

## High Risk for Hyperlipidemia and the Metabolic Syndrome after an Episode of Hypertriglyceridemia during 13-*cis* Retinoic Acid Therapy for Acne: A Pharmacogenetic Study

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**Background:** Administration of 13-*cis* retinoic acid (isotretinoin) for acne is occasionally accompanied by hyperlipidemia. It is not known why some persons develop this side effect.

**Objective:** To determine whether isotretinoin triggers a familial susceptibility to hyperlipidemia and the metabolic syndrome.

**Design:** Cross-sectional comparison.

**Setting:** University hospital in Lausanne, Switzerland.

**Participants:** 102 persons in whom triglyceride levels increased at least 1.0 mmol/L ( $\geq 89$  mg/dL) (hyperresponders) and 100 persons in whom triglyceride levels changed 0.1 mmol/L ( $\leq 9$  mg/dL) or less (nonresponders) during isotretinoin therapy for acne. Parents of 71 hyperresponders and 60 nonresponders were also evaluated.

**Measurements:** Waist-to-hip ratio; fasting glucose, insulin, and lipid levels; and *apoE* genotype.

**Results:** Hyperresponders and nonresponders had similar pre-

treatment body weight and plasma lipid levels. When reevaluated approximately 4 years after completion of isotretinoin therapy, hyperresponders were more likely to have hypertriglyceridemia (triglyceride level  $> 2.0$  mmol/L [ $> 177$  mg/dL]; odds ratio [OR], 4.8 [95% CI, 1.6 to 13.8]), hypercholesterolemia (cholesterol level  $> 6.5$  mmol/L [ $> 252$  mg/dL]; OR, 9.1 [CI, 1.9 to 43]), truncal obesity (waist-to-hip ratio  $> 0.90$  [OR, 11.0 (CI, 2.0 to 59)], and hyperinsulinemia (insulin–glucose ratio  $> 7.2$ ; OR, 3.0 [CI, 1.6 to 5.7]). In addition, more hyperresponders had at least one parent with hypertriglyceridemia (OR, 2.6 [CI, 1.2 to 5.7]) or a ratio of total to high-density lipoprotein cholesterol that exceeded 4.0 (OR, 3.5 [CI, 1.5 to 8.0]). Lipid response to isotretinoin was closely associated with the *apoE* gene.

**Conclusion:** Persons who develop hypertriglyceridemia during isotretinoin therapy for acne, as well as their parents, are at increased risk for future hyperlipidemia and the metabolic syndrome.

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Lipid abnormalities have been associated with the use of various pharmacologic agents, including  $\beta$ -blockers, diuretics, estrogens, HIV-1 protease inhibitors (1), and 13-*cis* retinoic acid (isotretinoin [Accutane], Roche, Basel, Switzerland) (2, 3). Isotretinoin is the treatment of choice for severe acne resistant to other treatments. In some patients (20%), isotretinoin causes a marked but reversible elevation in plasma concentrations of triglyceride-rich lipoproteins, which can result in acute pancreatitis (4). The severity of this complication has prompted dermatologists to systematically monitor fasting plasma lipid levels whenever they prescribe isotretinoin. The mechanism for isotretinoin-induced hyperlipidemia remains elusive, and it is not known why only a fraction of persons develop this side effect.

It is possible that isotretinoin elevates plasma triglyceride levels in patients with acne who have a latent, possibly familial and genetic predisposition to hyperlipidemia. The most common form of familial lipid disorder

is familial combined hyperlipidemia (5). This condition shares a series of features with the metabolic syndrome, a multifaceted condition characterized by hyperlipidemia, hypertension, hyperuricemia, insulin resistance, diabetes, and obesity (6–10). Familial combined hyperlipidemia and the metabolic syndrome are usually dormant during childhood and become progressively apparent in adults. Both conditions are major contributors to heart disease. Although these disorders have a familial component (5, 11), the responsible genes have not been identified. Elucidation of the genetic basis of familial combined hyperlipidemia and the metabolic syndrome has been hampered by the heterogeneity of these disorders and their incomplete penetrance, which are consistent with strong gene–environment interactions. We reasoned that isotretinoin is an environmental trigger that unmasks a latent familial predisposition to hyperlipidemia and the metabolic syndrome.

To test our hypothesis, we used a family-based cross-sectional comparison. We initially identified a large group of young adults who had developed a pronounced elevation in plasma triglyceride levels during isotretinoin therapy for acne (hyperresponders) and an equally large group whose plasma triglyceride levels had not changed during therapy (nonresponders). All participants were reevaluated for markers of the metabolic syndrome while not receiving therapy. Parents of hyperresponders and nonresponders were also evaluated.

