

Adverse effects of danazol prophylaxis on the lipid profiles of patients with hereditary angioedema

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Background: Hereditary angioedema (HAE) is a rare disorder caused by the deficiency of the C1-inhibitor gene (*C1INH*). Patients experience recurrent bouts of edema, which can occur in almost any region of the body. As regards the treatment of the disease, danazol (an attenuated androgen) is used, among other agents, for long-term prophylaxis.

Objective: The aim of this study was to investigate the possible adverse effects of danazol on serum lipid profile, as well as to ascertain whether danazol treatment is associated with an increased risk of atherosclerosis.

Methods: Serum concentrations of total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, apolipoprotein A-I, apolipoprotein B-100, and lipoprotein(a) were compared between danazol-treated patients with HAE and 2 control groups (ie, patients who did not receive long-term danazol prophylaxis and untreated healthy subjects). **Results:** Serum concentrations of HDL ($P = .0002$ and $P < .0001$) and apolipoprotein A-I ($P = .0015$ and $P < .0001$) were significantly lower, whereas LDL ($P = .0129$ and $P = .0127$) and apolipoprotein B-100 ($P = .0456$ and $P = .0013$) were higher in the danazol-treated patients compared with the 2 control groups, respectively. No significant difference was found in total cholesterol, triglyceride, or lipoprotein(a) levels. Patients who received danazol had an 11.6 (95% CI, 2.7-49.7) times higher risk for abnormally low HDL levels and a 4.4 (95% CI, 1.2-16.0) times lower risk for high LDL concentrations.

Conclusions: Our findings indicate that the long-term use of danazol is associated with an increased risk for early atherosclerosis in patients with HAE. Consequently, monitoring of HDL and LDL levels at regular intervals is recommended during follow-up. (J Allergy Clin Immunol 2005;115:864-9.)

Key words: Hereditary angioedema, danazol, adverse effects, lipids, high-density lipoprotein, low-density lipoprotein, atherosclerosis

Abbreviations used

Apo A-I: Apolipoprotein A-I
Apo B-100: Apolipoprotein B-100
C1-INH: C1 Esterase inhibitor
HAE: Hereditary angioedema
HDL: High-density lipoprotein
LDL: Low-density lipoprotein
Lp(a): Lipoprotein(a)

Hereditary angioedema (HAE), first described by Quincke in 1882¹ and named by Osler in 1888,² is a rare disease caused by deficiency of the C1 esterase inhibitor gene (*C1INH*). Patients experience recurrent bouts of edema, which can occur in almost any region of the body. The severity of edematous attacks ranges from swelling of the skin to potentially life-threatening laryngeal edema with complete airway obstruction. The disease has been reviewed in many journals.³⁻⁵ The treatment of HAE consists of long-term prophylaxis to prevent edematous attacks and emergency therapy during attacks to avert life-threatening complications.^{4,5} In clinical practice, attenuated androgens (danazol or alternatives) and antifibrinolytic agents (ϵ -aminocaproic acid or tranexamic acid) are the drugs of choice for long-term prophylaxis, whereas C1-INH concentrate is administered as emergency therapy.^{4,5} Danazol and tranexamic acid are also used in the management of minor attacks (only in mild subcutaneous swellings of the extremities) by increasing the daily dose or starting dose as early as the prodromal symptoms occur, and danazol is used preventively during maxillofacial or dental procedures as short-term prophylaxis.⁶ The severity and frequency of attacks vary among patients, and long-term prophylaxis or (occasionally) medical treatment is not always necessary. The use of danazol as long-term prophylaxis is common in most countries.^{4,5}

Danazol, a 17- α -alkylated attenuated androgen, is able to prevent the manifestations of HAE.⁷ However, it has diverse side effects, and therefore adequate prophylaxis and follow-up care are indispensable to prevent adverse reactions. Cicardi et al⁸ attribute the side effects of danazol to its residual hormonal activity, 17- α -alkylation, and changes in lipoprotein levels. The effects resulting from residual hormonal activity and 17- α -alkylation of the attenuated androgen have been described in various

