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Tendonopathy Due to Simvastatin and Ezetimibe, Amyloidosis or Both?

We reported in 2007 in AJC a patient with rupture of his left biceps tendon when lifting a box out of his car 4 months after starting the combination of simvastatin (20 mg) and ezetimibe (10 mg).[1] The tendon was surgically repaired. He was restarted on the combination of simvastatin (10 mg) and ezetimibe (10 mg) 2 months after the repair and promptly developed right biceps tendinitis. We attributed his tendonopathy to the combination of statin and ezetimibe and raised the possibility that statins caused tendonopathy by reducing matrix metalloproteinase activity.[1] Matrix metalloproteinases are required to cleave and clear damaged collagen as part of tendon repair.[1]

This patient was seen recently for evaluation of "hypertrophic cardiomyopathy" diagnosed by echocardiography. His echocardiogram showed normal left ventricular (LV) systolic function and global longitudinal strain, biatrial enlargement, and diastolic LV septal and posterior wall thicknesses of 1.8 and 1.4 cm, respectively. He was asymptomatic and had no history of hypertension or familial hypertrophic cardiomyopathy. His ECG did not show LV hypertrophy. Because transthyretin amyloidosis (ATTR) can cause biceps tendon rupture years before symptomatic cardiomyopathy,[2] we obtained a technetium-99m pyrophosphate cardiac amyloidosis scan which showed diffuse uptake, consistent with ATTR cardiac amyloidosis. Subsequent serum and urine testing showed no evidence of a monoclonal gammopathy, excluding AL amyloidosis, and genetic testing was negative for hereditary ATTR amyloid. The patient has been started on Tafamidis 61 mg daily.

We update this case to attribute less responsibility for the patient's tendonopathy to the statin/ezetimibe treatment. This case illustrates the importance of considering amyloidosis in even asymptomatic patients with increased cardiac wall thickness especially if they have a history of tendonopathy. This case also raises the question of whether statins increase tendonopathies in patients with tendon amyloidosis.

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Statins in primary prevention of cardiovascular disease – should we start while young and healthy?

Recently published meta-analysis by Kostis et al. indicates a definite, statistically significant and clinically relevant benefit of statin treatment for primary prevention of atherosclerotic cardiovascular disease (CVD) in elderly persons (>75 years of age).[1] However, it also prompts a question about the optimal time for initialization of such a treatment in primary CVD prevention. Atherogenesis often begins in childhood, with the rate of plaque progression and occurrence of CVD events depending on the present CVD risk factors, primarily plasma level and duration of exposure to LDL-C.[2,3] Higher LDL-C value at younger age is predictive for atherosclerotic disease later in life, independently of subsequent LDL-C values.[2] In almost 70% of the general population, with decades of exposure to borderline or slightly elevated LDL-C levels, the risk of atherosclerotic disease is 3-4 times higher than in people who have had decades of low LDL-C levels.[2] Finally, even when the increased levels of LDL-C were significantly reduced at later age with the use of statins, the risk of atherosclerotic disease remained significant.[2] At the same time, early intervention to significantly lower LDL−C levels may substantially reverse, or even eradicate, earlier stages of atherosclerosis.[3] Moreover, numerous evidence suggest that the atherosclerotic process would not occur if LDL-C levels were <50 mg/dl.[3]

In recently published study, early subclinical atherosclerosis was detected in 61.8% of apparently healthy middle-aged (40-54 years old) men and women and its progression was observed in ~40% of participants over a 3-year follow-up, even in those with low CVD risk; during the same period 31.2% of previously disease-free individuals developed atherosclerotic changes. Dyslipidemia was confirmed as the strongest modifiable independent predictor of onset and short-term atherosclerosis progression.[4] In light of these data, it can be expected that without lipid lowering therapy, majority of people will develop manifest CVD or will have clinically silent advanced calcified atherosclerotic lesions by the time they reach age >75 years. On the other hand, even the intensive statin therapy has significantly weaker effect on more advanced atherosclerotic lesions and, also, the statin-associated CVD risk reduction is achieved after in average 5 years of therapy.[2,5] Evidence suggest that despite a successful reduction in CVD events accomplished in patients with atherosclerotic diseases treated with intensive statin therapy, their incidence in this patient population is still significantly higher than that seen in individuals with long-standing low LDL-C levels.[2] Therefore, although elderly people with additional risk factors and no known CVD may benefit from statin treatment, the onset of statin administration in senior age did not provide maximal preventive effect and their application was nevertheless overdue. It is clear that initiation of statin therapy as primary CVD prevention should start much earlier, in men at the latest between 30 and 40 years of age, in women in the perimenopause or early menopause, because long-term exposure even to LDL-C values for which current guidelines do not

recommend statin treatment may results in CVD events in 6th or 7th decade of life.[3,6,7]

