President's Page

Cholesterol: "Targeting" the Enemy

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Cholesterol and triglycerides are the two main forms of lipid; the first is an essential structural component in the cell membrane and the synthesis of certain hormones, while the second is a basic energy storage molecule. Dyslipidaemias are disturbances (quantitative or qualitative) of the metabolism of lipoprotein particles (chylomicrons, VLDL, LDL, HDL) that transport lipids within the organism and are classified as primary, when they have a genetic (inherited) aetiology, or as secondary, when they are a concomitant finding with other pathological conditions (diabetes mellitus, hypothyroidism, nephrotic syndrome, gestation, Cushing syndrome, obesity, corticosteroids, diuretics in large doses, beta-blockers, antiretroviral drugs).

According to recent data from the World Health Organisation (WHO), the prevalence of dyslipidaemias in Greece is quite high, even though we are quite well-placed compared to most countries of the Western world: more than 50% of adult Greeks have total cholesterol levels ≥200 mg/dL, while 13% of the population has a total cholesterol level ≥240 mg/dL. It should be noted that preventative measures during the last 30 years have led to a progressive reduction in cholesterol levels. Thus, from 220 mg/dL, which was the mean value in 1980, we have reached 195 mg/dL today.[1]

The first correlation between cholesterol and cardiac events was found in 1961 and was based on the results of the Framingham study,[2] which also introduced the concept of risk factors for cardiovascular disease. Since then, many studies have quite definitively documented and established that elevated blood cholesterol, and dyslipidaemias in general, are responsible for the initiation and promotion of atherosclerotic processes and, together with diabetes mellitus, arterial hypertension, and smoking, are among the basic modifiable cardiovascular risk factors. Furthermore, the coexistence of multiple factors, apart from increasing the cardiovascular risk geometrically, is also a common finding in daily clinical practice. For this reason, the management of dyslipidaemias should always be ranked in the broader context of cardiovascular prevention, as defined in the guidelines of the European Society of Cardiology in 2012.

The first thing is to determine the population groups that need to undergo preventive laboratory screening. According to the 2011 ESC guidelines for the treatment of dyslipidaemias, a check of the lipid profile should be carried out:

- In men who are aged over 40 years and women who are aged over 50 years or are menopausal.
- In individuals with known atherosclerotic disease or findings of subclinical atherosclerosis.
- In patients with type 2 diabetes mellitus, regardless of age.
- In individuals with a family history of premature coronary artery disease or severe dyslipidaemia.
- In individuals with arterial hypertension.
- In overweight and obese individuals, and in those with abdominal obesity.
- In individuals with chronic inflammatory diseases (*lupus erythematosus*, rheumatoid arthritis, psoriasis).
- In patients with chronic kidney disease of stage ≥3.
- In patients with clinical manifestations of genetic dyslipidaemia, such as xanthomas, xanthelasmas, and premature *arcus senilis*.
- In patients taking antiretroviral medication.

The testing in the above cases should include levels of total cholesterol, LDL (preferably by direct measurement, given the limitations of Friedeward's indirect calculation), and HDL, as well as triglycerides. In recent years, new parameters have been proposed for the detection of lipidaemic load, such as the concentration of non-HDL cholesterol, apolipoprotein B (apoB) and A1 (apoA1), as well as their ratio (apoB/apoA1), and levels of lipoprotein alpha (Lp[α]). Their indication is still class IIa and up to now their determination is recommended in individuals with diabetes mellitus, metabolic syndrome, chronic kidney disease, and in patients with a family history of early coronary artery disease (Lp[α]), while levels of total cholesterol and LDL are the primary targets of treatment. Blood samples for the determination of lipid profile should be taken after 12 hours' fasting, so that the triglyceride level is not distorted.[3] However, recent studies claim that postprandial triglycerides may offer additional information about lipoprotein residues that promote atheromatosis,[4] while standard meals for the fat tolerance test are already commercially available.

In individuals who have no signs of clinical or subclinical atherosclerotic disease, the next basic step is the determination of the total cardiovascular risk, as it is on this basis that the type and level of intervention will be determined. Large epidemiological studies have given rise to various algorithms for calculating both the 10-year risk (Framingham Risk Score, PROCAM Risk Score, Reynolds Risk Score, QRISK2, Heart Score), and the lifetime risk, using a recent algorithm published by the American Heart Association that was derived from the accumulated data of multiple studies carried out in the USA. The recent ESC guidelines recommend the use of the Heart Score, which estimates the 10-year risk of cardiovascular mortality based on sex, age, smoking, blood pressure and total cholesterol levels, while the latest edition also included levels of HDL cholesterol. A Heart Score ≥10% indicates an individual at very high risk, ≥5% is high risk, ≥1% is moderate risk, while <1% indicates low risk. Of course, we must keep in mind that the risk will be greater than the calculated value in individuals with central obesity, diabetes mellitus, kidney failure, or a positive family history. Additional attention should be paid to young people who, in spite of having low cardiovascular mortality, may be at particularly high relative risk.

