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HYPERCHOLESTEROLEMIA - NON-PHARMACOLOGICAL TREATMENT, MONOTHERAPY OR COMBINATION THERAPY. REVIEW OF THE LITERATURE

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Abstract

Introduction:

As the number of scientific studies on lipid metabolism disorders increases, awareness among the medical community and the general population about the impact of hypercholesterolemia on the risk of cardiovascular diseases is growing. Elevated cholesterol levels in the blood are a major factor in the development of atherosclerosis, thereby increasing the likelihood of sudden cardiovascular events such as heart attacks or strokes. Maintaining normal cholesterol levels in the blood requires effective collaboration between the doctor and the patient, combining optimal pharmacotherapy with effective non-pharmacological methods based on the introduction of a balanced diet and moderate, regular physical activity. Current guidelines, based on numerous scientific studies, provide a clear framework for lipid-lowering treatment, with statins being an integral part. In cases where monotherapy is ineffective, ezetimibe and monoclonal antibodies, among others, can be used. In our work, we will discuss the possibilities of both non-pharmacological therapy and pharmacotherapy.

Aim of the study:

The aim of this study is to review current knowledge on non-pharmacological and pharmacological therapy in hypercholesterolemia.

Material and method:

This article presents the current state of knowledge about non-pharmacological and pharmacological therapy in hypercholesterolemia. Publications reviewed using the PubMed platform contain recent report in field of lipid metabolism disorders. The search included the keywords: ‚Hypercholesterolemia', ‚LDL-C', ‚Statin', ‚Ezetimibe', ‚PCSK9 inhibitors'.

Keywords: Hypercholesterolemia, LDL-C, Statin, Ezetimibe, PCSK9

1. Introduction

Hypercholesterolemia is a condition characterized by elevated cholesterol levels in the blood (plasma). It is not a disease but a disruption of lipid metabolism homeostasis. This disorder is classified as a lifestyle disease because LDL cholesterol is the main risk factor for atherosclerosis and poses a threat of cardiovascular diseases, including heart attack and stroke.

Hypercholesterolemia is an example of dyslipidemia, a condition in which the levels of lipoproteins and lipids in the blood exceed the values considered desirable.

According to the accepted classification, we distinguish two types of hypercholesterolemia:

1. **Primary:**
    - **Monogenic:** Resulting from a defect in a single gene, leading to high LDL cholesterol levels in the blood.
    - **Polygenic:** Resulting from the interaction of environmental (dietary) and genetic factors. Compared to monogenic hypercholesterolemia, polygenic hypercholesterolemia is associated with a lesser increase in triglycerides and LDL cholesterol levels. Noteworthy examples include familial hypercholesterolemia and polygenic hypercholesterolemia (the most common form of hypercholesterolemia, with an improper diet being the most significant risk factor for its manifestation).
2. **Secondary:** A symptom of other diseases. The main causes of secondary increased LDL cholesterol levels in plasma include:
    - Hypothyroidism
    - Nephrotic syndrome
    - Liver diseases with cholestasis
    - Medications: progestogens, corticosteroids, protease inhibitors used in the treatment of HIV infection, thiazide diuretics, some β-blockers
    - Cushing's syndrome
    - Anorexia nervosa

Hypercholesterolemia is rarely diagnosed based on physical symptoms; however, in some patients, the following may be observed: xanthomas (Achilles tendon and extensor tendons of the hands), corneal arcus (pathognomonic for familial hypercholesterolemia in patients under 45 years old) [1].

Many factors can influence the development of hyperlipidemia, known as predisposing factors for hypercholesterolemia, including:

- Diet rich in saturated fatty acids, carbohydrates, coffee, and alcohol
- Smoking

- Pregnancy
- Medications such as corticosteroids, estrogens, progestogens, androgens, thiazide diuretics, vitamin A derivatives
- Coexisting diseases such as hypothyroidism, diabetes, hypoalbuminemia, chronic kidney disease, or hepatic cholestasis [2].

It is possible to influence many of the above factors. Informing patients about implementing appropriate preventive measures can reduce the risk of hyperlipidemia. The principles of preventing hypercholesterolemia include:

- Maintaining adequate physical activity
- Eliminating other risk factors, such as smoking
- Following healthy dietary principles.

