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Case Report

Collaborative Management of Estrogen-Induced Severe Hyperlipidemia in Transsexual Female

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Abstract

Estrogen therapy is commonly used in male to female transsexual individuals to replace endogenous sex hormones with desired sex hormones. We describe a 52 year old transsexual female who developed severe hypertriglyceridemia, without symptoms of pancreatitis, while taking esterified estrogen (Menest®) 3.75 mg daily. After discontinuing estrogen, starting rosuvastatin 20 mg daily and following a no fat diet, the patient's triglycerides fell to 983 mg/dL. Subsequent changes, resulting in a lipid medication regimen of omega-3 fatty acids 4 g daily and gemfibrozil 600 mg twice daily, led to a lipid panel of: TC = 142 mg/dL; TG=361 mg/dL; HDL-C = 33 mg/dL; LDL-C = 37 mg/dL while on transdermal estrogen. Although it is known that oral estrogens may lead to hypertriglyceridemia, to our knowledge this is only the second case report of estrogen-induced hypertriglyceridemia in a transsexual female. Management of hypertriglyceridemia in this patient was complicated by the financial status of the patient; therefore, the patient was managed within a family medicine clinic in collaboration with a clinical pharmacist and an outside endocrinologist. This case emphasizes an important, yet often overlooked, adverse effect of hypertriglyceridemia with oral estrogen therapy in this population. The risk of pancreatitis from elevated triglycerides is real and can be life-threatening; thus, monitoring for hypertriglyceridemia should not be overlooked, and when hypertriglyceridemia is present transdermal estrogen should be used and monitored.

Keywords: Hypertriglyceridemia; Estrogen; Transsexual; Triglycerides; Cholesterol

Abbreviations

TC: Total Cholesterol; TG: TriGlycerides; HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; mg: milligrams; dL: deciliter; DHA: Docosahexaenoic Acid; EPA: Eicosapentaenoic Acid; DES: DiEthylStilbestrol; WPATH: World Professional Association for Transgender Health

Case Presentation

A 52 year old, 74 inch, 114kg, Caucasian biological male who self-identifies as a female was referred to pharmacotherapy clinic for a pharmacoeconomic evaluation due to issues affording her estrogen therapy. She had not been able to afford gender reassignment surgery due to unemployment. She expressed concern regarding recent laboratory results and reported very elevated total cholesterol and triglycerides levels. Upon review, her previous laboratory values from one week prior were: total cholesterol (TC) = 1298 mg/dL, high density lipoprotein cholesterol (HDL-C) = 60 mg/dL, and triglycerides (TG) = 7018 mg/dL. A fasting lipid panel was repeated and revealed the following: TC = 1142 mg/dL; HDL-C = 50 mg/dL; TG = 9255 mg/dL (Table 1). She denied abdominal pain and xanthomatosis. Laboratory values for kidney and liver function were all within normal limits. The patient reported no signs or symptoms of pancreatitis.

A review of diet revealed the patient typically skipped breakfast and occasionally skipped lunch. When she did eat lunch she ate a peanut butter or turkey sandwich on multi-grain bread. The night prior to the most recent fasting lipid panel, the patient had eaten 2 homemade hamburgers with mustard, pickles, and barb-b-que sauce for dinner. She occasionally snacked on chips and ate out about 2 times per month (at fast food restaurants). Her diet was significantly dictated by her limited financial resources, and she reported spending ~$120 per month on food.

The patient's past medical history was significant for hypertension and hearing loss. Her family history was significant for high cholesterol and colon cancer. The patient denied alcohol and tobacco use.

She was taking oral esterified estrogen (Menest®) 3.75 mg daily, medroxyprogesterone 5 mg daily 7 days of every month, spironolactone 25 mg four times daily and olmesartan-hydrochlorothiazide 20-12.5 mg daily. The patient reported no known drug allergies. She was not on any lipid-lowering medications at the time of her laboratory evaluation. She reported using rosuvastatin in the past but discontinuing it due to fatigue. She was uncertain when she took rosuvastatin and what dose she had taken. The patient reported taking oral estrogen for years, but she could not quantify an exact duration. She reported when she was in school to become a medical assistant, the instructor would use her blood as an example as it would become lactescent when it sat overnight.

Due to financial limitations, she was unable to afford referral an endocrinologist and was therefore managed within the family medicine setting. Management was a collaborative effort among a family medicine physician, nurse practitioner, clinical pharmacist

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Table 1: Fasting Lipid Panel Trends and Medication Regimen.