## METHODS

### Study Design and Participants

Initially, we examined the medical records of 613 persons with acne who had been treated with isotretinoin for at least 4 weeks between 1988 and 1998 at the dermatology division of CHUV University Hospital and at the practices of four dermatologists in the area of Lausanne, Switzerland. For 601 participants (98%), fasting plasma lipid levels had been measured once before initiation of isotretinoin therapy and had then been monitored monthly by the same laboratory. A total of 18 persons were excluded because they had fasting pretreatment plasma cholesterol levels of 7.0 mmol/L or more ( $\geq 271$  mg/dL), triglyceride levels of 3.0 mmol/L or more ( $\geq 266$  mg/dL), or both. Thus, 583 persons were included in the analysis (Figure 1). Mean duration of isotretinoin course was 6 months, and an average of six lipid values were available for each participant during treatment. We determined isotretinoin-associated changes in fasting plasma triglyceride level by calculating the difference between the highest value recorded during isotretinoin therapy and the pretreatment level. Hyperresponders ( $n = 117$ ) were identified as persons who had developed an increase in plasma triglyceride level of 1.0 mmol/L or more ( $\geq 89$  mg/dL) (corresponding to the upper quintile in the distribution); 145 participants whose plasma triglyceride levels had remained unchanged or decreased during isotretinoin therapy (a difference  $\leq 0.1$  mmol/L [ $\leq 9$  mg/dL], corresponding to the lower quartile in the distribution) were considered nonresponders. We contacted the hyperresponders and the nonresponders and asked them to participate in our study and to be reevaluated while not receiving therapy. Only 15 hyperresponders and 45 nonresponders were not found or declined to participate. Participation rate was higher for hyperresponders (87%) than nonresponders (69%) ( $P = 0.001$ ) because of

### Context

Isotretinoin (Accutane, Roche, Basel, Switzerland) is the treatment of choice for severe acne that is resistant to topical treatment.

Approximately 20% of patients develop marked elevations in triglyceride levels.

The mechanism responsible for isotretinoin-induced hyperlipidemia is unknown.

### Contribution

This study showed that isotretinoin-induced hypertriglyceridemia identifies patients at high risk for chronic hyperlipidemia, truncal obesity, and hyperinsulinemia.

The *apoE* gene and  $\epsilon 2$  and  $\epsilon 4$  alleles were more common in patients with isotretinoin-induced hypertriglyceridemia than in patients who had no lipid abnormalities while taking the drug.

### Implications

People with isotretinoin-induced hypertriglyceridemia have increased risks for chronic hyperlipidemia and the metabolic syndrome that are possibly related to the *apoE* gene.