Currently, there is no single, specific value of LDL cholesterol concentration in the blood that defines hypercholesterolemia. For healthy individuals, an LDL cholesterol concentration in plasma/serum ≥3.0 mmol/l (115 mg/dl) is considered abnormal. However, for patients with more complex medical histories, different threshold values for normal LDL cholesterol levels are applied:

- Below 115 mg/dl for low cardiovascular risk,
- Below 100 mg/dl for moderate cardiovascular risk,
- Less than 70 mg/dl for high cardiovascular risk,
- Below 55 mg/dl for very high cardiovascular risk.

These LDL cholesterol concentration values determine the plan for further action, such as lifestyle changes through diet modification and physical activity or the initiation of pharmacotherapy. For patients not previously treated with lipid-lowering drugs, intervention strategies are established based on the total cardiovascular risk and serum LDL cholesterol concentration. The risk of death is assessed using the SCORE system (%), which is correlated with the LDL cholesterol level, and specific treatment recommendations are made accordingly [1].

Risk of death according to SCORE (%)	cholesterol concentration LDL					
	<55 mg/dl	55-69 mg/dl	70-99 mg/dl	100-115 mg/dl	116-189 mg/dl	>190 mg/dl
less then 1	lifestyle modification	lifestyle modification	lifestyle modification	lifestyle modification	lifestyle modification, consider pharmacological treatment	lifestyle modification, consider pharmacological treatment
between 1 and (<)5	lifestyle modification	lifestyle modification	lifestyle modification	lifestyle modification, consider pharmacological treatment	lifestyle modification, consider pharmacological treatment	lifestyle modification, consider pharmacological treatment
between 5 and (<)10	lifestyle modification	lifestyle modification	lifestyle modification, consider pharmacological treatment	lifestyle modification, consider pharmacological treatment	lifestyle modification, consider pharmacological treatment	lifestyle modification, consider pharmacological treatment
more then 10	lifestyle modification	lifestyle modification, consider pharmacological treatment	lifestyle modification, consider pharmacological treatment	lifestyle modification, consider pharmacological treatment	lifestyle modification, consider pharmacological treatment	lifestyle modification, consider pharmacological treatment
very high risk of death/second ary prevention	lifestyle modification, consider pharmacological treatment	lifestyle modification, consider pharmacological treatment	lifestyle modification, consider pharmacological treatment	lifestyle modification, consider pharmacological treatment	lifestyle modification, consider pharmacological treatment	lifestyle modification, consider pharmacological treatment

Table 1. Intervention strategy based on LDL cholesterol level and SCORE result.

Hypercholesterolemia can increase the risk of cardiovascular complications. These include atherosclerotic changes in the coronary arteries, which can lead to ischemic heart disease and heart attack; atherosclerotic changes in the carotid arteries, potentially resulting in stroke; and

atherosclerotic changes in the peripheral arteries, which can threaten lower limb ischemia and even necessitate amputation.

Both in Poland and globally, dyslipidemias are the most common risk factors for cardiovascular diseases. In Poland, the problem of hypercholesterolemia affects about 21 million citizens. Among the adult population, elevated LDL cholesterol levels are found in over 60% of individuals, and among patients over the age of 65, even 70%. The underlying cause of this problem is very low awareness among patients, with only 2 out of 10 people knowing their total cholesterol and/or LDL cholesterol levels [1,3-6].

2. NON-PHARMACOLOGICAL TREATMENT

DIET

The impact of dietary habit changes on total cholesterol and LDL cholesterol levels has been demonstrated in numerous scientific studies. Among dietary factors, saturated fatty acids have the strongest influence on LDL cholesterol levels, increasing LDL cholesterol by 0.8–1.6 mg/dl for each additional 1% of energy derived from saturated fats [7]. The presence of trans fatty acids in the diet causes an increase in LDL cholesterol levels comparable to that caused by saturated fatty acids. However, unlike saturated fats, trans fats also HDL cholesterol levels [8]. Trans unsaturated fatty acids are found in small amounts in dairy products and beef, while their main source in food is partially hydrogenated fats resulting from industrial food processing. The average intake of trans fatty acids ranges from 0.2% to 6.5% of total energy intake in different populations [9]. It has been shown that replacing products high in saturated fatty acids, such as butter or lard, with those rich in unsaturated fatty acids, such as sunflower, canola, flaxseed, or olive oils, reduces LDL cholesterol levels by 0.20 to 0.42 mmol/l [10].