Date	1/31/2013	2/7/2013	2/19/2013	2/26/2013	3/11/2013	3/19/2013	3/26/2013	4/2/2013	4/30/2013
TC (mg/dL)	1298	1142	4425	267	123	111	137	123	98
TG (mg/dL)	7018	9255	2165	983	435	402	429	474	262
HDL-C (mg/dL)	60	50	25	27	32	34	37	34	33
LDL-C (mg/dL)	UTC	UTC	UTC	UTC	UTC	UTC	UTC	UTC	13
Treatment Regimen	None	None	Rosuvastatin 20 mg daily	Rosuvastatin 20 mg daily	Rosuvastatin 40 mg daily	Rosuvastatin 40 mg daily Lovaza 2 g BID	Rosuvastatin 40 mg daily Lovaza 2 g BID	Rosuvastatin 40 mg daily Lovaza 2 g BID	Rosuvastatin 40 mg daily OTC fish oil 4 g daily
Treatment Regimen Changes	None	Started rosuvastatin 20 mg daily	None	Increased rosuvastatin to 40 mg daily Prescribed fenofibrate 134 mg daily	Fenofibrate 134mg daily started by patient; discontinued after 1 day due to rash Started on Lovaza 2 g BID	None	None	None	Rosuvastatin decreased to 10 mg daily

Table 1: Continuation.

Date	5/23/2013	6/14/2013	7/5/2013	8/16/2013	1/21/2014	3/18/2014
TC (mg/dL)	126	132	147	117	117	142
TG (mg/dL)	370	312	309	250	306	361
HDL-C(mg/dL)	35	36	39	34	30	33
LDL-C(mg/dL)	17	34	46	33	25.8	36.8
Treatment Regimen	Rosuvastatin 10 mg daily, OTC fish oil 4 g daily	Rosuvastatin 10 mg daily, OTC fish oil 4 g daily	Rosuvastatin 10 mg daily, OTC fish oil 4 g daily	Rosuvastatin 10 mg daily, OTC fish oil 4 g daily	Rosuvastatin 10 mg daily, OTC fish oil 4 g daily	Gemfibrozil 600 mg BID, OTC fish oil 4 g daily
Treatment Regimen Changes	Patient refusing gemfibrozil	Patient refusing gemfibrozil	Patient refusing gemfibrozil	Patient refusing gemfibrozil	Discontinued rosuvastatin Started gemfibrozil 600 mg BID	Referred to endocrinologist

HDL-C = high-density lipoprotein cholesterol; ; LDL-C = low-density lipoprotein cholesterol ;TC = total cholesterol; TG = triglycerides; UTC = unable to calculate

and an outside endocrinologist. She was started on a no fat diet (e.g. vegetables, fruits, brown rice) and rosuvastatin 20 mg daily as the clinic had free samples available. Oral estrogen was stopped. She was instructed to return to clinic for fasting lipid panels every 3 days until her triglycerides fell to less than 1000 mg/dL. Due to patient specific limitations, the patient opted to get fasting lipid panels measured once weekly. After approximately 3 weeks, the patient's triglycerides fell to 983mg/dL, fenofibrate 134 mg daily was prescribed, and rosuvastatin was increased to 40 mg daily. The patient was unable to pick up fenofibrate, but after another 2 weeks of rosuvastatin 40 mg daily, the patient's triglycerides fell to 435 mg/dL. At this time, transdermal estradiol was initiated, and a moderate amount of fat was slowly reintroduced into her diet. When the patient was able to obtain fenofibrate, it was discontinued after 1 day due to the development of a rash. Omega 3 fatty acids were initiated. The patient was initially started on Lovaza® 2 g twice daily, but she then switched to over the counter fish oil 4 grams daily after her free samples were exhausted. The patient was instructed to take 4 grams of docosahexaenoic acid/eicosapentaenoic acid (DHA/EPA). Over the next several months, rosuvastatin was decreased to 10 mg daily and then discontinued (due to low density lipoprotein cholesterol (LDL-C) levels ranging from 13-46 mg/dL) and gemfibrozil 600 mg twice daily was initiated. After 4 weeks of gemfibrozil and omega-3 fatty acids, her fasting lipid panel had improved: TC = 142 mg/dL; TG=361 mg/dL; HDL-C = 33 mg/dL; LDL-C = 37 mg/dL (Table 1).

Discussion

Hyperlipidemia, especially hypertriglyceridemia, is an established adverse effect of hormone replacement therapy. In particular, unopposed oral estrogen therapy may increase triglycerides by 40% [1]. Triglyceride levels greater than 1000-2000 mg/dL, or very severe hypertriglyceridemia, increase the risk of pancreatitis [2]. However, several clinical guidelines recommend treating with triglyceride lowering drug therapy in patients with elevated fasting triglyceride levels as low as 500 mg/dL [3-5].

