STATIN THERAPY: CLC-1 CHLORIDE CHANNEL AS A BIOLOGICAL MARKER OF MYOPATHY IN HUMANS

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Statin therapy can produce skeletal muscle dysfunction that range from myalgia to severe rhabdomyolysis. Statin-induced adverse effects represents an important obstacle to therapy, exposing the patients to life-threatening cardiovascular event. The causes are still unknown. Our preclinical studies in the rat model showed that statin-induced myopathy involve the reduction of ClC-1 chloride channel expression and of resting chloride conductance (gCl), sustained by this channel (Pierno et al., 2009). This reduction is detrimental for muscle function and leads to myotonic-like symptoms as observed during Myotonia Congenita, a rare disease characterized by hyperexcitability and a delay in muscle relaxation after contraction (Desaphy et al. 2013). The reduction of gCl is also due to statin-induced activation of protein kinase C (PKC), which negatively regulate the ClC-1 channel activity and contribute to destabilize sarcolemma excitability (Camerino et al., 2014). A reduction of ClC-1 expression and activity also occurs during aging, suggesting a possible worsening of statin-induced side-effects in the Elderly, that are the main statin users. Our goal is to translate these observations into clinical studies at the aim to identify biological markers useful to predict and prevent statin-induced muscle damage especially during aging. For this we examined ClC-1 mRNA and protein expression in muscle biopsies of 10 patients of different age (50-77 years-old) under statin-therapy who experienced myalgia and hyper-CK-emia after starting statins, and compared the results with those of age-matched untreated subjects. We found a marked reduction of ClC1 protein by 40% in statin-treated patients, independently from their age. Also, PKC expression and activity was increased, contributing to ClC-1 channel inactivation. However, the ClC-1 mRNA was not significantly changed suggesting post-transcriptional modification. Yet, compensatory mechanism are elicited, since Notch-1, a gene involved in muscle cell proliferation, was highly expressed in statin-treated patients, indicating active regeneration. An increase of PGC-1-alpha and of isocitrate dehydrogenase suggest mitochondrial biogenesis in accord with increased citrate synthase activity. Thus, the reduction of ClC-1 protein and increase of related sarcolemma hyperexcitability appears to be among the most important alterations associated with statin-related risk of myopathy in humans. This effect was not worsened in the older subjects examined, suggesting that other factors may be involved in the increased incidence of statin-related side-effects in the Elderly.

Pierno et al. (2009). Br J Pharmacol. 156: 1206-1215.

Desaphy et al. (2013). Exp Neurol. 248: 530-540.

Camerino et al. (2014). Pflugers Arch. 466: 2215-2228.