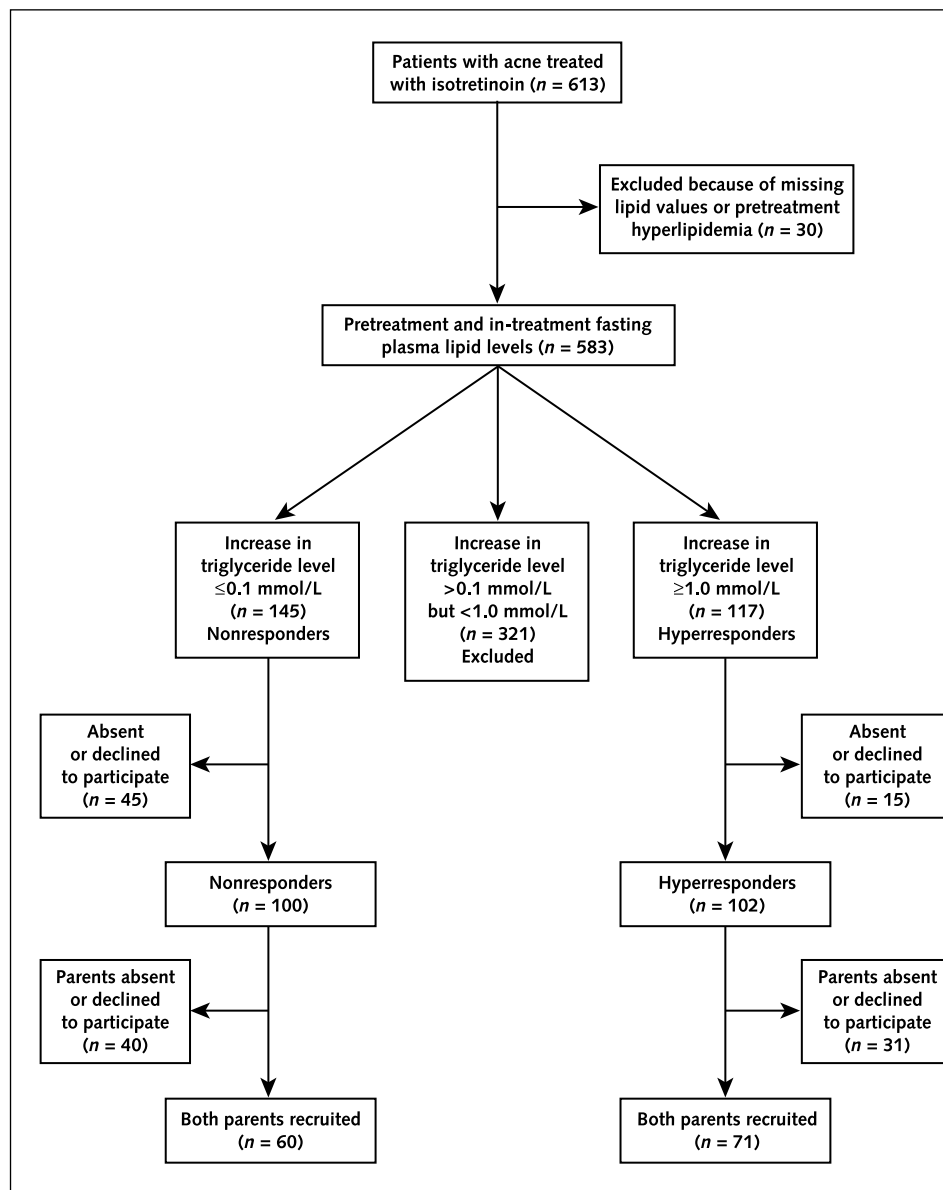
—The Editors

difficulties in motivating healthy persons who had shown no change in plasma lipid levels during isotretinoin therapy. A total of 102 hyperresponders and 100 nonresponders were reevaluated while not receiving therapy. We also contacted the parents of these participants (when both parents were available) and eventually recruited both parents of 71 hyperresponders and 60 nonresponders. The procedures were in accordance with institutional guidelines. The local Ethics Committee approved the protocol, and each participant provided informed consent.

### Measurements

Participants filled out a questionnaire and had a physical examination, including measurement of height, body weight, waist-to-hip ratio, and blood pressure (evaluated using a sphygmomanometer while participants were seated for  $\geq 10$  minutes). Fat mass was estimated by bioelectric impedance using the Bio-Z generator (Eugédia, Paris, France), as described elsewhere (12). Venous blood was collected on EDTA after a 12-hour fast and was processed within 2 hours. Nineteen parents receiving lipid-lowering therapy were asked to stop therapy at least 1 week before they were examined. The clinical chemistry laboratory of Lausanne University Medical Policlinic performed bio-

Figure 1. Flow chart of the study.



To convert mmol/L to mg/dL, divide by 0.0113.

chemical measurements, as described elsewhere (1). Genomic DNA was isolated from peripheral blood cells, and a series of sequence variations was examined by using polymerase chain reaction amplification and restriction digest, according to published protocols: the  $\epsilon 2$ ,  $\epsilon 3$ , and  $\epsilon 4$  alleles within the *apoE* gene (13); the *Pro12Ala* polymorphism within the peroxisome proliferator-activated receptor (*PPAR*)- $\gamma$  gene (14); the C to A substitution at position -278 within the 5' flanking region of the cholesterol 7 $\alpha$ -

hydroxylase (*CYP7 $\alpha$* ) gene (15); and the *SstI*, *XmnI* and *MspI* polymorphisms within the *apoA1-CIII-AIV* genes (16).

### Statistical Analyses

Data are presented as the mean ( $\pm$ SD). Statistical analyses were performed by using SPSS, version 10.0 (SPSS, Inc., Chicago, Illinois). We used *t*-tests, or Wil-

coxon rank-sum tests when appropriate, to compare clinical characteristics. For comparison of frequency distribution, we used the chi-square test or the Fisher exact test. Logistic regression analysis was used to calculate the risk for metabolic disorders associated with a previous elevation in plasma triglyceride levels during isotretinoin therapy. The same type of analysis was performed to evaluate the risk in hyperresponders and nonresponders having one or two parents with metabolic disorders.

### Role of the Funding Sources

None of the funding sources had any role in the design of the study; the collection, analysis, and interpretation of the data; or the decision to submit the manuscript for publication.

