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Effect of thyroid hormone status and concomitant medication on statin induced adverse effects in hyperlipidemic patients

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Statins are effective treatment for the prevention of cardiovascular diseases and used extensively worldwide. However, adverse effects induced by statins are the major barrier of maximalizing cardiovascular risk reduction. Hypothyroidism and administration of drugs metabolized on the same cytochrome P450 (CYPP450) pathways where statin biotransformation occurs represent a significant risk factor for statin induced adverse effects including myopathy. Simvastatin, atorvastatin and lovastatin are metabolized by CYP3A4, fluvastatin by CYP2C9, while rosuvastatin by CYP2C9 and 2C19. We investigated the levels of the free thyroid hormones and CYP metabolism of concomitant medication in 101 hyperlipidemic patients (age 61.3 ± 9.9 ys) with statin induced adverse effects including myopathy (56 cases; 55.4%), hepatopathy (39 cases; 38.6%) and gastrointestinal adverse effects (24 cases; 23.8%). Abnormal thyroid hormone levels were found in 5 patients (4.95%); clinical hypothyroidism in 2 and hyperthyroidism in 3 cases. 11 patients had a positive history for hypothyroidism (10.9%). Myopathy occured in one patient with hypothyroidism and two patients with hyperthyroidism. There were no significant differences in the TSH, fT4 and fT3 levels between patients with statin induced myopathy and patients with other types of adverse effects. 78 patients (77.2%) were administered drugs metabolized by CYP isoforms also used by statins (3A4: 66 cases (65.3%); 2C9: 67 cases (66.3%); 2C19: 54 cases (53.5%)). Patients with myopathy took significantly more drugs metabolized by CYP3A4 compared to patients with other types of adverse effects ($p < 0.05$). More myopathy cases were found in patients on simvastatin treatment (52% vs. 38%, ns.), while significantly less patients with myopathy were on fluvastatin treatment (13% vs. 33%, $p < 0.05$) compared to patients with other types of statin induced adverse effects. Both abnormal thyroid hormone status and administration of drugs metabolized by CYP3A4, 2C9 and 2C19 are common in our patients with statin induced adverse effects. Normalizing the thyroid hormone status and optimizing of the concomitant medication may reduce the risk of statin induced adverse effects.

1. Introduction

Results of previous randomized clinical trials have shown that interventions that lower serum total and LDL cholesterol concentrations can significantly reduce the incidence of coronary heart disease (CHD) and other major vascular events (Baigent et al. 2005). Statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are extremely effective in the treatment of dyslipidaemia, thus are effective treatment for the prevention of cardiovascular diseases and used extensively worldwide (Rosenson 2004). However, adverse effects induced by statins are the major barrier of maximalizing cardiovascular risk reduction (Nichols et al. 2007).

Hypothyroidism is one of the most common endocrine diseases, which, in addition to its classic signs and symptoms, can present with primary complaints of myopathy (Rush et al. 2006). Polymyositis-like syndrome, with weakness of the proximal muscles and elevation of muscle enzymes, may be a first clinical manifestation of hypothyroidism (Madariaga et al. 2002). Even in subclinical hypothyroidism a positive correlation was observed between creatine kinase levels (CK) and thyroid stimulating hormone (TSH) (Beyer et al. 1998). The occurrence of hypothyroidism with concomitant statin treatment increases the risk of developing myopathy. The underlying metabolic mechanisms that are responsible for muscle disease in these two settings show some common etiologies. The overlap of symptoms associated with hypothyroidism and statin-induced myopathy should prompt the treating physician to screen all patients presenting with myopathic symptoms with or without elevated CK levels and all hyperlipidemic patients before initiating statin therapy for hypothyroidism by measuring the serum TSH (Rush et al. 2006). In addition, hyperthyroidism is usually accompanied by a significant dysfunction of both proximal and distal skeletal muscles (Olson et al. 1991).

The desirable and also the unwanted effects of a specific drug are generally related to its concentration at the sites of action, which in turn correlates with the amount administered (dose) and to the drug's pharmacokinetic properties like absorption, distribution, metabolism, and/or excretion. All these processes are

influenced by both intrinsic and extrinsic factors such as age, race, gender, coexistent diseases, concomitantly administered drugs, food, and fluids (Huang et al. 2008). Many pharmacokinetic drug–drug interactions involve inhibition of one or more metabolizing enzymes and transporters, resulting in increased systemic exposure and subsequent adverse drug reactions. In other cases, induction of metabolizing enzymes and transporters results in reduced systemic active drug metabolites leading to a risk of efficacy loss of co-administered drugs (Huang et al. 2007, 2008).

