Association between statin-associated myopathy and skeletal muscle damage


Statin-associated myopathy presents clinically with muscle weakness and myalgia. Myalgia is reported to occur in up to 15% of patients taking statins and is generally considered to be a minor adverse effect. Continuation of the statin is recommended as long as serum creatine phosphokinase levels remain less than 10 times the upper limit of normal (ULN). In order to investigate whether statin-associated myopathy is associated with underlying structural damage, whether the extent of muscle damage is reflected by the level of circulating creatine phosphokinase, and whether the expression in myocytes of certain genes provide an insight into the cause of statin-associated myopathy, these investigators examined biopsy samples from the vastus lateralis muscle of 4 different patient groups: i) clinically diagnosed statin-associated myopathy, still taking a statin (n=29); ii) clinically diagnosed statin-associated myopathy, discontinued taking a statin (n=15); iii) taking a statin, with no myopathy (n=19); iv) never taken a statin and no myopathy (n=20).

Muscle injury was defined as ≥2% damaged muscle fibres in the biopsy sample, and was present in 57% of the patients with myopathy and in 1 patient who had no myopathy, but who was on long-term statin therapy. Only one of these patients had creatine phosphokinase >10 times ULN. The prevalence of muscle damage was similar in patients who were currently taking a statin and in those who had discontinued statin therapy and there was no significant difference in the amount of damage between the groups, or any correlation between the muscle damage and length of statin therapy. No control subjects had muscle damage.

Compared to subjects without structural muscle damage, the expression of ryanodine receptor 3 mRNA was significantly higher among those with muscle damage. However, it is unclear whether expression of this gene was increased before or after statin therapy.

The results of the study suggest that elevated creatine phosphokinase is not a good marker of muscle damage in patients with statin-associated myopathy and guidelines for instituting alternative treatment strategies for such patients need to be re-evaluated.

Reviewer's / editor's comment

Statin myopathy is associated with muscle pain and weakness, but the extent of muscle injury is unknown. In this small, important, histological study muscle injury was defined as greater than 2% muscle fibre damage in any given sample. Of the 26 patients with muscle injury only 1 patient had a CPK level more than 1950 U/L (10x upper limit of normal).

The typical histo-pathological appearance of statin-associated myopathy is characterized by vacuolation of the T-tubular system with an intact sarcolemma. The intact lateral sarcolemma therefore prevents CPK enzyme leak into the bloodstream. Mildly elevated or normal CPK levels therefore cannot be used to exclude/confirm persistent muscle injury. Comparisons with steroid-induced myopathy, show that the latter manifests as a diffuse decrease in myofibrils, without intra-cellular vacuolation or subsarcolemmal detachment.

This study reveals important insights into cellular mechanisms of injury and enzyme profiles of statin-induced myopathy. Caution is advised on reliance of CPK and aldolase levels.

Intracoronary eptifibatide bolus administration during percutaneous coronary revascularization for acute coronary syndromes with evaluation of platelet glycoprotein IIb/IIIa receptor occupancy and platelet function

The Intracoronary Eptifibatide (ICE) Trial.


In patients undergoing percutaneous coronary intervention (PCI) for acute coronary syndromes (ACS), cardiac outcomes may be improved by administration of eptifibatide. Although the glycoprotein (GP) IIb/IIIa inhibitors have been shown to reduce the incidence of major adverse cardiac events, thrombus and vascular debris may still embolize and plug the microvasculature, causing myocardial infarction (MI). Because high local concentrations of GP IIb/IIIa inhibitors disrupt platelet cross-linking they may improve myocardial perfusion after MI. The aim of this study was to investigate whether intracoronary administration of eptifibatide would be associated with greater platelet GP IIb/IIIa receptor occupancy (RO) in the coronary bed, reduced thrombus burden and improve measures of coronary artery blood flow.

Forty three patients with ACS and undergoing PCI were randomised to receive an initial bolus of intracoronary eptifibatide followed by a continuous infusion via a peripheral vein, which was continued for 18 hours after the initial bolus, and a second intracoronary bolus 10 minutes after the initial bolus, or 2 peripheral boluses and a peripheral continuous infusion. The primary endpoint was local coronary bed platelet GP IIb/IIIa (RO) in the coronary sinus and secondary endpoints included measures of microvascular perfusion, myocardial infarction and major cardiac events.

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Compared to peripheral administration, GP IIb/IIIa RO and post-PCI microvascular perfusion (measured by the corrected thrombolysis in myocardial infarction frame count; cTFC and adjusted for pre-PCI measurements) were significantly greater with intracoronary eptifibatide (Table 1). In multivariate analysis, the only variable associated with post-PCI cTFC score was the first bolus GP IIb/IIIa RO, indicating that an early high level of GP IIb/IIIa RO was important to improve perfusion.