## RESULTS

### Changes in Plasma Triglyceride Levels during Isotretinoin Therapy

Isotretinoin-associated changes in fasting plasma triglyceride level ranged from  $-0.95$  mmol/L ( $-84$  mg/dL) to  $3.75$  mmol/L ( $332$  mg/dL). Average change was  $0.57 \pm 0.67$  mmol/L ( $50 \pm 59$  mg/dL). Compared with nonresponders ( $n = 100$ ), hyperresponders ( $n = 102$ ) had similar pretreatment body weight ( $63.3 \pm 9.6$  kg vs.  $64.4 \pm 11.4$  kg;  $P > 0.2$ ) and plasma levels of total cholesterol ( $4.6 \pm 0.8$  mmol/L [ $176 \pm 32$  mg/dL] vs.  $4.8 \pm 1.0$  mmol/L [ $186 \pm 37$  mg/dL];  $P = 0.07$ ) and triglycerides ( $1.1 \pm 0.4$  mmol/L [ $101 \pm 38$  mg/dL] vs.  $1.2 \pm 0.5$  mmol/L [ $104 \pm 42$  mg/dL];  $P > 0.2$ ). Hyperresponders had received a 10% higher dosage of isotretinoin ( $0.53 \pm 0.11$  mg/kg of body weight vs.  $0.59 \pm 0.14$  mg/kg of body weight;  $P = 0.003$ ).

### Characteristics of Hyperresponders and Nonresponders When Not Receiving Isotretinoin Therapy

Hyperresponders and nonresponders were reevaluated  $3.8 \pm 2.5$  years (median, 4 years) after completion of isotretinoin therapy. Mean age was  $27.4 \pm 7.2$  years (range, 16 to 49 years; median, 26 years). In contrast to the pretreatment period, hyperresponders had a higher body mass index and higher fasting plasma concentrations of total cholesterol and triglycerides than nonresponders (Table 1). Moreover, waist-to-hip ratio; fat mass content; systolic blood pressure; plasma levels of low-density lipoprotein cholesterol, apolipoprotein B,

and insulin; ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol; and ratio of insulin to glucose were all higher in hyperresponders.

To further characterize the relationship between the lipid response to isotretinoin therapy and the subsequent development of metabolic disorders, we performed logistic regression analysis, using age, sex, *apoE* genotype, and dose of isotretinoin as covariates (Figure 2). This analysis indicated that a previous elevation of 1.0 mmol/L or greater ( $\geq 89$  mg/dL) in plasma triglyceride levels during isotretinoin therapy was associated with an increased risk for hypertriglyceridemia (triglyceride level  $> 2.0$  mmol/L [ $> 177$  mg/dL]; odds ratio [OR], 4.8 [95% CI, 1.6 to 13.8]), hypercholesterolemia (cholesterol level  $> 6.5$  mmol/L [ $> 252$  mg/dL]; OR, 9.1 [CI, 1.9 to 43]), truncal obesity (waist-to-hip ratio  $> 0.90$ ; OR, 11.0 [CI, 2.0 to 59]), and hyperinsulinemia (insulin–glucose ratio  $> 7.2$ ; OR, 3.0 [CI, 1.6 to 5.7]).

The metabolic syndrome is characterized by the aggregation of various disorders. We determined how many of five disorders were present in each participant while not receiving therapy. We considered hypertriglyceridemia ( $> 2.0$  mmol/L [ $> 177$  mg/dL]), hypercholesterolemia ( $> 6.5$  mmol/L [ $252$  mg/dL]), hyperinsulinemia (insulin–glucose ratio  $> 7.2$ ), elevated body weight (body mass index  $> 25$  kg/m<sup>2</sup>), and hypertension (systolic blood pressure  $\geq 140$  mm Hg, diastolic blood pressure  $\geq 90$  mm Hg, or both). Hyperresponders had, on average, two times more disorders than nonresponders ( $1.5 \pm 1.3$  vs.  $0.8 \pm 0.8$ ;  $P < 0.001$ ). Moreover, 40 of 102 hyperresponders had two or more of these conditions, compared with 13 of 100 nonresponders (adjusted odds ratio, 5.6 [CI, 2.5 to 12.4];  $P < 0.001$ ).