The majority of phase I reactions are accomplished by a superfamily of enzymes termed cytochrome P450 (CYP450). Polymorphisms in the CYP450 gene can influence metabolic activity of the subsequent enzymes. A poor metabolizer (PM) has no or very poor enzyme activity, while individuals presenting normal activity are labeled "intermediate" or "extensive" metabolizers (IMs or EMs, respectively) (McConnachie et al. 2004). A consequence of PM is drug toxicity if no other metabolic route is available, or when multiple drugs are metabolized on the same cytochrome pathway. The members of the CYP450 enzyme family can detoxify endogenous and exogenous compounds and also generate toxic compounds in the process of catalyzing the metabolism of xenobiotics. Thus, inhibition and induction of CYP enzyme activities are also the key mechanisms in drug-drug interactions (Jarin et al. 2000; Li et al. 1997). The induction or inhibition of metabolizing enzymes by a great deal of substances (including drugs, foods, inflammatory factors, etc.) influences the toxicological or pharmacological effects of their substrates (xenobiotics or drugs) (Harris et al. 2003; Paolini et al. 1999; Nicholson and Renton 1999).

Six members of the cytochrome P450 superfamily are responsible for the metabolism of the majority of pharmaceutical agents: CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6 and CYP2E1 (Sikka et al. 2005). Cytochrome P450 2D6 (CYP2D6) is responsible for the oxidative metabolism of more than 25% of the currently prescribed medications, including anti-arrhythmic, β-adrenoceptor blocking agents, opioid analgesics, tricyclic antidepressants and serotonin-selective reuptake inhibitors (Ho et al. 2011). The CYP3A4 isoenzyme metabolizes more than 50% of all marketed pharmaceuticals (Guengerich 1998; Evans and Relling 1999). Therefore, CYP2D6 and CYP3A4 are the key metabolic enzymes involved in drug-drug interactions.

Simvastatin, atorvastatin and lovastatin are metabolized by CYP3A4, fluvastatin by CYP2C9 while rosuvastatin by CYP2C9 and 2C19 (Shitara et al. 2006; Bailey et al. 2010). Thus, administration of drugs metabolized in the same cytochrome P450 (CYPP450) pathways where statin biotransformation occurs represents a significant risk factor for statin induced adverse effects including myopathy.

In our present study we investigated the thyroid function by measuring the levels of serum thyrotropin and free thyroid hormones together with assessing the CYP metabolism of concomitant medication in 101 hyperlipidemic patients with statin induced adverse effects including myopathy, hepatopathy and gastrointestinal adverse reactions.

2. Investigations and results

Patients were recruited at the First Department of Medicine, University of Debrecen. 101 hyperlipidemic patients (age 61.3 ± 9.9 years) with statin induced adverse effects were enrolled into the study. The statin treatment was initiated by family doctors who referred the patients presenting symptoms related to the adverse events which occurred within 1 week to 12 months after the administration of the different antihyperlipidemic agents to our department. The patients enrolled in this study were treated with

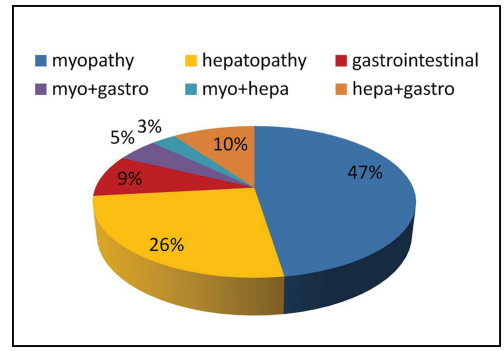

Fig. 1: The distribution of statin induced adverse effects (myopathy 47%, hepatopathy 26%, gastrointestinal adverse effect 9% and combination 10, 5 and 3%) among our patients.

simvastatin, atorvastatin, fluvastatin, rosuvastatin or pravastatin. In 56 cases statin-induced myopathy (myalgia with or without creatinine-kinase elevation), in 39 cases statin-induced liver enzyme elevation (hepatopathy) and in 24 cases statin-induced severe gastrointestinal symptoms were observed (Fig. 1).

Patients with alcoholism, any drug dependence, malignant diseases, pregnancy or lactation, as well as patients on anticoagulant therapy were excluded. Informed consent was obtained from all patients after explaining the nature and the purpose of the study. The Ethics Committee of the University of Debrecen approved the study.

At baseline after 12 h fasting, a 10 ml venous blood sample was taken between 07:30 and 08:00 in the morning. Lipid parameters, serum cholesterol (LDL-Cholesterol and HDL-C) and triglyceride levels were measured. Apolipoprotein (ApoA and ApoB) examination was also performed. Creatine-kinase activities and C-reactive protein (CRP) levels were determined. We investigated the levels of the free thyroid hormones (triiodothyronine (T3) and thyroxine (T4)) and thyroid stimulating hormone (TSH)). The general and laboratory results and the reference ranges are shown in Tables 1 and 2.

