment changes in serum LDL-C levels and serum p53 levels, values of BP and serum TRAIL levels, levels of fasting glucose and levels of serum FoxO3, and between serum FoxO3 and serum TRAIL levels. These findings suggest that isotretinoin's metabolic side effects may involve TRAIL, p53, and FoxO3. Further studies are needed to clarify these mechanisms, as isotretinoin remains a highly effective acne treatment.

Disclosures

Ethics Committee Approval: The study was approved by the Prof. Dr. Cemil Tascioglu City Hospital Clinical Research Ethics Committee (date: 02.03.2021, no: E-48670771-514.99).

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