<table>
<thead>
<tr>
<th>Table 1.</th>
<th>Intracoronary 1st bolus</th>
<th>Peripheral 1st bolus</th>
<th>Intracoronary 2nd bolus</th>
<th>Peripheral 2nd bolus</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP IIb/IIIa RO</td>
<td>94%</td>
<td>51% (P&lt;0.001)</td>
<td>99%</td>
<td>91% (P=0.001)</td>
</tr>
<tr>
<td>Post-PCI microvascular perfusion (cTFC)</td>
<td>Intracoronary eptifibatide</td>
<td>18 (25th &amp; 75th percentiles: 10 &amp; 22)</td>
<td>25 (25th &amp; 75th percentiles: 22 &amp; 35) (P=0.007)</td>
<td>Peripheral eptifibatide</td>
</tr>
</tbody>
</table>

There were no significant differences between groups in procedure-related myonecrosis.

**Reviewer’s / editor’s comment**

For interventional cardiologists and particularly for primary PCI in AMI this very important mechanistic study has huge clinical implications for better outcomes in acute coronary syndromes. It was previously demonstrated (THIELE et al CIRCULATION 2008; 118 : 49-57) that intracoronary administration of abciximab in patients with STEMI undergoing primary PCI was associated with decreased infarct size, smaller microvascular obstruction (measured by delayed-enhancement MRI), and improved myocardial perfusion measured by ST-segment resolution, than the same bolus delivered intravenously (IV), followed by an IV infusion.

This study clearly demonstrates significantly higher local platelet GP IIb/IIIa receptor occupancy (RO) - hence better platelet disaggregation - by eptifibatide with intracoronary versus intravenous bolus administration. There is also improved coronary flow and microvascular perfusion demonstrated by improved corrected TIMI frame count (cTFC). In a multivariate analysis, an early high level of local GP IIb/IIIa RO with the first intracoronary bolus was the only factor associated with an improved cTFC.

I have been using a similar intracoronary bolus strategy for at least 12 years with no complications at all; the very nature of interventional cardiology often compels us to test new frontiers and uncomfortable zones, provided safety and complications are always respected and carefully considered. The potential of this intracoronary, local bolus delivery in conjunction with thrombectomy devices looks even more promising for improving myocardial salvage. This perspective will be explored with abciximab in the CICERO (Comparison of IntraCoronary versus intravenous abciximab administration during Emergency Reperfusion Of ST-segment elevation myocardial infarction) trial.

**Clinical aspects of co-enzyme Q10: an update**


Coenzyme Q10 (CoQ10) plays a major role in mitochondrial oxidative phosphorylation, as an antioxidant and also has effects on gene expression. This article is a review of recent clinical findings pertaining to its use in clinical practice and as a food supplement.

In the cardiovascular system, CoQ10 antagonizes the oxidation of plasma low-density lipoprotein (LDL) and improves endothelial function, thereby improving vascular flow in patients with coronary artery disease and reducing blood pressure in patients with hypertension. In patients with hypertrophic cardiomyopathy, it has been shown to improve diastolic function, NYHA class, quality of life and treadmill performance. By antagonizing ischemia reperfusion damage, CoQ10 supplementation improved outcomes in patients after coronary artery bypass surgery. Low plasma CoQ10 levels are predictive of a worse prognosis in patients with chronic heart failure.

Results of studies investigating the effects of CoQ10 supplementation in patients with statin-induced myopathy remain equivocal. In studies pertaining to reproductive medicine, CoQ10 supplementation has been shown to improve semen quality in men with idiopathic infertility and reduce the risk of pre-eclampsia in pregnant women.

In healthy individuals, CoQ10 supplementation may improve subjective fatigue sensation and improve physical performance during exercise, while opposing exercise-related damage.

CoQ10 supplementation may also have a role to play in illnesses characterised by oxidative stress and damage and mitochondrial chain dysfunction, including mitochondrial myopathies and neurodegenerative diseases, such as Parkinson's disease and Friedreich's ataxia. It has also been shown to significantly decrease headache frequency in patients with migraine and low plasma CoQ10 levels.

**Reviewer’s / editor’s comment**

This concise review summarizes the potential of CoQ10 in a variety of cardiac conditions, and other uses in non-cardiac conditions. The recognised biochemical functions of CoQ10 include mitochondrial bio-energetics, uncoupling proteins, anti-oxidant properties and gene induction.

The CoQ10 effect on blood pressure is mainly due to improvement in endothelial dysfunction. Recently (Adarsh et al, BIOFACTORS 2008; 32:145-9) reported improvement in diastolic dysfunction, exercise capacity and LVH regression in hypertrophic cardiomyopathy. There is also evidence of benefit - by antagonising ischemia reperfusion damage - in the peri-operative period of coronary bypass surgery, by pre-treatment with CoQ10 7-10 days prior (J. CARDIOTHORAC. VASC ANESTH 2008; 22:832-9). There are several studies pointing to a potential benefit of CoQ10 in heart failure patients, and statin-induced myopathy is another potential benefactor of CoQ10 supplementation.
The potential benefits of CoQ10 have also been explored in migraine, neuro-degenerative conditions such as Parkinson’s and Friedreich’s ataxia as well as in pre-eclampsia and reproductive medicine. As new uses of CoQ10 are tested it is expected to generate much debate amongst protagonists, antagonists and doubters.