Concomitant drug intake was evaluated and recorded in every single case. Cytochrome P450 metabolism was evaluated using FDA and local database (http://www.pharmindex-online.hu, http://www.fda.gov)

Abnormal thyroid hormone levels were found in 5 patients (4.95%); clinical hypothyroidism in 2 and hyperthyroidism in 3 cases. 11 patients had a positive history for hypothyroidism (10.9%). Myopathy occurred in one patient with hypo- and in two patients with hyperthyroidism. There were no significant differences in the TSH, fT4 and fT3 levels between patients with statin induced myopathy and patients with other types of adverse effects (Table 2).

Sixty-six patients received drugs metabolized by CYP3A4 (65.3%), in 67 cases patients took medication metabolized by CYP2C9 (66.3%) and 54 patients received drugs metabolized by 2C19 (53.5%).

Seventy-eight patients (77.2%) received drugs metabolized by CYP isoforms also used by statins (Table 3), such as antihypertensive and anti-diabetic agents. Patients with myopathy took significantly more drugs metabolized by CYP3A4 than patients with other types of adverse effects ($p < 0.05$).

More myopathy cases were found in patients on simvastatin treatment (52% *vs.* 38%, ns.), while significantly less patients with myopathy were on fluvastatin treatment (13% *vs.* 33%, $p < 0.05$) compared to patients with other types of statin induced adverse effects (Fig. 2).

3. Discussion

The increasingly widespread use of hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) has drawn attention

Table 1: Laboratory parameters and anthropometric data of the patients with and without statin induced myopathy

	Myopathy (n = 56)	No myopathy (n = 55)	All patients (n = 101)	Reference range
Age (years)	62.6 ± 8.9	59.5 ± 10.9	61.3 ± 9.9	NA
BMI (kg/m2)	28.9 ± 4.0	27.2 ± 4.5	28.2 ± 4.29	NA
Waist circumference (cm)	101.6 ± 10.9	94.0 ± 11.6	98.5 ± 11.7	NA
Total cholesterol (mmol/l)	7.33 ± 1.57	7.63 ± 1.69	7.46 ± 1.62	< 5.2
LDL-C (mmol/l)	4.64 ± 1.59	4.66 ± 1.45	4.65 ± 1.52	< 3.4
HDL-C (mmol/l)	1.39 ± 0.4	1.53 ± 0.44	1.45 ± 0.43	> 1.3
Triglyceride (mmol/l)	2.45 (1.6–4.4)	2.4(1.6–4.3)	2.43(1.5–4.3)	< 1.7
ApoB (g/l)	1.30 ± 0.35	1.31 ± 0.36	1.30 ± 0.35	< 1,0
ApoA (g/l)	1.60 ± 0.32	1.72 ± 0.41	1.65 ± 0.36	> 1,15
CRP (mg/l)	3.11(1.6–5.8)	2.67(1.7–8.1)	2.79(1.7–5.8)	< 4.6
Creatinine kinase (U/l)	198 (121–308)	94(67–128)	131.5(87–235)	24–195

Table 2: Thyroid hormone levels (sTSH, fT3 and fT4) of the patients with and without statin induced myopathy

	Myopathy (n = 56)	No myopathy (n = 55)	All patients (n = 101)	Reference range
sTSH (mU/l)	5.05 ± 16.35	2.09 ± 2.26	3.78 ± 12.5	0.3–4.2
fT3 (pmol/l)	5.1 ± 2.38	4.74 ± 0.96	4.94 ± 1.88	2.4–6.3
fT4 (pmol/l)	15.38 ± 4.8	14.55 ± 4.3	15.2 ± 4.58	12.0–22.0

to their safety, and particular consideration has been given to the potential for interactions with concomitant medications (Alawi et al. 2005; Pasternak et al. 2002). Thyroid diseases seriously affect the composition and the transport of lipoproteins. In overt hypothyroidism a reduced number of low-density lipoprotein (LDL) receptors in the liver results in decreased fractional clearance of LDL which leads to hypercholesterolaemia and a marked increase in LDL and apolipoprotein B (apo B). Besides, the high-density lipoprotein (HDL) levels remain normal or become even elevated since hepatic lipase and cholesteryl-ester transfer protein enzymes has a decreased activity due to the fact that they are regulated by the thyroid hormones (Duntas 2002; Tan et al. 1998).

During our one-year follow-up we found abnormal thyroid hormone levels in 5 patients presenting with statin-induced side effects (4.95%); clinical hypothyroidism in two and hyperthyroidism in three cases. These data are in concordance with the incidence of thyroid dysfunction in the normal population. According to our findings, the occurrence of thyroid dysfunction among these patients did not differ from the one observed within healthy subjects. Eleven patients had a positive history for hypothyroidism (10.9%). This result is slightly higher than expected from the normal population (2.8–4.5%) (Vanderpump et al. 1995). The difference might be explained by the fact that these patients were on levothyroxin substitution, which is metabolized by CYP 3A4 as well. As a result the risk of statin-induced side-effects among hyperlipidemic patients might increase. However, thyroxine therapy, in a thyrotropin (TSH)-suppressive dose, usually leads to a clinically detectable improvement of the lipid profile (Duntas 2002). Myopathy occurred in one patient with hypo- and in two patients with hyperthyroidism. There were no significant differences in the TSH, fT4 and fT3 levels between patients with statin induced myopathy or other types of adverse effects.

