LITERATURE REVIEW

The role of severe OSAS in the atherosclerotic disease: pharmacological treatment with statins

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ABSTRACT

There is a lot of scientific evidence demonstrating the close relationship between obstructive sleep apnea syndrome (OSAS) and atherosclerosis in patients without comorbidities such as hypertension, cigarette smoking and obesity. Statins proved to reduce the risk of vascular events in adult patients with metabolic syndrome by about 20%. On the basis of these results, patients older than fifty years of age, with severe OSAS at high risk for coronary heart disease and stroke, could take statins, as they can reduce the carotid and coronary early vascular risk.

Strengthening the prevention strategies against primary atherosclerosis will need to be one of the focal aims of future health-care programs.

KEYWORDS: obstructive sleep apnea syndrome, statins, atherosclerosis, metabolic syndrome

INTRODUCTION

There is a lot of scientific evidence demonstrating the close relationship between obstructive sleep apnea syndrome (OSAS) and atherosclerosis in patients without comorbidities such as hypertension, cigarette smoking and obesity[1-3]. Currently, there is no evidence for drug use in early atherosclerosis in OSAS patients[4]. OSAS through nocturnal intermittent hypoxia is responsible for early atherosclerosis by two molecular mechanisms: oxidative stress, sympathetic hyper-reactivity leading to an inflammatory process with vascular and endothelial dysfunction, platelet hyperaggregability and, finally, metabolic dysfunction characterized by hyperinsulinemia, hypercholesterolemia and alteration of leptin and ghrelin. Other risk factors are sex, age, genetic factors and cigarette smoking[5]. Obstructive sleep apnea syndrome occurs in all age groups[6,7] and is certainly more common in males than females. 4% of men and 2% of women in the general population, between 30 and 60 years old, have a high number of apneas per night and complain of excessive sleepiness during the day. Higher rates of about 11% have been observed in individuals over 60 years old.

Obstructive sleep apnea syndrome is classified into three grades of severity based on the apnea/hypopnea index (AHI), corresponding to the number of episodes of apnea and / or hypopnea per hour of sleep[8]. OSAS is slight if the AHI is between 5 and 15, moderate if the AHI is between 15 and 30, severe if the AHI is greater than 30 events per hour of sleep.

Metabolic syndrome (MS) is diagnosed on the basis of these fundamental data: increased abdominal circumference, hypertension, fasting hyperglycemia with hyperinsulinemia, increased serum triglycerides and a decrease of low-density lipoprotein (LDL). MS in obese patients with hypertension is a proinflammatory and prothrombotic condition; a similar condition coexists in patients with OSAS. Obesity and MS[9] are confounding factors in severe OSAS and are present in 51.2% of patients with severe OSAS. 67% of patients with OSAS[10], who were asymptomatic for chronic obstructive coronary disease, showed a picture of coronary artery disease (CAD) with coronary artery calcifi-

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cation (CAC). These data strongly support the theory that OSAS is an independent risk factor for CAC. In addition, a recent study[11] showed that in OSAS patients the intense sound vibration caused by nocturnal loud snoring could cause direct mechanical damage to vascular endothelium and its dysfunction may promote the early onset of atherosclerosis.

The only drugs that have shown scientific evidence[4] in the pharmacological treatment of OSAS are mirtazapine and protriptyline (degree B of recommendation for mirtazapine and protriptyline, degree C of recommendation for folate, vitamin B6, B12, C, E). A recent study[12] based on the analysis of data obtained from Wisconsin Sleep Cohort and conducted on 1546 patients followed for a period of 22 years, showed a strong association between OSAS and long-term mortality by tumors that exceeds the one previously observed for all-cause and cardiovascular mortality.

THE ROLE OF STATINS IN THE CONTROL OF EARLY VASCULAR RISK

Statins reduce the risk of vascular events in adult patients with MS by about 20%. Regardless of their cardiac status, the benefits of therapy are much higher than the known risks. A recent meta-analysis[13] conducted by the Cholesterol Treatment Trialists' (CTT) Collaboration and published online in *The Lancet* is making a noise in the scientific world. In the conclusion, the authors note that, according to current international guidelines, low cardiovascular risk subjects would normally not be considered suitable for treatment with statins and therefore, according to the results of the study, these guidelines should be reviewed. The analysis included data from 22 trials comparing statins and a control group, and five trials comparing statins at different dosages, with approximately 175,000 total patients enrolled. The researchers divided the participants into five categories of baseline risk for major cardiovascular events at 5 years (<5%, ≥ 5% to <10%, ≥ 10% to <20%, ≥ 20% to <30% and ≥ 30%) and calculated for each one the reduction in the risk of these events (major coronary events, stroke and coronary revascularization). According to these calculations, statins reduced the risk of serious vascular events by 21% for each 1 mmol/L reduction in LDL cholesterol in each of the five groups, including patients from the two lowest risk categories, i.e. those with a 5-year risk of major vascular events less than 10%, generally considered unsuitable for treatment with statins. Since most statins can reduce LDL cholesterol much more than 1 mmol/L, the researchers note, even higher absolute reductions of serious vascular events could be achieved if these hypolipidemic agents were used more.

