CASE REPORT

TAMOXIFEN-INDUCED HYPERTRIGLYCERIDEMIA IN ASSOCIATION WITH DIABETES MELLITUS

H.J. MILIONIS, E.N. LIBEROPoulos, M.S. ELISAF

SUMMARY - Several pharmacological agents are associated with hyperlipidemia. Tamoxifen is an example of a drug-induced increase of serum triglyceride levels. However, there are only scarce reports on how inborn errors in lipid metabolism as well as secondary dyslipidemias, including diabetes mellitus, influence the hypertriglyceridemic effect of tamoxifen. Herein, we describe a case of a breast cancer patient receiving tamoxifen who presented with remarkable hypertriglyceridemia in the context of diabetes mellitus. We also provide a brief review of the relevant literature and discuss the mechanisms underlying the pathogenesis of hypertriglyceridemia related to tamoxifen.

Key-words: diabetes mellitus, hyperlipidemia, hypertriglyceridemia, tamoxifen.

RE´SUME´ - Hypertriglycéridémie induite par le tamoxifène en association avec un diabète.
Plusieurs agents pharmacologiques sont incriminés dans les hyperlipidémies. Le tamoxifène fournit un exemple de médicament hypertriglycéridémiant. Cependant peu de publications ont rapporté l’influence des erreurs innées du métabolisme lipidique ou des dyslipidémies secondaires, comme celles liées au diabète, sur les effets hypertriglycéridémiants du tamoxifène. Nous décrivons ici le cas d’une patiente atteinte de cancer du sein traitée par tamoxifène qui a présenté une hypertriglycéridémie franche dans un contexte de diabète sucré. Nous présentons aussi une brève revue de la littérature et discutons les mécanismes sous-jacents aux effets hypertriglycéridémiants du tamoxifène.

Mots-clés : diabète sucré, hyperlipidémie, hypertriglycéridémie, tamoxifène.

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everal pharmacological agents have been shown to induce hyperlipidemia. These include anabolic steroids, oral contraceptives, thiazide diuretics, beta-blockers and retinoids, which are sometimes associated with marked hypertriglyceridemia [1]. Tamoxifen is another example of a drug-induced increase of serum triglyceride (TG) levels [2, 3]. However, there is limited information on how inborn disturbances of lipid metabolism and secondary dyslipidemias, including diabetes mellitus (DM), can influence the hypertriglyceridemic effect of tamoxifen.

We describe a case of a female patient on tamoxifen who presented with remarkable hypertriglyceridemia in the context of DM.

**CASE REPORT**

A 46-year-old woman was referred to our outpatient lipid clinic with a recent history of dyslipidemia. She was a mother of two. Three years ago she suffered a right radical mastectomy for breast cancer and received six cycles with cyclophosphamide, methotrexate and 5-fluorouracil. She was currently on oral tamoxifen 20 mg twice daily. There was a positive family history of diabetes; a history of dyslipidaemia was less well defined. The patient recalled that during a routine laboratory evaluation five years ago her triglyceride levels were about 300 mg/dL. She also claimed that her only sister had ‘mild hypercholesterolemia’. On physical examination her body mass index was 28 kg/m². Blood glucose was 280 mg/dL, total cholesterol (TC) 320 mg/dL, HDL-cholesterol (HDL-C) 29 mg/dL, and TG 650 mg/dL. Lipoprotein (a) [Lp(a)] was 8 mg/dL. The patient’s apolipoprotein (apo) E phenotype was E3/E3. She was given a dietary advice by a registered dietitian and she was started on metformin 850 mg once daily per os together with gemfibrozil at 900 mg daily. Six weeks later, diabetes was partially controlled (blood glucose 140 mg/dL, HgA₁c 7.6%), and the lipid profile was as follows: TC 280 mg/dL, HDL-C 33 mg/dL, TG 350 mg/dL and Lp(a) 7 mg/dL.

**DISCUSSION**

Since the 1970s tamoxifen has been widely used in the prevention and treatment of breast cancer [4-7]. As it is usually prescribed in postmenopausal women, an age group vulnerable to ischemic heart disease (IHD), its lipid-related actions were intensely studied [8, 9]. Although tamoxifen acts both as an estrogen agonist and antagonist, it is the estrogenic effect in the liver that mainly influences lipid metabolism [9-11]. Several reports suggest that the predominant effects of tamoxifen on lipids are favorable. A reduction of total and LDL cholesterol (by increasing LDL clearance) and an increment of HDL levels follow its administration [1, 12, 13]. Moreover, tamoxifen has a favorable effect on Lp(a), but it produces a significant elevation in the pretreatment TG levels [13-15]. The hypertriglyceridemic effect of tamoxifen has been occasionally associated with life-threatening complications, such as pancreatitis [16, 17].