### Clinical Characteristics of the Parents

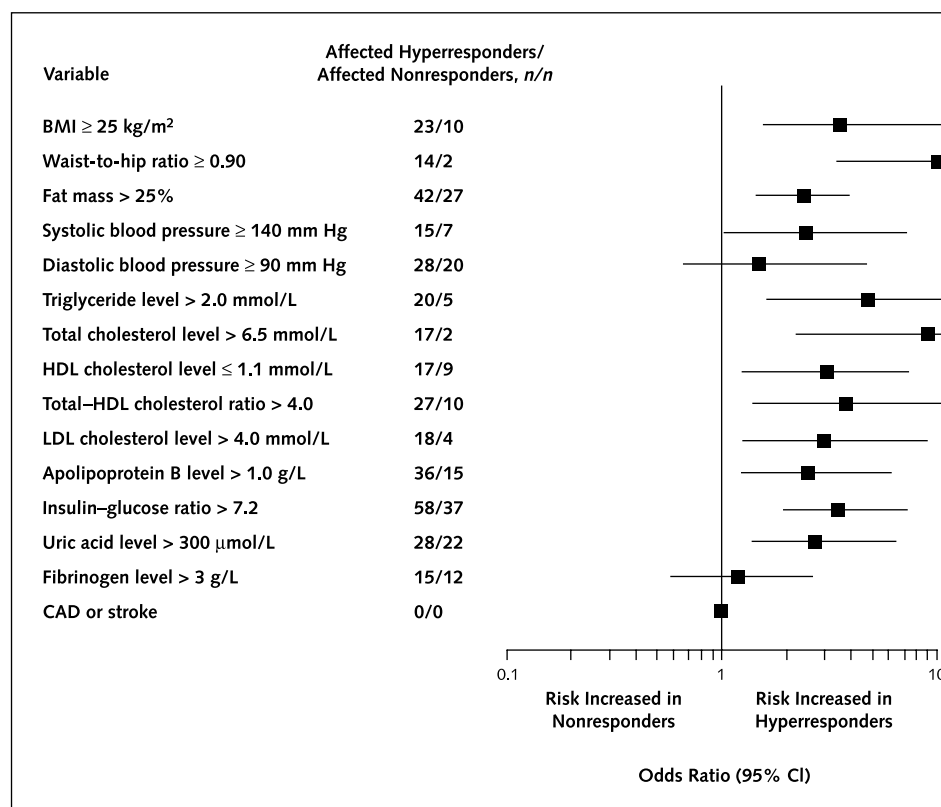
To explore the familial component of the lipid response to isotretinoin therapy, we also examined both parents of 71 hyperresponders and 60 nonresponders for markers of the metabolic syndrome. Both fathers and mothers of hyperresponders had higher plasma triglyceride levels and a higher ratio of total to HDL cholesterol than fathers and mothers of nonresponders (Table 1). In addition, the proportion of hyperresponders who had none, one, or two parents with hypertriglyceridemia

**Table 1. Characteristics of Hyperresponders and Nonresponders and Their Parents While Not Receiving Isotretinoin Therapy**

Characteristic	Hyperresponders (n = 102)	Nonresponders (n = 100)	P Value	Fathers of Hyperresponders (n = 71)	Fathers of Nonresponders (n = 60)	P Value
Age, y	28.1 ± 7.0	26.7 ± 7.3	0.17	55.8 ± 7.5	56.5 ± 7.4	>0.2
Sex (male/female), n/n	50/52	52/48	>0.2			
Body mass index, kg/m <sup>2</sup>	22.9 ± 3.5	21.7 ± 2.7	0.005	26.6 ± 4.4	26.3 ± 3.0	>0.2
Waist-to-hip ratio	0.80 ± 0.08	0.77 ± 0.06	0.02	0.94 ± 0.06	0.93 ± 0.06	>0.2
Fat mass, %	21.9 ± 7.1	19.5 ± 6.7	0.02	23.3 ± 7.5	23.0 ± 7.4	>0.2
Systolic blood pressure, mm Hg	125 ± 13	121 ± 10	0.03	137 ± 14	136 ± 17	>0.2
Diastolic blood pressure, mm Hg	85 ± 8	83 ± 7	0.11	93 ± 8	91 ± 8	0.14
Triglycerides, mmol/L (mg/dL)	1.5 ± 0.7 (132 ± 60)	1.0 ± 0.4 (91 ± 39)	<0.001	2.0 ± 1.5 (174 ± 134)	1.5 ± 0.7 (136 ± 65)	0.05
Total cholesterol, mmol/L (mg/dL)	5.1 ± 1.2 (197 ± 47)	4.7 ± 0.9 (180 ± 37)	0.004	6.3 ± 1.2 (246 ± 46)	6.0 ± 0.9 (234 ± 34)	0.10
HDL cholesterol, mmol/L (mg/dL)	1.5 ± 0.4 (58 ± 16)	1.6 ± 0.4 (63 ± 15)	0.05	1.4 ± 0.3 (55 ± 13)	1.5 ± 0.3 (58 ± 13)	0.16
LDL cholesterol, mmol/L (mg/dL)	2.9 ± 1.1 (112 ± 41)	2.6 ± 0.8 (99 ± 31)	0.01	4.0 ± 1.1 (157 ± 43)	3.8 ± 0.8 (148 ± 31)	>0.2
Ratio of total to HDL cholesterol	3.6 ± 1.1	3.0 ± 0.7	<0.001	4.8 ± 1.6	4.2 ± 1.1	0.01
Apolipoprotein B level, g/L	1.0 ± 0.3	0.8 ± 0.2	<0.001	1.3 ± 0.3	1.2 ± 0.2	0.08
Insulin, pmol/L	49 ± 48	38 ± 22	0.03	51 ± 38	41 ± 29	0.09
Insulin–glucose ratio	9.7 ± 10.0	7.2 ± 3.9	0.02	8.6 ± 6.5	7.2 ± 5.7	0.11
Uric acid, μmol/L	264 ± 66	250 ± 58	0.09	321 ± 60	303 ± 54	0.07
Fibrinogen, g/L	2.6 ± 0.5	2.4 ± 0.4	0.10	2.8 ± 0.7	2.8 ± 0.5	>0.2