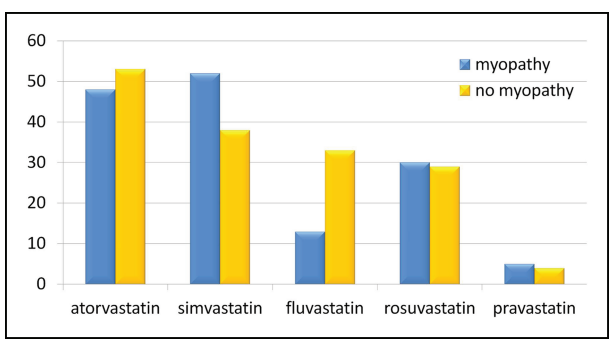

Fig. 2: Ratio of statin users among patients with and without myopathy.

In our study 77.2% of the patients with adverse effects caused by lipid-lowering therapy received drugs for the treatment of coexisting illnesses metabolized by CYP isoforms also used by statins (3A4: 66 cases (65.3%); 2C9: 67 cases (66.3%); 2C19: 54 cases (53.5%)). Patients with myopathy took significantly more drugs metabolized by CYP3A4 compared to patients with other types of adverse effects ($p < 0.05$). More myopathy cases were found in patients on simvastatin treatment compared to other statin administrations, probably due to the competition between the HMG-CoA reductase inhibitors and other drugs on CYP3A4 (52% *vs.* 38%, ns.). In contrast, significantly less patients with myopathy were on fluvastatin treatment (13% *vs.* 33%, $p < 0.05$) compared to patients with other types of statin induced adverse effects, most likely because of the different metabolization pathway of this antihyperlipidemic drug.

In conclusion, both abnormal thyroid hormone status and concomitant administration of drugs metabolized by CYP3A4, 2C9 and 2C19 enzymes that are responsible for the first step degradation of the widely used lipid-lowering agents are relatively frequent among our patients with statin induced adverse effects. Normalizing the thyroid hormone status and selecting the most suitable concomitant medication with respect to the known

Table 3: Number of patients using concomitant drugs and number of drugs metabolized by CYP isoforms also used by statins

	CYP3A4	%	CYP2C9	%	CYP2C19	%
Patients	66	65.3	67	66.3	54	53.5
Drugs	147		128		81	

metabolization pathways may reduce the risk of statin induced adverse effects.

4. Experimental

Lipid parameters were determined from fresh serum. Serum cholesterol and triglyceride levels were measured using enzymatic, colorimetric tests (GPO-PAP, Modular P-800 Analyzer; Roche/Hitachi, Basel, Switzerland), whereas HDL-C was assessed by homogenous, enzymatic, colorimatic assay (Roche HDL-C plus 3rd generation). LDL-Cholesterol was measured by homogenous, enzymatic, colorimetric assay (Roche LDL-C plus 2nd generation, Basel, Switzerland). Apolipoprotein examination was performed by the immunoturbidimetric assay Tina-Quant APO A (Version 2; Roche), Tina-Quant APO B (Version 2; Roche). Accuracy ((mean/target) x100) was in the range 97.3–106%, precision (run to run CVa) of lipid measurements was in the range 1.39–5.15% on Cobas6000 analyzer (Roche).

Creatine-kinase activities were determined by UV kinetic assay (CK liquid), in accordance with the IFCC recommendations on Roche/Hitachi Modular P800 analyzer, and C-reactive protein (CRP) was analyzed on the same equipment by immunoturbidimetric assay (CRPLX).

Triiodothyronine (T3), thyroxine (T4) were assessed by one-step sequential competitive electrochemiluminescence assay with SPALT polyclonal rutenium-labelled antibody, Elecsys 2010, Roche; and thyroid stimulating hormone (TSH) was determined using two-site immunochemiluminometric assay with two monoclonal antibodies, analytical sensitivity: 0.005 mIU/L, Elecsys 2010, Roche.

The statistical analysis was performed with Windows 7 and IBM Statistical Package for the Social Sciences (SPSS) Statistics Version 19. Normality of distribution was tested by the Kolmogorov-Smirnov test. For correlation analysis we used the Anova program and the "t" probe was performed. Data was expressed as means ± standard deviation (SD) in case of normal distribution, and median (lower/upper quartile) in case of non-normal distribution. We considered the results significant when $p < 0.05$.

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