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TABLE I. Descriptive statistics of patients with HAE and healthy control subjects

	Patients with HAE		Healthy Control subjects
	Taking danazol	Not taking danazol	
No. of individuals, n	37	27	66
Age, y	40.0 (32.0-47.5)	36.0 (22.0-49.0)	36.0 (20.0-49.0)
M/F sex, %	18/19 (48.6%/51.4%)	9/18 (33.3%/66.7%)	28/38 (42.4%/57.6%)
HAE severity, class	2.0 (1.0-2.0)	3.5 (1.0-4.5)	—
Duration of therapy, mo	45.1 (23.4-84.9)	25.08 (19.6-44.3)	—
Medication			
No medication, n (%)	0 (0)	7 (25.9)	66 (100)
Danazol long-term prophylaxis, n (%)	37 (100)	0 (0)	—
Daily dose, mg/d	100.0 (81.7-169.2)	—	—
Danazol occasionally, n (%)	0 (0)	2 (7.4)	—
Dose, mg/occasion	—	200.0 (200.0-200.0)	—
TA long-term prophylaxis, n (%)	0 (0)	6 (22.2)	—
Daily dose, g/d	—	1.99 (1.23-2.00)	—
TA occasionally, n (%)	0 (0)	12 (44.4)	—
Dose, g/occasion	—	2.50 (2.00-3.00)	—

Values are presented as absolute numbers (percentages) and medians (interquartile ranges).

TA, Tranexamic acid.

reports,⁸⁻¹⁵ but only meager data are available on the changes in lipid and lipoprotein levels in patients with HAE undergoing long-term danazol prophylaxis.¹⁶ Danazol has been shown to alter lipoprotein profiles of women treated for endometriosis, but to our knowledge, similarly detailed data on patients with HAE are unavailable.¹⁷⁻²⁰ The use of danazol in HAE differs from that in endometriosis. In HAE daily doses are 3- to 20-fold lower (33-200 mg compared with 400-600 mg in endometriosis), the duration of the therapy is longer (potentially life-long prophylaxis compared with 2-6 months in endometriosis), and men, who are at a higher risk of atherosclerosis, are also treated if they have HAE, whereas this is obviously not the case in endometriosis.

Therefore the aim of our study was to characterize the lipid and lipoprotein profiles of patients with HAE undergoing long-term prophylaxis with danazol and to compare their results with those of patients with HAE who had never received long-term androgen treatment, as well as with those of untreated healthy control subjects. Serum concentrations of total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, apolipoprotein A-I (Apo A-I), apolipoprotein B-100 (Apo B-100), and lipoprotein(a) (Lp[a]) were determined in this study.

METHODS

Study subjects

All 64 adult patients with HAE (37 women and 27 men; age, 18-71 years) registered at and managed by the Hungarian HAE Center until November 2003 were included in this study.²¹ The history of sudden edematous attacks, family history, and laboratory findings of low functional activity and antigen concentration of C1-INH and low C4 levels established the tentative diagnosis, which was confirmed by detecting the mutation of the *C1INH* gene.²² In our clinical practice,