However, one of the most frequent causes for the lack of implementation of adequate statin treatment in primary CVD prevention is the rigid adherence to the guideline recommendations by the medical practitioners and their attitude towards statin therapy.[8] At the educational meeting on the prevention of atherosclerotic CVD entitled: "*A new paradigm in atherosclerotic CVD prevention*", held for general practitioners (GPs) in September 2019 in Split, Croatia, out of 286 surveyed GPs, 32% of respondents pointed out dyslipidemia as the most important atherosclerotic risk factor, 8% smoking, 8% hypertension, 4% obesity, while 48% of GPs considered all CVD risk factors equally significant. At the same time, 6.5% of the surveyed GPs believe that LDL-C values <50 mg/dl achieved in young age and maintained throughout life may decrease the incidence of CVD slightly, 54.5% significantly, 16.4% in full and 22.6% only if other CVD risk factors were corrected. Nevertheless, when prescribing statins in primary prevention, as much as 78% of the GPs are guided by the current patient's absolute risk rather than by the long-term risk and they are not ready to recommend statin therapy to the apparently healthy young and middle-aged people with LDL-C value around or slightly above 116 mg/dl. At the same time, 42.9% of the GPs do not prescribe statin therapy to elderly in fear of its potential side-effects, and 39.3% due to the restrictive rules of insurance companies. Finally, only 16% of the GPs knew their own LDL-C values and none of them were taking statin as a measure of primary CVD prevention!

Therefore, one of the most important measures for improving primary CVD prevention is to educate medical professionals, especially GPs, that statin treatment should start in young or early middle age, thereby focusing on preventing atherosclerotic plaques rather than on decreasing the risk of CVD events, with the target LDL-C values as low as possible, preferably <50 mg/dl.[3,6] These LDL-C levels prevent or completely regress early atherosclerotic plaques, even in persons with additional CVD risk factors.[3,6] If medical professionals accept the paradigm - *if atherosclerotic plaques are prevented, atherosclerotic consequences do not occur* -[3] only a very small number of middle-aged people will not use an inexpensive, efficacious and safe statin therapy, and the dilemma about starting statin treatment as a measure of primary CVD prevention in elderly individuals will no longer exist. As the most important result of these preventive measures, the vast majority of population will be spared of potentially life-threatening and disabling CVD events and/or percutaneous or surgical coronary interventions.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The Right Ventricle in COVID-19 Patients

The acute coronavirus disease 2019 (COVID-19), due to Severe Respiratory Syndrome Coronavirus-2 causes an inflammatory state with cytokine release.[1] Heart function may be affected, particularly in patients presenting with comorbidities and previous cardiovascular disease.[2] In the meantime, the COVID-19 causes lung injury and acute respiratory distress syndrome (ARDS), a frequent complication in critically ill patients.[3] The ARDS management requires specific lung ventilation strategies using recruiting maneuvers, prone position, high level of positive end-expiratory pressure and low tidal volumes. However, in intensive care unit, ARDS may be associated with hemodynamic instability and right ventricular (RV) dysfunction. The RV, in comparison with the left ventricle, discloses a thin wall with high dispensibility and acts normally in a low resistance system, in spontaneous ventilation. The afterload of the RV is determined by the pulmonary vascular resistance. In ARDS, the presence mechanical ventilation reduces the venous return, due the positive intrathoracic pressure. Also, in this situation, the RV afterload increases, secondary to the increase of the transpulmonary pressure and of the pulmonary vascular resistance and the vasoconstriction related to hypoxemia and hypercapnia.[4] The onset of RV dysfunction and RV dilation (Figure 1) may also affect the left ventricular function and loading. This is explained by ventricular interdependence and paradoxical septum. In this case, a reduced cardiac output occurs, depressing the systemic perfusion and exposing the patient to RV ischemia. In addition, COVID-19 patients disclose a hyper coagulate state avec a significant incidence of pulmonary thrombotic