A recent meta-analysis of more than 170,000 patients showed that LDL levels are inversely proportional to cardiovascular risk. Decreasing LDL to levels <70 mg/dL, or a decrease of at least 50%, brings the optimum result regarding the reduction in cardiovascular risk.[5] Thus, these limits have also been adopted as targets in patients with very low risk. In high-risk patients LDL levels <100 mg/dL should be achieved, while in patients at moderate risk levels <150 mg/dL are recommended.

The treatment of a patient with dyslipidaemia should primarily include health and dietary interventions. The adoption of a Mediterranean diet, with daily consumption of fruits, vegetables, and plant fibres, a reduction in the intake of fat to levels <35% of total energy intake, with a preference for mono- and polyunsaturated fats, daily exercise, maintenance of normal body weight, and smoking cessation, all improve the lipid profile.

In cases where these targets cannot be achieved through health and dietary interventions alone, and especially in patients who are at high or very high cardiovascular risk, drug treatment should be started. Statins are the cornerstone of the treatment of dyslipidaemias. Since the 1970s, when they were discovered by Akira Endo,[6] and 1987, when the first statin, lovastatin, became commercially available, they have been one of the most widely studied drugs with the highest level of sales at a world level. Apart from spectacularly reducing LDL levels, they also lead to a parallel reduction in triglycerides and an increase in HDL. Hence, many large randomised studies have shown that they significantly reduce the risk of cardiovascular disease and mortality. Apart from their hypolipidaemic action, they also have pleiotropic effects on atheromatous plaque and atherogenesis; they have an antithrombotic and anti-oxidative action; and they slightly lower blood pressure levels, as well as the risk of osteoporotic fractures.

The administration of statins for primary prevention in individuals with a low risk of cardiovascular disease should be carried out with caution, since there may be adverse effects. The most common are myalgia, with a frequency of 5-10%, myopathy that may rarely lead to rhabdomyolysis, and asymptomatic transaminasaemia. The risk of side-effects is greater in the elderly, the underweight, women, and patients with hypothyroidism or kidney or liver failure. However, in 2008 the JUPITER trial,[7] followed by the WHI trial,[8] showed an increased incidence of diabetes mellitus in patients under treatment with statins, while subsequent meta-analyses determined the relative risk to be between 9-13%.[9] There is a real risk

of developing diabetes mellitus, mainly in individuals with fasting glucose disorders, but this should not affect the decision regarding the initiation of therapy, since the reduction of the cardiovascular risk clearly takes priority.

Recently, the American Heart Association published guidelines for the treatment of hypercholesterolaemia, introducing some basic changes.[10] the most significant difference from the older guidelines is that the recommended targets for LDL and non-HDL cholesterol are absent, while according to the authors there is no evidence from randomised controlled clinical trials to support the therapeutic regulation to a specific "target" value. Furthermore, apart from statins, the lipid reduction offered by other hypolipidaemic agents has not been proved to translate into a further clinical benefit for the patient, remaining as a class IIb indication. Only statins, in intensified or moderately intensive treatment models, should be used, in specific patient groups of course, which include:

1. Individuals with known cardiovascular disease.
2. Individuals with LDL levels ≥190 mg/dL.
3. Diabetic patients aged 40-75 years with LDL in the range 70-189 mg/dL.
4. Individuals with estimated 10-year risk ≥7.5%.

In contrast, hypolipidaemic medication is prohibited in patients with NYHA class II-IV heart failure or kidney failure under haemodialysis. However, according to recent guidelines from the working group on Kidney Disease – Improving Global Outcomes (KDIGO) in the USA, all patients aged 50 years and above with kidney failure stages 1-5 should take statins, the only exception being those under dialysis.[11]

Despite the apparent differences between the recent guidelines from Europe and from the American Heart Association, what we can glean as readers is the need for intervention with both primary and secondary prevention. Our primary goal must be health and dietary conformance and the correct selection of patients who will benefit from drug treatment. "Moderation", not "moderation in all things"!

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