



## EDITORIAL

## Familial hypercholesterolemia in high performance athletes: A case series and short clinical review



### Hipercolesterolemia Familiar en deportistas de alto rendimiento: una serie de casos y una breve revisión clínica

Chronically elevated cholesterol levels in the blood cause hypercholesterolemia, when total cholesterol levels are over 200 mg/dl or 5.172 mmol/L. Total cholesterol levels consist of high-density lipoprotein (HDL), low-density lipoprotein (LDL). High levels of LDL increase the risk of cardiovascular disease (CVD) and HDL is related to the healthy cardiovascular system. The presence of high levels of triglycerides in blood elevates the risk of cardiovascular complications. There are two types of hypercholesterolemia: primary and secondary. Primary is related to genetic disorders and secondary is caused by other systems pathology like hepatic, endocrine or renal. The children are not excluded from this pathology and usually, the early or familial hypercholesterolemia (FH) is related to genetic predispose. It must be treated in early ages because there is a direct relationship between chronically elevated cholesterol levels and coronary heart disease (CHD) in adult ages.<sup>1</sup> Individuals with elevated total cholesterol levels (>200 mg/dl) have approximately twice the CDH risk of those with optimal levels (<180 mg/dl).<sup>2</sup> It has been demonstrated that reduction in serum cholesterol can reduce CHD risk, for example, reductions of around 0.6 mmol/L can reduce the incidence of ischemic heart disease by 54% at the age of 40, reducing to 19% at 80 years of age.<sup>3</sup> A reduction in total cholesterol is considered the gold standard in preventative cardiovascular medicine.<sup>4</sup> Actually, statins, the hydroxy-methyl-glutaryl CoA reductase inhibitors, are the most effective medication for reducing LDL high concentrations in the blood. Statins therapy is usually related to muscle complaints like myalgia, weakness, cramp, that could compromise the treatment. It has been reported that the incidence of myalgia can arrive at 25% of subjects<sup>5</sup> and cause muscle weakness<sup>6</sup> during statin therapy. Another report demonstrated that there was no effect of statin daily treatment on muscle strength or exercise performance in healthy subjects<sup>7</sup> but it significantly increased the frequency

of myalgia. There are several papers that are describing the benefits of exercise in the improvement of the lipid profile. In addition, Aadahl et al.<sup>8</sup> reported significant associations between physical activity and improvements in total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides among 4039 participants in the five-year follow-up study. Kesaniemi et al.<sup>9</sup> reported benefits of physical activity in increasing HDL cholesterol (mean of 4.6%), but the effects of LDL cholesterol and triglycerides were reported as being inconsistent after reviewing 51 papers. We must know that the terms 'physical activity' and 'exercise' are usually confused<sup>10</sup> because they representing two different ideas. 'Physical activity' refers to any bodily movement produced by skeletal muscles that always results in an expenditure of energy (expressed in kilocalories), and which includes a broad range of occupational, leisure and daily activities. 'Exercise' instead refers to the planned or structured physical activity, performed for a reason, which can be aerobic exercise, resistance training or combined aerobic and resistance training.<sup>11</sup> It is very rare that high sports performers could suffer from elevated cholesterol but there are several cases of familial hypercholesterolemia in professional athletes and they need to be treated with the statin in early ages. Sinzinger H and O'Grady concluded that the great majority of professional athletes with severe FH do not tolerate any of statin available.<sup>12</sup> We would like to talk about the following two cases of FH in two young football players from elite football academy.

### Case 1

An 11-years-old male primary school student was diagnosed with hypercholesterolemia with the total cholesterol of 350 mg/dl and LDL 250 mg/dl. Physical exploration had not revealed any physical stigmata of hypercholesterolemia (arcus senilis corneae, xanthoma, or tendinous xanthoma). The patient's family history was remarkable, his father had hypercholesterolemia and his grandfather had premature coronary disease. Bilateral carotid artery ultrasound demonstrated normal intimal thickening and no plaques. The patient's cardiac stress test showed no ischemic changes and echocardiogram demonstrated a normal aortic valve, without any regurgitation, or aortic stenosis. Due to patient's

clinical history, laboratory and genetic analysis he was diagnosed with hyperlipidemia type IIa of monogenic heterozygous FH with LDLR mutation. The patient followed medical treatment with atorvastatin 20 mg daily and dietary modifications and after 2 years his cholesterol and LDL levels were at 228 mg/dl and 172 mg/dl. The patient's cardiac stress test showed no ischemic changes. He plays in elite football academy (323 h of soccer exposure per season) and he had never presented myalgia, muscles weakness or other symptoms related statin side effects.