danazol (according to the Budapest protocol^{15,23}) and tranexamic acid (not available in the United States) are the drugs of choice for long-term prophylaxis, whereas C1-INH concentrate is administered in acute attacks. In 37 of 64 patients, long-term danazol prophylaxis was necessary to prevent the occurrence of occasionally life-threatening attacks. The duration of treatment ranged from 5 to 195 months, and danazol was administered in daily doses of 33 to 200 mg. The other 27 patients, who have never received prolonged prophylactic treatment with danazol, were enrolled as HAE-positive control subjects. The details of the medication used in the HAE control group are presented in Table I. Disease severity class of patients was determined according to the criteria for evaluating disease severity developed by experts from the Novel Methods for Predicting, Preventing, and Treating Attacks in Patients with Hereditary Angioedema group and as described by Agostoni et al⁴ in the first year of treatment (Table I). It is important to note that patients receiving long-term danazol had more severe disease (classified as severe [class 1] or moderate [class 2]) compared with the HAE control group ($P < .0001$, χ^2 test for trend), the severity of which ranged from asymptomatic (class 5) to severe (class 1). The reason is that the indication for continuous danazol therapy is dependent on disease severity (ie, patients with more severe disease need long-term treatment with danazol) and is therefore a major determinant in severity classification. Blood samples of patients were collected between December 2000 and November 2003 and stored deep frozen at -70°C until laboratory testing. All samples were obtained during regular control visits of patients; that is, none of them was suffering from an acute angioedematous attack. Sixty-six age- and sex-matched healthy individuals (38 women and 28 men; age, 22-72 years) served as HAE-negative control subjects. None of them had clinical or laboratory signs suggestive of HAE. Table I summarizes the descriptive statistics of patients and control subjects. The study was approved by the institutional review board, and all subjects provided informed consent.

Laboratory procedures

Laboratory measurements of lipid parameters were performed on computerized laboratory analyzers: Cobas Integra 400 (Roche, Basel, Switzerland) was used for measuring total cholesterol, triglyceride,

TABLE II. Lipid and lipoprotein concentrations of patients with HAE and healthy control subjects

	Patients with HAE		Healthy control subjects
	Taking danazol	Not taking danazol	
N	37	27	66
TC, mmol/L	5.17 (4.24-6.37)	5.03 (3.97-5.59)	5.11 (4.44-5.81)
<i>P</i> value vs control subjects	.4312	.2639	—
<i>P</i> value vs not taking danazol	.2859	—	—
HDL, mmol/L	1.10 (0.93-1.37)	1.38 (1.26-1.74)	1.54 (1.29-1.83)
<i>P</i> value vs control subjects	<.0001	.3628	—
<i>P</i> value vs not taking danazol	.0002	—	—
LDL, mmol/L	3.40 (2.81-4.12)	2.72 (2.04-3.37)	2.79 (2.41-3.64)
<i>P</i> value vs control subjects	.0127	.3241	—
<i>P</i> value vs not taking danazol	.0129	—	—
Triglycerides, mmol/L	1.20 (0.93-1.54)	0.89 (0.68-1.80)	1.03 (0.76-1.34)
<i>P</i> value vs control subjects	.0928	.6265	—
<i>P</i> value vs not taking danazol	.1675	—	—
Lp(a), mg/dL	6.76 (1.71-32.82)	6.37 (2.30-37.49)	2.82 (1.24-16.95)
<i>P</i> value vs control subjects	.2344	.0377	—
<i>P</i> value vs not taking danazol	.3955	—	—
Apo A-I, g/L	1.23 (1.04-1.45)	1.50 (1.36-1.71)	1.57 (1.40-1.82)
<i>P</i> value vs control subjects	<.0001	.2376	—
<i>P</i> value vs not taking danazol	.0015	—	—
Apo B-100, g/L	0.94 (0.80-1.19)	0.80 (0.55-1.01)	0.79 (0.66-0.96)
<i>P</i> value vs control subjects	.0013	.8061	—
<i>P</i> value vs not taking danazol	.0456	—	—

Values are presented as absolute numbers and medians (interquartile ranges). *P* values were calculated with the Mann-Whitney nonparametric test.
TC, Total cholesterol.

Apo A-I, and Apo B-100 concentrations, and Cobas Mira (Roche) was used for measuring HDL. LDL was calculated according to the Friedewald formula.²⁴

Lp(a) quantification was performed by means of double-antibody ELISA with an affinity-purified polyclonal rabbit anti-apolipoprotein(a) antibody for coating and the horseradish peroxidase-conjugated mAb 1A2 for detection (Boehringer Mannheim, Mannheim, Germany), as described elsewhere.²⁵ The antibody recognizes an epitope of the repetitive K-IV motif of apolipoprotein(a) and does not cross-react with plasminogen.²⁶ Commercially available Lp(a)-positive plasma, Human Lp(a) Reference Standard (IMMUNO Ag, Vienna, Austria), served as the standard.