\* Values presented with a plus/minus sign are the mean ± SD. HDL = high-density lipoprotein; LDL = low-density lipoprotein.

**Figure 2. Risk for metabolic disorders according to the previous lipid response to isotretinoin therapy for acne in 102 hyperresponders and 100 nonresponders.**



Odds ratios were calculated by using logistic regression analysis after adjustment for age, sex, *apoE* genotype, and dosage of isotretinoin. BMI = body mass index; CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein. To convert triglyceride values to mg/dL, divide by 0.0113; to convert total, HDL, and LDL cholesterol values to mg/dL, divide by 0.0259.

Table 1—Continued

Mothers of Hyperresponders (n = 71)	Mothers of Nonresponders (n = 60)	P Value
53.9 ± 5.5	52.8 ± 6.9	>0.2
25.0 ± 4.9	24.0 ± 3.9	>0.2
0.81 ± 0.08	0.79 ± 0.08	0.14
29.9 ± 8.3	29.3 ± 6.7	>0.2
137 ± 19	131 ± 15	0.07
88 ± 9	88 ± 9	>0.2
1.5 ± 0.6 (137 ± 56)	1.2 ± 0.4 (107 ± 39)	0.001
6.2 ± 1.1 (239 ± 44)	5.9 ± 0.9 (228 ± 37)	0.11
1.8 ± 0.4 (71 ± 16)	1.9 ± 0.4 (75 ± 16)	0.10
3.6 ± 1.1 (140 ± 43)	3.4 ± 0.9 (131 ± 38)	0.19
3.6 ± 1.1	3.2 ± 0.9	0.02
1.1 ± 0.3	1.0 ± 0.2	0.05
41 ± 28	35 ± 22	0.16
7.2 ± 4.3	6.5 ± 3.6	0.16
242 ± 62	226 ± 53	0.12
2.8 ± 0.7	2.8 ± 0.5	>0.2

was 57%, 34%, and 9%, respectively, compared with 78%, 22%, and 0% in nonresponders ( $P = 0.01$ ). Sixteen percent, 64%, and 20% of hyperresponders and 40%, 55%, and 5% of nonresponders had no parents, one parent, or both parents with a ratio of total to HDL cholesterol exceeding 4.0 ( $P = 0.002$ ). The odds ratios for having one or two parents with markers of the metabolic syndrome are described in **Figure 3**. In hyperresponders, the risk for having at least one parent with hypertriglyceridemia and a ratio of total to HDL cholesterol greater than 4.0 was 2.6 (CI, 1.2 to 5.7) and 3.5 (CI, 1.5 to 8.0), respectively. Overall, parents of hyperresponders had, on average, more disorders than parents of nonresponders ( $2.3 \pm 1.5$  vs.  $1.8 \pm 1.4$ ;  $P = 0.01$ ). In addition, 64 of 138 parents of hyperresponders had three or more disorders, compared with 39 of 114 parents of nonresponders ( $P = 0.03$ ) (adjusted odds ratio, 1.7 [CI, 1.0 to 2.9];  $P = 0.04$ ). Alcohol consumption and drug use (antihypertensive agents or hormone replacement therapy) did not differ between the two groups. Similar findings were observed when 19 parents who were taking lipid-lowering therapy were excluded from the analysis.