It has been proposed that tamoxifen raises serum TG concentrations:
- by increasing hepatic synthesis and secretion of very low density lipoproteins (VLDL), which constitute the main carrier molecule of TG, and
- by reducing VLDL and intermediate density lipoproteins (IDL) catabolism as the result of decreasing plasma lipoprotein lipase (LPL) and hepatic triglyceride lipase (h-TGL) activities [16, 18, 19].

However, in a study of 16 postmenopausal breast cancer patients, Hozumi et al reported that the mean mass of LPL significantly increased after tamoxifen treatment [19]. The authors concluded that tamoxifen treatment induced an increase in the proportion of inactive LPL, whereas the enzyme’s overall activity was decreased [19].

Severe hypertriglyceridemia (> 1000 mg/dL) due to tamoxifen has been infrequently reported [15-18]. Tamoxifen may need prolonged therapy (i.e., more than 2 years) to increase TG levels, since studies lasting shorter periods failed to observe any changes in serum TG levels [1, 16, 20]. In the vast majority of these patients a positive family history of dyslipidemia together with high pretreatment TG levels were evident. Certain patient groups have been reported to be susceptible to tamoxifen-induced hypertriglyceridemia, such as women with underlying primary hypertriglyceridemia and obesity [1, 16]. Although in patients receiving tamoxifen severe hypertriglyceridemia was related to specific apoE phenotypes (mainly type apoE2/E2), Hozumi et al demonstrated that the increase in TG concentrations during tamoxifen treatment can occur in any apoE phenotype. For example our patient had the wild apoE3/E3 phenotype [16, 21].

Raised TG levels have been occasionally demonstrated in patients with impaired glucose tolerance (IGT) or diabetes mellitus following the administration of tamoxifen [16]. Hozumi et al described a 49-year-old patient who presented with severe hypertriglyceridemia and hyperglycemia while on tamoxifen for 15 months [18]. TG and glucose levels improved after tamoxifen withdrawal [18]. Taira et al. reported a case of a 71 year-old woman with a long history of diabetes and dyslipidemia who presented with severe hypertriglyceridemia (TG 2106 mg/dL) after seven years on tamoxifen [22].

Our patient had a vague family history of dyslipidemia and DM. She had a recent history of DM herself while on tamoxifen for almost three years. The
unfavorable effect of diabetes on TG metabolism was reinforced by tamoxifen resulting in a clinically significant raise of serum TG levels. There is evidence that the drug reduces glucose utilization, at least in experimental models [7, 23]. In addition, it may influence glucose metabolism in humans. Therefore, the possibility that tamoxifen increases insulin resistance should also be considered [7, 16].

In most reported cases, the elevated serum TG levels returned to pretreatment values after stopping tamoxifen. Patients at risk should be advised to keep on a low fat diet as well as alcohol abstinence. However, in some patients with very high serum TG concentrations, lipid-lowering medication may be necessary. In these cases, fibric acid derivatives (fibrates) are mostly indicated [16, 24].

Discontinuation of tamoxifen is a difficult decision in the case of severe hypertriglyceridemia. Another estrogen antagonist, toremifene may be a useful alternative. There is evidence that toremifene has antiatherogenic properties with potency to improve all lipoproteins that are associated with increased risk for IHD, including TGs [25]. Specific estrogen receptors modifiers (SERMs) may also be considered but their actions on lipids are currently under investigation [26].

It is mandatory to screen all patients and determine their lipid profiles before initiating tamoxifen. Recognition and monitoring patients with pretreatment dyslipidemia (especially hypertriglyceridemia) together with additional predisposing conditions, such as diabetes mellitus and obesity, will substantially be of help in obviating clinically relevant consequences.

Concluding remarks

There is enough evidence that tamoxifen in breast cancer patients can induce hypertriglyceridemia, which could have clinically relevant consequences. Although there are no specific recommendations regarding the use of tamoxifen, it would be advisable to follow a plan before treatment initiation:

− All patients should be screened at a pretreatment stage for the detection of lipid abnormalities (mainly hypertriglyceridemia).
− A positive family history for dyslipidemia, IHD, and diabetes mellitus should be recorded.
− Individual patients with IGT, diabetes mellitus, and obesity should be identified and considered as “high-risk” patients.
− Periodical determination (e.g. every six months) of the lipid profile should be performed (including normolipidemic patients).
− All patients should be advised on a hypolipidemic diet and a moderate alcohol use.
− Toremifene and SERMs may be an option in cases of pretreatment hypertriglyceridemia.
− In cases of tamoxifen-induced severe life-threatening hypertriglyceridemia most authorities would agree on the cessation of the drug and the addition of a lipid-lowering agent (preferably a fibrate).

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