## Case 2

16-years-old secondary school student, the elite football academy resident, being 7 years of age has been diagnosed with FH. His family history was presented, his father and two older brothers were diagnosed with FH and were following the treatment with statins. Due to patients and family history, he was diagnosed with hyperlipidemia type IIa of heterozygous FH. He underwent the treatments with atorvastatin 20 mg daily and the last cholesterol and LDL level were at 187 mg/dl and 135 mg/dl. During the last season the patient had two episodes of vasovagal syncope (VVS) and due to FH history the patient was studied with cardiac stress test, echocardiogram, cardiac magnetic resonance imaging (MRI), Holter monitoring test, Tilt table test (TTT). TTT was positive and it confirmed the suspected diagnosis of VVS and the rest of tests were normal. During his first years in high-performance football academy, he presented several muscular and tendon injuries probably related with his adaptation processes to the elevated volume of training and not with the statin treatment because actually he does not have any muscular or tendon symptoms after applying preventive exercises daily and he is following the therapy with atorvastatin daily.

## Discussion

There are very few publications related to FH and high-performance athletes. FH is an autosomal dominant genetic disorder that produces elevations in LDL cholesterol.<sup>13</sup> High levels of circulating LDL lead to the rapid development of atherosclerotic cardiovascular disease (ASCVD).<sup>14</sup> Recent research suggests that the diagnosis of FH is quite common in hospitalized patients with premature acute coronary syndromes (ACS).<sup>15</sup> FH needs to be treated to reduce the circulating LDL cholesterol levels in order to decrease ASCVD risk. Statins are the most successful and most employed lipid-lowering agents; their efficacy to significantly reduce LDL levels, cardiovascular disease (CVD) risk, morbidity, and cardiovascular mortality were demonstrated by randomized clinical trials and by meta-analysis. The meta-analysis of 20 interventional studies with monotherapy statins showed that each mmol/l reduction in LDL was related with 20% reduction in CVD risk.<sup>16</sup> It is documented that statins increase mild muscle complaints, like myalgia, weakness, cramps. The incidence of myalgia during statin therapy could vary from 1%<sup>17</sup> to 27%.<sup>18</sup> New research concluded no effect of atorvastatin 80 mg daily on muscle strength or exercise performance in healthy subjects, but significantly increase the frequency of myalgia.<sup>7</sup>

That is could be the reason why athletes do not tolerate the treatment with the statin, for example, Sinzinger H and O'Grady<sup>12</sup> observed that only six from the 22 athletes finally tolerated at least one statin and possibly because this population were more alert to the possible muscular injury. Cholesterol-lowering diet could be prescribed to the athletes and it will be well tolerated but actually, the effectiveness of cholesterol-lowering diets or any other dietary interventions suggestions (omega 3 fatty acids, plant sterol or stanols, soy protein, dietary fibers) for familial hypercholesterolemia, without combination with drugs therapy, is doubtful because we need more parallel, randomized controlled trials to know potential benefits of this intervention.<sup>19</sup>

In our cases, the soccer players with FH were treated with atorvastatin, one of the athletes never presented any muscular injury, and another one suffered mild tendon injuries and muscular complaints. Then we introduced injury preventive exercises and the control of loads of training and after several months he stops presenting that complains. The daily statin therapy was not suspended. Athletes under the age of 40 who die suddenly during exercise are more likely to have had hypertrophic cardiomyopathy. However, some young athletes who die suddenly during exercise are likely to have had severe coronary artery disease as a result of familial hypercholesterolemia. Our opinion is that all professional athletes with FH should be advised the treatment with the statin to reduce blood LDL cholesterol concentrations and CVC risk. The muscle complaints could be controlled with preventive exercises program or control of training loads or modifying statin therapy. However, in professional sports the good perception of wellness is very important, that why the majority of professional athletes probably will not follow the recommendations of the treatment with statin<sup>12</sup> but the sportsphysicians aim will be to convince the athletes and to take care about his health, wellness, and good performance.

## Conflicts of interest

There are no conflicts of interest.

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