Use of an estrogen agent with an antiandrogen (e.g. spironolactone, cyproterone acetate) is typically recommended for male to female transsexual individuals [6]. The main goals of this hormonal therapy approach are to reduce endogenous hormone levels leading to a reduction in sex characteristics of the patient's biological sex and to replace endogenous sex hormones with sex hormones of the desired sex [6]. The optimal dosages and formulations of hormone therapy in transsexuals is unknown, and little data exist regarding the long term safety of hormone therapy in these patients [7]. In a transsexual female who has not had her testes removed, the dosages of estrogen therapy needed to suppress testosterone to an extent that will result in the desired level of feminization is 4-8 times more than what would be used in a non-transsexual post-menopausal female for routine estrogen replacement therapy [8]. The effects of oral estrogen therapy on triglycerides are dose dependent [1]. In general, the long term effects of estrogen in male to female transsexuals is unknown

[7] and it is unknown if estrogen is harmful or beneficial overall in male to female transsexuals [6]. Therefore, the Endocrine Society recommends to evaluate medical conditions that may be worsened by hormonal treatment and to perform appropriate clinical monitoring in transsexual patients receiving hormonal therapy [6].

We conducted a Pub Med search for all published reports on estrogen induced hypertriglyceridemia and identified several case reports in biological females [9-15], but only one case report in a transsexual female [16]. This case report describes a 37 year old male taking conjugated estrogens 0.625 mg and cyproterone 2 mg and oral ethinyl estradiol 0.035 mg daily for 3 months prior to sex reassignment surgery. The patient developed severe necrotizing pancreatitis with initial triglycerides of 5174 mg/dL. The patient's triglyceride levels fell to 181 mg/dL at the time of discharge [16]. Another case report of estrogen induced pancreatitis describes a male with familial type V hyperlipoproteinemia after taking oral estrogen and chlorotrianesene 25 mg daily for 3 months for prostate cancer [14]. After discontinuing the oral estrogen, the patient's triglycerides fell from 2800 mg/dL to 720 mg/dL [14].

A study comparing various treatment options for men with prostate cancer examined the effects of diethylstilbestrol (DES), a synthetic, non-steroidal oral estrogen, on triglycerides [17]. The study found men treated with DES had higher triglycerides compared to untreated men [17]. Transsexual men taking 100 mcg of oral ethinyl estradiol and cyproterone acetate for 1 year experienced an 86% rise in triglyceride levels [18]. One meta-analysis summarizing evidence surrounding the effects of hormone therapy in transsexual females found triglycerides were increased by approximately 23% with estrogen use. The route of administration was important in this meta-analysis; only oral estrogen led to an increase in triglycerides [19]. Another study investigating the impact of hormonal therapy on male to female transsexuals found triglycerides were higher in male to female patients than both male and female patients [20]. The World Professional Association for Transgender Health (WPATH) recognizes that oral estrogen may greatly increase triglyceride levels and recommends that patients with preexisting lipid disorders preferentially use transdermal estrogen over oral estrogen [21].

Hypertriglyceridemia is not an unusual reaction to oral estrogen and has been explained by first pass hepatic metabolism of oral estrogens leading to alteration in liver metabolism and an increase in triglyceride production [22]. However, the case presented is unique in that the patient receiving the oral estrogen therapy was biologically male, and her financial status complicated the management of her hypertriglyceridemia and led to collaborative management in the family medicine setting. Use of the Naranjo algorithm indicated a probable score (score = 7) between the patient's hypertriglyceridemia and oral estrogen use. This provides support that this patient's severe hypertriglyceridemia was associated with oral estrogen use.

In patients with underlying genetic disorders leading to dyslipidemia, secondary causes may lead to severe or very severe hypertriglyceridemia putting the patient at risk for pancreatitis [2]. Therefore, it is important to evaluate and treat secondary causes of hypertriglyceridemia in patients with elevated triglycerides [2]. Common secondary causes of hypertriglyceridemia include: excessive alcohol intake, uncontrolled diabetes mellitus, other endocrine disorders, renal and liver disease, pregnancy and certain medications (e.g., thiazides, beta blockers, corticosteroids, antipsychotics, estrogens) [2]. The use of transdermal estrogen can mitigate the triglyceride elevation in patients who have experienced hypertriglyceridemia from oral estrogen therapy [12]. In transsexual women over 40 years of age without hypertriglyceridemia, transdermal estrogen is recommended [7]. In women with preexisting hypertriglyceridemia, as indicated by baseline triglycerides above 500 mg/dL, it is recommended to avoid oral estrogens [9]. Finally, monitor lipid levels regularly and manage abnormalities according to the established guidelines [6, 23].

Conclusion

This case emphasizes an important, yet often overlooked, adverse effect of hypertriglyceridemia with oral estrogen therapy. This is a unique case in that the estrogen-induced hypertriglyceridemia occurred in a transsexual female, and her financial situation complicated her management. Even without the development of pancreatitis, this case is important in that the risk of pancreatitis from elevated triglycerides is real and can be life-threatening. Caution should be used when prescribing oral estrogen to patients with elevated triglycerides, and when possible, transdermal estrogen should be considered ahead of oral estrogen therapy in similar patients. Monitoring for both secondary causes of hypertriglyceridemia, and hypertriglyceridemia itself, should not be overlooked.

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