Two atherogenic indices, ratios of LDL/HDL and Apo B-100/Apo A-I, were calculated and used as additional indices to characterize the abnormality of lipid metabolism.

Statistical analysis

Calculations were performed with SPSS for Windows 11.5.1 (SPSS Inc, Chicago, Ill) and Prism 4.01 (GraphPad Software, San Diego Calif). Because many variables had non-Gaussian distributions, we used the Mann-Whitney nonparametric test for between-group comparisons, the Spearman rho coefficient to calculate correlations, and the χ^2 test for trend. Multiple logistic regression analyses were also performed. Values presented in the text are presented as medians with interquartile ranges.

RESULTS

Serum lipid and lipoprotein profiles of patients and control subjects

Determining the lipid and lipoprotein profiles of the study groups revealed highly significant differences between patients with HAE receiving long-term danazol

prophylaxis and the 2 control groups. Serum HDL and Apo A-I levels were lower and the concentrations of LDL and Apo B-100 were higher in the danazol group, whereas total cholesterol, triglyceride, and Lp(a) levels did not differ either from those of HAE-positive or from those of healthy (HAE-negative) control subjects. We found slightly higher Lp(a) levels in HAE-positive control subjects (Table II).

The 2 atherogenic indices, ratios of LDL/HDL and Apo B-100/Apo A-I, were also significantly higher in the danazol-treated group compared with those in both control groups. No significant difference was observed between the untreated HAE-positive control subjects and the healthy subjects, showing that HAE alone is not responsible for the abnormalities of lipid metabolism (Fig 1).

Risks for abnormal HDL and LDL levels in patients with HAE, regardless of other factors

Multiple logistic regression analyses were performed to estimate the risks of abnormal HDL and LDL levels as an adverse effect of danazol therapy in patients with HAE. HDL concentrations of lower than 1.10 mmol/L (in model A) and LDL concentrations of at least 2.70 mmol/L (in model B) were considered abnormal. Adjustments were made for parameters that differed in the 2 patient groups (HDL, LDL, Apo A-I, and Apo B-100; Table II). However, HDL levels showed a strong positive correlation with Apo A-I levels ($\rho = 0.8968$, $P < .0001$), whereas LDL levels correlated with Apo B-100 levels ($\rho = 0.9263$, $P < .0001$) in the patients. Therefore Apo A-I and Apo B-100 were omitted from the analyses in

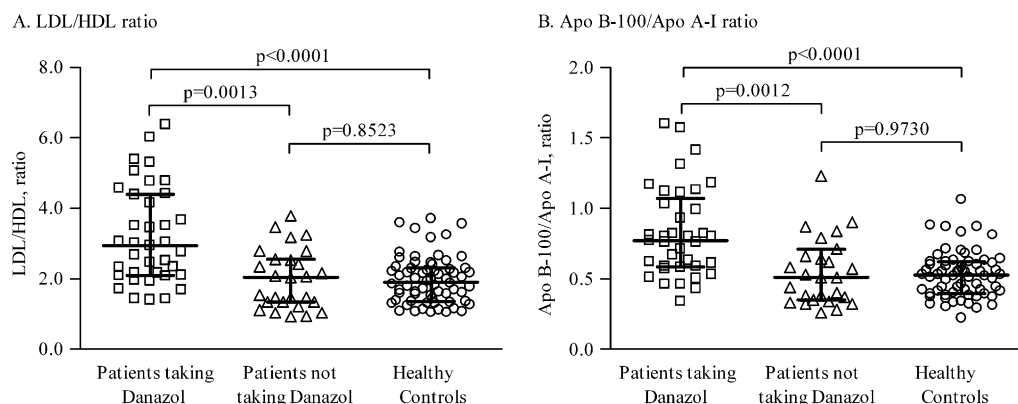


FIG 1. Atherogenic indices of patients and control subjects. Both atherogenic indices, ratios of LDL/HDL (**A**) and Apo B-100/Apo A-I (**B**), were significantly higher in patients receiving long-term danazol prophylaxis than in the 2 control groups. No significant difference was found between untreated HAE-positive control subjects and healthy subjects.