**Thyroid replacement therapy and heart failure**

Gerdes AM, Lervasi G. *Circulation* 2010; 122: 385-393.

Thyroid hormones (TH) have important effects on the contractile and relaxation properties of the heart, and appear to be essential for maintaining cardiac structure and function in both healthy hearts and after myocardial injury. Healthy cardiac function is dependent on normal TH homeostasis and both hyper- and hypothyroidism are associated with cardiovascular disease (CVD) and heart failure. The biologically active form of TH is T3 and the degree of its effect on the heart is dependent on cardiac levels of T3, which in turn are influenced by T3 production and uptake into cardiac tissue and degradation either systemically or in the heart; and the state of TH transporters and TH nuclear receptors, which influence signalling. Alterations at any of these levels may adversely affect cardiac structure and function and, because cardiomyocytes are relatively unable to convert T4 to T3, the heart is particularly sensitive to changes in TH. Even mild alterations in TH function are associated with a CVD and a worse prognosis in patients after myocardial infarction and in those with heart failure.

Animal studies suggest that supplementing T3 to normalise TH levels after myocardial infarction or in heart failure may improve cardiac function, left ventricular function and remodelling. These observations have been supported by limited studies in humans and studies in cardiac patients are ongoing. However, currently the optimal dose and timing of therapeutic thyroid replacement pharmacotherapy in patients with cardiovascular disease is unknown and more studies are needed to determine its effect in preventing and treating these patients.

**Reviewer’s / editor’s comment**

There is increased interest in the role of thyroid hormones (TH) in heart failure for 3 main reasons: the known effects of TH on contractile and relaxation properties of heart muscle; TH signalling is crucial in preserving cardiac structure and function in normal and diseased conditions; and evidence that mildly deranged thyroid function is strongly associated with worsening prognosis in cardiac patients in general and in heart failure patients in particular.

This important review highlights the powerful role of bio-active T3 in inotropic and lusitropic properties of the heart; it also highlights the deleterious effects of subclinical hypothyroidism and low T3 syndrome in coronary disease and heart failure. There is also a worsening prognosis in post-MI patients with persistently low plasma T3; thyroid hormones also have a central role in cardiac remodelling.

In the clamour of treating heart failure in all its aspects, clinicians should be reminded of the central or crucial role of normal thyroid homeostasis in optimising outcomes in these patients.

**Nutrition, supplements and vitamins in platelet functions and bleeding**


Observational and interventional studies have demonstrated that diet, consumption of fruit and vegetables, essential fatty acids (especially from consumption of fish) and the use of specific nutrients may significantly reduce the incidence of cardiovascular events. This article is a review of clinical studies investigating the effects of dietary components on platelet function and their possible role in cardiovascular protection.

n-3 omega essential fatty acids from fish (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) have been shown to reduce the incidence of CVD and especially cardiovascular death. Clinical studies suggest that a dose-independent inhibition of platelet function or prolongation of platelet survival, and other antithrombotic effects may play a role. However, studies have not consistently demonstrated comparable effects with alpha-linolenic acid, suggesting that the effect of fish and plant-derived n-3 fatty acids on platelets may not be the same.

Although the effects of olive oil and oleic acid on platelet function are uncertain, experimental evidence does support a cardioprotective effect of polyphenols present in wine, non-alcoholic juices and chocolate through an influence on platelet function.

Studies of vitamin E have inconsistently demonstrated antiplatelet effects and, although many studies are difficult to interpret due to flaws in methodology and design, there is little evidence that vitamin E supplementation is cardioprotective and some evidence that it may actually increase the risk of haemorrhagic stroke through alternative anticoagulant effects. Similarly, the cardiovascular benefit of beta-carotene and vitamin C is doubtful.

Currently there is little evidence that any nutrient or supplement should be considered an antiplatelet tool for use in either healthy individuals or those at risk of cardiovascular disease. Epidemiological and interventional studies support the role of healthy diet choices as a whole to help reduce the risk of cardiovascular events.

**Reviewer’s / editor’s comment**

Much has been written about particular diets and specific nutrients - ‘anti-atherosclerotic diets’, such as the Mediterranean diet and Eskimo diet as non-pharmacological measures to prevent vascular disease and influence platelet function.

This rather interesting review focuses on the benefits and weaknesses of specific diets and their biochemical components which are reported to be anti-atherogenic. The authors discuss the basic science behind n-3 polyunsaturated fatty acids, n-3 and platelet function, oleic acid - the principle component olive oil -, wine (polyphenols), and Vitamin E and C.

Since cardiologists and physicians are always encouraging lifestyle and dietary changes, this review gives important insights to key components of recommended diets.