#### Molecular Analyses of Selected Gene Polymorphisms

To examine the genetic basis of the lipid response to isotretinoin therapy, we analyzed a series of common

sequence variants known to be associated with familial forms of lipid disorders (**Table 2**). A significant association was observed between the *apoE* gene and isotretinoin-induced elevation in plasma triglyceride levels. Both *apoE*  $\epsilon 2-$  and *apoE*  $\epsilon 4-$  containing genotypes were overrepresented among hyperresponders. In addition, the frequency of the *apoE*  $\epsilon 2$ ,  $\epsilon 3$ , and  $\epsilon 4$  alleles differed significantly among hyperresponders (14.0%, 70.5%, and 15.5%, respectively), nonresponders (6.5%, 85.0%, and 8.5%, respectively;  $P = 0.002$ ), and a population of 174 nondiabetic persons recruited locally (17) (10.7%, 82.1%, and 7.2%, respectively;  $P = 0.005$ ). The frequency of *apoE* alleles was similar in nonresponders and in the local population ( $P > 0.2$ ). The frequency of distribution of the sequence variants examined within the genes encoding *PPAR- $\gamma$* , *apoAI-CIII-AIV*, or *CYP7- $\alpha$*  was similar to that reported in the literature (13, 15, 16). Apart from the *XmnI* polymorphism within the *ApoAI* gene, the difference in the frequency of distribution of the various alleles or genotypes between hyperresponders and nonresponders did not reach statistical significance, and no significant association was detected on transmission disequilibrium tests (18).

#### DISCUSSION

Our study shows that young adults who previously had developed elevated plasma triglyceride levels during isotretinoin therapy for acne are at increased risk for future truncal obesity, hypercholesterolemia, hypertriglyceridemia, hyperinsulinemia, and hyperuricemia, all of which are markers of the metabolic syndrome (6–8). Hyperresponders were more likely than nonresponders to have one or two dyslipidemic parents. Finally, the lipid response to isotretinoin therapy was closely associated with the *apoE* gene. Taken together, these data are consistent with the hypothesis that isotretinoin exacerbates the phenotypic expression of a latent, partly familial and genetic predisposition to hyperlipidemia and the metabolic syndrome in hyperresponders. Conversely, nonresponders may be protected against these conditions.

This family-based study takes advantage of the adverse side effects of a particular drug to investigate the genetics of hyperlipidemia. We believe that this type of study may pave the way to a pharmacogenetic approach to familial combined hyperlipidemia and the metabolic syndrome and, possibly, to other complex traits. In ad-

dition, our data indicate that pharmacogenetics may prove useful in identifying patients with acne who are at increased risk for isotretinoin-induced hyperlipidemia.

We selected participants by using retrospective analysis of medical records. This approach was possible because dermatologists routinely monitor fasting lipid levels before and during isotretinoin therapy. Although this strategy was limited, it had several advantages. The metabolic syndrome is barely apparent in young adults at the age when they develop acne, and a follow-up period of several years would have been necessary to detect differences between hyperresponders and nonresponders in a prospective study. This strategy also enabled us to identify a large number of persons with acne who were previously treated with isotretinoin at a single medical center. Finally, this design allowed us to compare hyperresponders with nonresponders rather than with persons who had an average lipid response to isotretinoin. By increasing the contrast between the two groups, we were able to limit the sample size of participants