TABLE III. Odds ratios of abnormal HDL and LDL levels in patients with HAE, regardless of other lipid parameters

	B	SE	Significance	OR	95% CI for OR
HDL					
HDL low-high*	2.447	0.983	.0010	11.556	2.685-49.749
LDL	1.346	0.721	.0622	3.840	0.934-15.793
Apo B-100	-2.516	2.265	.2667	0.081	0.001-6.8849
Constant	-2.345	0.983	.0171	0.096	
LDL					
LDL high-low†	1.474	0.663	.0264	4.365	1.189-16.022
HDL	-1.094	1.608	.4962	0.335	0.014-7.824
Apo A-I	-1.780	2.160	.4099	0.169	0.002-11.623
Constant	1.815	1.538	.2381	6.140	

*Low values were less than 1.10 mmol/L, and high values were 1.10 mmol/L or greater for HDL in model A.

†High values were 2.70 mmol/L or greater, and low values were less than 2.70 mmol/L for LDL in model B.

models A and B, respectively. Thus HDL low-high values were adjusted to LDL and Apo B-100 levels, whereas LDL high-low values were adjusted to HDL and Apo A-I. The dependent variable was the use of long-term danazol prophylaxis in both models.

The adjusted odds ratio was 11.556, with a 95% CI of 2.685 to 49.749 ($P = .0010$) for abnormal HDL concentrations and 4.365 (95% CI, 1.189-16.022; $P = .0264$) for high LDL levels of patients with HAE undergoing long-term danazol prophylaxis (Table III).

DISCUSSION

We demonstrated that long-term danazol prophylaxis significantly modifies the lipid and lipoprotein profiles of patients with HAE. The study population included 2 control groups: (1) patients with HAE who have never received long-term danazol prophylaxis and (2) healthy subjects without suspected or diagnosed HAE. Both groups were compared with patients with HAE receiving

continuous androgen prophylaxis. We found that the long-term use of danazol decreases HDL levels and increases LDL levels as an adverse effect, whereas total cholesterol and triglyceride concentrations remain unchanged. Parallel with these changes, the serum concentration of Apo A-I decrease, whereas Apo B-100 levels increase. Drug therapy had no influence on Lp(a) levels. Atherogenic indices calculated from these parameters (LDL/HDL and Apo B-100/Apo A-I ratios) increased as an effect of the attenuated androgen. According to our results, patients with HAE receiving long-term danazol prophylaxis are at 11.6 and 4.4 times higher risk of abnormally low HDL or high LDL concentrations, respectively, regardless of other affected parameters.

Although the adverse effects of danazol on lipid metabolism were thoroughly studied in endometriosis,¹⁷⁻²⁰ insufficient data are available in HAE.^{8,16} Hoogerbrugge et al¹⁶ report on danazol-related changes of lipoprotein profiles by presenting lipid concentrations and postheparin lipase activities of 5 patients with HAE. Their results are similar to the data presented herein, with one exception:

they reported high total cholesterol levels explained by high LDL levels. Cicardi et al⁸ summarized the side effects of attenuated androgens in HAE and found unchanged total cholesterol concentrations during the treatment of 60 patients with HAE. Their report was not focused on the detailed characterization of lipid profiles but nevertheless warns of the possible risk for atherosclerosis in patients receiving long-term androgen treatment.