The authors also calculated that lowering the threshold for the prescription of Statins to a 10-year cardiovascular risk of 10%, five million more people would be taking these drugs, and this would prevent 2,000 deaths and 10,000 heart attacks and strokes each year. About half of these deaths occur in previously apparently healthy people. These data suggest the possibility of treating also low cardiovascular risk patients. Analysis of the data also does not provide evidence that lowering LDL cholesterol with a statin increases the incidence of cancer and cancer mortality or mortality from other non-vascular causes. The authors of the work conclude that statins can cause a slight increase in the risk of hemorrhagic stroke and diabetes, but the proven benefits of these drugs far outweigh these potential risks. Nonetheless, the results of the meta-analysis suggest that treating patients at a lower than 1% risk is probably expedient in terms of cost-effectiveness. Following this study, the British National Institute for Health and Clinical Excellence (NICE)[14] announced that it would update its guidelines, in the light of the new evidence available on the threshold for statin treatment, including that emerging from the newly published work on *The Lancet*.

Another recent study[15] on the importance of statins in the treatment of atherosclerosis was presented during the 2012 conference of the American College of Cardiology in Chicago. It showed that aggressive treatment with statins (rosuvastatin 40 mg/day) can significantly reduce the lipid content of atherosclerotic plaques in a few weeks. Previous studies conducted by Saturn and Stradivarius[16,17] have shown that statins can lead to regression of non-obstructive coronary atheromas, demonstrated by intravascular ultrasonography (IVUS), but up until now it was not clear whether statins were able to modulate the coronary plaque composition or the physiology of the flow of obstructive lesions. The patients participating to the trials were affected by multivessel coronary lesions of hemodynamic significance, and were candidates to percutaneous coronary revascularization. The researchers evaluated the fractional flow reserve (FFR) of the remaining non-target lesions in order to determine whether they had hemodynamic significance. Patients with FFR <0.8 were enrolled in the study, and their lesions were analyzed by gray scale imaging; then they were treated in a randomized way with the statin they were already previously receiving, plus dual antiplatelet therapy or an aggressive treatment with 40 mg/day rosuvastatin. The imaging analyses were repeated 6 to 8 weeks later.

It was observed that the group treated aggressively showed a significant reduction in the lipid load index compared to the group treated with standard therapy. The study has shown that aggressive statin therapy (rosuvastatin 40 mg/day) may change the composition of

a plaque and stabilize it within two months. The authors are already planning a follow-up clinical study, in which many more patients will be enrolled, and where this concept will be tested; an evaluation will also be made as to whether there can be changes in hemodynamic parameters within 8-9 months that will allow patients to avoid coronary heart surgery.

A recent study[18] has demonstrated that Simvastatin in patients with primary hypertension without hyperlipidemia reduces muscle sympathetic nerve activity (MSNA), without altering the modulation of arterial baroreflex for MSNA or heart rate (HR) and blood pressure (BP) and flow-mediated vasodilation. The MSNA can in fact be increased in patients with artery hypertension without hyperlipidemia. This study suggests a role for statins in the modulation of MSNA. Statins are in fact known to have effects that go beyond the single lowering cholesterol, but they can also play a role in hypertension, as reflected OSAS patients.

A recent meta-analysis[19] show that all statins exert only a reduction of blood pressure, but this effect is significant, especially in patients with poorly controlled hypertension. Therefore, adding to the cardiovascular risk reduction conferred by statin therapy, such pleiotropic mechanism becomes clinically significant in patients at high or intermediate cardiovascular risk.

CONCLUSIONS

The recently published meta-analysis on The Lancet CTT (Cholesterol Treatment Trialists' Collaborators) provides further evidence of statins being a safe and effective way to reduce the risk of heart attack and stroke, even among people at very low risk for major cardiovascular events. A recent review, on the usefulness of long-term statin in primary prevention of cardiovascular disease, concluded by inviting clinicians to exercise caution in prescribing statins for primary prevention in patients at low cardiovascular risk[20]. On the basis of these results, patients older than fifty years of age with severe OSAS, at high risk for coronary heart disease and stroke, could take statins as they can reduce the carotid and coronary early vascular risk. One study[21] showed that 20% of severe OSAS patients developed an early carotid atherosclerosis.

On the basis of the CTT study, the suggestion can be made that it may be appropriate to prescribe statins to subjects aged >50 years, since 83% of men over 50 have a 10-year cardiovascular risk of 10%. In fact, the benefits to be gained by giving statins to anyone older than 50 years of age would probably result in a net saving for the public health service, by reducing health care costs resulting from heart attacks and strokes, prevented by statins.

OSAS is, among cardiac-metabolic disorders, still underestimated from an epidemiological point of view; it is associated in 67% of cases with an asymptomatic coronary syndrome, and in 51.2% with MS. In the future, a lot of public health resources will be needed to diagnose and early treat it.

Strengthening the prevention strategies against primary atherosclerosis will need to be one of the focal aims of future healthcare programs. Furthermore, as an increased protection from risk factors hinges on an increased level of education, this means that education to healthy lifestyles needs to be greatly enhanced by the administrations and to become an integral part of public healthcare policies. This is a public health service yielding slower effects, but certainly more efficacious also for the economy of the entire public healthcare system. Authors interpret these results by suggesting that chronic hypoxia-induced apnea makes cancer cells more resistant and accelerate their growth. This study provides important evidence that OSAS is associated with increased tumor mortality, as well as general and cardiovascular mortality.

Competing interests

The authors declare that have no competing interests.

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