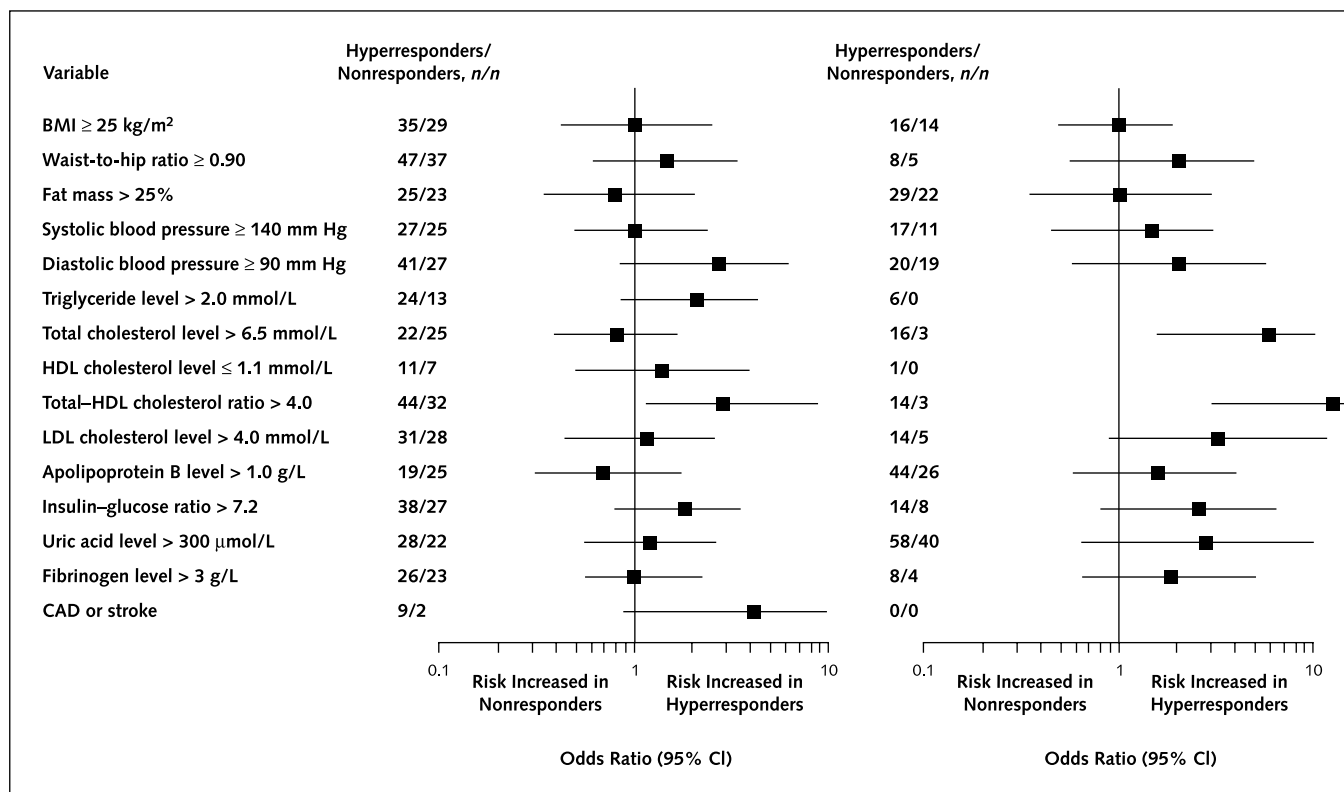
who were reevaluated when not receiving therapy. However, we cannot formally exclude the possibility that our design may have slightly overestimated the association between the lipid response to isotretinoin therapy and the subsequent risk for hyperlipidemia and the metabolic syndrome.

In summary, our study shows that persons who become hypertriglyceridemic during isotretinoin therapy for acne, as well as their parents, are at increased risk for hyperlipidemia and the metabolic syndrome. We propose that close, long-term monitoring of blood pressure, plasma lipid levels, and body weight should be performed for such persons.

From CHUV University Hospital, University Medical Policlinic, and University of Lausanne, Lausanne; and Kantonsspital, St-Gallen, Switzerland.

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Figure 3. Risk for metabolic disorders in parents of 71 hyperresponders and 60 nonresponders.



Logistic regression analysis was used to calculate the risk for having one (left) or two (right) parents with metabolic disorders. BMI = body mass index; CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein. To convert triglyceride values to mg/dL, divide by 0.0113; to convert total, HDL, and LDL cholesterol values to mg/dL, divide by 0.0259.

**Table 2. Genotype Frequency of Selected Genes in 102 Hyperresponders and 100 Nonresponders\***

Gene	Genotype	Hyperresponders, %	Nonresponders, %	P Value†	Odds Ratio (95% CI)‡	P Value†
ApoE	E3-E3	50	72	0.006	1.0 (reference)	
	E2-E2, E2-E3, or E2-E4	25	13		2.6 (1.2–5.6)	0.01
	E3-E4 or E4-E4	25	15		2.6 (1.2–5.4)	0.02
PPAR- $\gamma$	Pro12-Pro12	81	88	0.14	1.0 (reference)	
	Pro12-Ala12 or Ala12-Ala12	19	12		1.7 (0.8–3.6)	0.20
CYP7- $\alpha$	–278A–278A	34	37	>0.2	1.0 (reference)	
	–278A–278C	44	50		0.6 (0.2–1.3)	0.17
	–278C–278C	22	13		0.5 (0.2–1.2)	0.13
ApoA1-Msp1§	M1-M1	62	59	>0.2	1.0 (reference)	
	M1-M2 or M2-M2	38	41		0.9 (0.5–1.7)	>0.2
ApoA1-Xmn1§	X1-X1	83	68	0.01	1.0 (reference)	
	X1-X2 or X2-X2	17	32		0.5 (0.2–1.0)	0.04
ApoC3-Sst1§	S1-S1	74	82	0.09	1.0 (reference)	
	S1-S2 or S2-S2	26	18		1.6 (0.8–3.3)	0.19

\* For technical reasons, genotypes were missing for 1 to 4 of 202 participants.

† Determined by using the chi-square test.

‡ Risk for being a hyperresponder in carriers of the rarer genotype, after adjustment for age, sex, and dosage of isotretinoin.

§ According to the nomenclature in reference 16.

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