Danazol possibly affects 3 essential processes of lipoprotein metabolism: (1) increase of the activity of the hepatic lipase, (2) inhibition of LDL receptors, and (3) decrease of the activity of the lecithin cholesterol acyltransferase.²⁰ This leads to the following: (1) increased conversion of intermediate-density lipoprotein to LDL and of HDL₂ to the smaller HDL₃ (which is catabolized faster), (2) decreased elimination of circulating LDL particles, and (3) reduced formation of HDL₂. Thus LDL (and its major structural protein Apo B-100) levels increase and HDL (including Apo A-I and Apo A-II) levels decrease dramatically, and the LDL/HDL ratio (as well as the Apo A-I/Apo B-100 ratio) increases.^{17-20,27} These changes are reversible: lipid and lipoprotein parameters return to normal within 8 weeks of discontinuing therapy in patients with endometriosis.^{19,20} Therefore the abnormalities of lipid metabolism are not regarded as important risk factors for atherosclerosis in patients with endometriosis. These patients do not need lifelong danazol treatment, and the risk of cardiovascular disease is higher during the use of androgen treatment only.

Lp(a) is an important and independent risk factor for atherosclerosis: high concentrations are associated with rapid progression of vascular disease.^{28,29} Lp(a) consists of an LDL-like core and apolipoprotein(a). In the present study, we demonstrated that long-term danazol prophylaxis does not reduce Lp(a) levels in HAE. Crook et al¹⁸ found that danazol decreases the Lp(a) levels of patients with endometriosis. In a later study, Crook et al³⁰ demonstrated that compared with levels in control subjects, the serum level of Lp(a) was 5 times higher in patients with endometriosis, possibly because of an immune response inherent to this disorder. Our findings, along with those of Crooke et al,^{18,30} are in agreement with the assumption that in endometriosis, where baseline Lp(a) levels are increased because of the dysregulation of Lp(a) metabolism, danazol lowers Lp(a) concentration by controlling the inflammatory response. This is not the case in HAE, where baseline Lp(a) levels are normal and danazol has no significant influence on Lp(a) levels. Thus danazol does not lower Lp(a) concentration in HAE, and therefore it does not reduce the risk of atherothrombotic complications either.

We conclude that long-term danazol prophylaxis should be considered a significant risk factor for atherosclerosis in patients with HAE. Unfavorable changes of serum lipid profile might lead to increased plaque formation in the arteries and thereby to the initiation or worsening of atherosclerosis. Seemingly, danazol does not reduce Lp(a) levels, and therefore patients are not protected from thromboembolic complications. In fact, danazol affects coagulation parameters unfavorably.

Rheologic changes occurring during treatment indicate higher risks of arterial complications in endometriosis.³¹ However, this finding has to be interpreted with caution because the deficiency of the *C1INH* gene per se affects the coagulation system, and therefore further studies are necessary to investigate its consequences in HAE. In addition to influencing lipid metabolism and blood coagulation, danazol affects further risk factors as well. Cicardi et al⁸ found a higher prevalence of hypertension, a major risk factor for cardiovascular complications and stroke, among patients with HAE treated with danazol. These data are in agreement with the assumption that long-term danazol treatment is proatherogenic. However, it is important to stress that we observed changes only in biochemical markers during the present study but not in the actual state of atherosclerosis in our patients. It would be interesting and important to estimate the prevalence of advanced atherosclerosis by further clinical studies conducted on patients with HAE. Still, as recent studies have demonstrated, the complement system itself might play an important role in the pathogenesis of atherosclerosis,³² and we have no experimental or clinical data on possible mechanisms whereby the deficiency of *C1INH* function affects the atherosclerotic process. Again, our assumption on the probable proatherogenic adverse effect of danazol is based on unfavorable changes in the lipid profile of the patients and not on clinical evidence on the state of atherosclerosis.

The treatment and prevention of angioedematous attacks has improved during the last few decades and enabled many of the patients to live a better life. However, controlling various adverse effects of treatment is important to improve the quality of life of patients in the long term, as well as to protect them from early-onset atherosclerosis. We recommend continuous monitoring of HDL and LDL levels during the follow-up of danazol-treated patients with HAE. This is especially important because unchanging total cholesterol levels can mask pathologic changes in serum lipid profile, and abnormal lipid levels warrant appropriate intervention.

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