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Statin-Induced Myopathy: A Clinical Perspective

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Statins are at the forefront of treatments for hyperlipidemia, coronary artery disease and stroke. Patients may not adhere to Statins therapy due to hepatic or neuromuscular side effects that include neuropathy and myopathy. The latter include myalgia, lassitude, fatigue, proximal muscle weakness with or without elevated creatine kinase (CK) or myoglobinuria. Studies suggest that these symptoms are under reported and may occur in as much as 5% or more. This article reviews the definition, incidence, possible mechanisms, risk factors, clinical presentation and suggested management of Statin-induced myopathy.

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Statins, 3-hydroxy-3-methlglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are essential in the prevention and treatment of patients with hyperlipidemia, ischemic heart disease and stroke[1]. Recently statins are being investigated for use in patients with dementia[2]. Since their introduction in 1987, statins have shown to be safe and effective but several serious adverse effects including hepatic and neuromuscular complications[3]. The latter are mainly myopathy and to a lesser extent neuropathy[4]. The incidence of neuromuscular complications is expected to rise with the widespread use of statins. It seems pertinent therefore to alert physicians about the potential risk factors, clinical features and management of Statin-induced myopathy.

Definitions

Myopathy in general terms refers to any muscle disease regardless of etiology. Pasternak and colleagues defines the spectrum of statins myopathy as follows: myalgia refers to muscle aches or weakness without creatinine kinase (CK) elevation and myositis refers to muscle symptoms with increased CK. Rhabdomyolysis is muscle symptoms with marked CK elevation more than 10 times the upper limits of normal[5]. This definition has been challenged because there is no reference to specific histopathological terms particularly evidence of inflammatory changes[6].

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Epidemiology of Statin-Induced Myopathy

It is not clear how often myo-toxic symptoms occur during Statins therapy. Meta analysis of clinical trials have shown that the incidence of myopathic abnormalities per 100,000 is less than 0.1%[7-8]. Myalgia accounted for 25% of reported statins adverse events although minor muscle related symptoms are often under reported and could be 5-7%[9,10].

Risk Factors for Statin-Induced Myopathy

Patients with co-existing medical conditions such as diabetes mellitus, renal dysfunction, hepatic disease or on concomitant medications like fibrates and macrolides are more likely to develop myopathy than others[11,12]. See Table1.

Table 1: Risk Factors for Statin-Induced Myopathy

Risk Factor
Age
Female gender
Small body mass index
Physical Exercises
Coexisting Medical Illness
Hepatic disease
Renal disease
Diabetes Mellitus
Hypothyroidism
Pre-existing muscle disease
Concomitant Medications
Fibrates (Gemfibrozil)
Vitamin K antagonists (Warfarin)
Macrolide antibiotics (Azithromycin)
Azole antifungals (Itraconazole)
HIV protease inhibitors
Verapamil
Amiodarone
Alcohol
Surgery

The myopathy that may occur with any of the statins is dose dependent and is more likely in the lipophilic than hydrophilic forms of the statins[13]. This factor does not appear to correlate to the cholesterol lowering effect[14], see table 2.

Table 2: The Statins Available for the Therapy of Hypercholesterolemia*

Type of Statin	Year	Formulation	Dose	$t_{1/2}$ (hr)	Solubility	Protein Binding %
Hydrophilic						
Pravastatin (Pravachol)	1991	10/20/40/60 mg per tab	10-80 mg/day	1-3-2.8	Hydrophilic	40-55
Fluvastatin (Lescol)	1999	80 mg per tab	20-80 mg/day	0.5-2.3	Hydrophilic	>99
Rosuvastatin (Crestor)	2003	5/10/20/40 mg per tab	5-40 mg/day	19	Hydrophilic	88
Lipophilic						
Lovastatin (Mevacor, Altoprev)	1987	10/20/40/60 mg per tab	20-80 mg/day	2.9	Lipophilic	>95
Cerivastatin** (Baycol, Lipobay)	1999	0.3/0.4/0.8 mg per tab	0.3 mg-0.4 mg/day	2.1-3.1	Lipophilic	>99
Simvastatin (Zocor)	2000	5/10/20/40 mg per tab	10-80 mg/day	2-3	Lipophilic	>95
Combined						
Atorovastatin (Lipitor)	1999	10/20/40mg per tab	10-80 mg/day	15-30	Lipophilic/ Hydrophilic	80-90

*all undergo hepatic metabolism
**voluntarily withdrawn from market by manufacturer

Mechanism of Statin-Induced Myopathy

Although the exact mechanisms of Statins' myotoxicity are unknown, impaired cholesterol synthesis with secondary abnormal membrane function has been incriminated[15,16]. Other possible mechanisms include deficiency of relevant compounds like mevalonate and ubiquinone (Co Q10) leading to mitochondrial dysfunction or prenylated protein causing altered intracellular messaging which induce vacuolation of the myofibers, degeneration and swelling of organelles, and eventually apoptosis[17,18].

Clinical Presentation of Statin-Induced Myopathy

There are no specific clinical characteristic for Statin-induced myopathy; it ranges from myalgia, lassitude and fatigue to frank proximal muscle weakness, bulbar muscles are usually spared and electromyography shows myopathic potentials[19]. The symptoms usually develop within four weeks but can be delayed up to four years after starting

Statins therapy. Serum CK is elevated with or without myoglobinuria and normal values do not exclude Statin-induced myopathy[20]. Careful neurologic screening for pre-existing myopathy or myopathy-mimics is indicated[21]. Diagnostic morphologic markers for Statins myotoxicity are lacking on muscle biopsy but a constellation of myopathic findings can be used to recognize the entity although muscle biopsy is seldom needed to confirm the diagnosis[22].

Management of Statin-Induced Myopathy

Physicians should advise their patient about statins use and their potential side effects. Monitoring serum CK level is not required but may be useful in high-risk patients or those patients with non-specific symptoms, but CK serum level is needed to confirm the diagnosis and assess severity of muscle damage[23]. It is important to note that CK values may be normal in patients with overt symptoms[20]. In the absence of other causes, persistent muscle complaints or CK elevation should prompt discontinuation of statins[20,21,23]. CK elevation more than 10 times its normal levels indicates rhabdomyolysis and such patients may need hospital admission and administration of supportive therapies. Discontinuation of statins leads to complete resolution of symptoms usually within one week to four months[8]. Once full recovery is achieved, other forms of Statins could be tried. Other forms of lipid lowering medications like ezetimibe have been associated with myopathy[24]. There is no specific therapy to prevent or treat Statin-induced myopathy. The role of CoQ10 supplement is not clear. Case reports of patients with Statin myopathy described some improvement with CoQ10, but others have not[18].

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