PHYSICAL ACTIVITY

Lifestyle modification aimed at improving lipid parameters should be an integral part of hypercholesterolemia treatment. The increasing number of adults with overweight or obesity, particularly abdominal obesity, contributes to a higher prevalence of dyslipidemia. In such cases, it is crucial to reduce caloric intake and increase energy expenditure to reduce body fat and improve fitness. Weight loss in overweight patients improves lipid parameters even with

a modest weight reduction (5-10%), which positively affects other cardiovascular risk factors [11]. The beneficial impact of weight reduction on metabolic parameters is well-documented, although no correlation has been established between weight loss and a reduction in mortality risk from cardiovascular events [12]. Weight loss can be achieved by limiting the consumption of high-calorie foods, making it easier to achieve a caloric deficit (300-500 kcal/day). Lifestyle modification should combine a balanced diet with physical activity. This approach improves both quality of life and physical fitness while reducing bone and muscle loss, which is especially important for the elderly [13]. Every patient with dyslipidemia, even if their body weight is normal, should be encouraged to engage in regular, moderate physical activity for at least 30 minutes a day [14].

SUBSTANCES

It has been shown that quitting tobacco smoking has a positive effect on overall cardiovascular disease risk and particularly beneficially affects HDL cholesterol levels [15].

ADHERENCE TO MEDICAL RECOMMENDATIONS

A significant part of any treatment process, including treatment for hypercholesterolemia, is the patient's adherence to medical recommendations after returning home. After diagnosing the condition, initiating treatment, and communicating essential information to the patient, the role of the doctor becomes passive. From that point on, it is the patient's responsibility to implement treatment and make necessary lifestyle changes. From a medical standpoint, the doctor should address any doubts the patient may have, reassure them with empathy, and ensure that the treatment implemented is optimal. Moreover, it is crucial to inform the patient that adhering to medical recommendations is a vital part of the treatment process. This requires well-developed interpersonal skills and an individualized approach to each patient, facilitating the doctor's ability to motivate the patient to actively participate in their treatment process [16].

DIETARY SUPPLEMENTS

The evaluation of dietary supplements not only involves demonstrating clinical effectiveness in improving health conditions or their potential use in disease prevention but also considers their positive tolerance by the body. The evidence so far regarding dietary supplements does

not provide complete certainty regarding their effectiveness. In our work, we have selected supplements with the highest potential effectiveness.

Phytosterols

Phytosterols, including sitosterol, campesterol, and stigmasterol, are primarily found in plant oils, as well as vegetables, nuts, grains, fresh fruits, and legumes. The main mechanism of action of phytosterols is their competition with cholesterol in the intestinal absorption process, thereby modulating total cholesterol levels. It has been demonstrated that consuming 2 grams of phytosterols per day effectively lowers total cholesterol and LDL cholesterol levels by 7-10% in individuals (effectiveness can vary between individuals). However, the impact on HDL cholesterol levels is minimal [17]. Considering the positive effect of reducing LDL cholesterol and the absence of reported side effects, phytosterol consumption (≥2 g/day with the main meal) may be considered:

1. In individuals with elevated cholesterol levels and moderate or low overall cardiovascular risk who do not qualify for pharmacological treatment.
2. As a supplement to pharmacotherapy in patients at high or very high cardiovascular risk who do not achieve target LDL cholesterol levels with statin therapy or cannot tolerate statins.
3. In adults and children (aged >6 years) with familial hypercholesterolemia (FH), according to current recommendations [18].

Monacolin and Red Yeast Rice (RYR)

The primary mechanism by which Red Yeast Rice (RYR) reduces cholesterol levels is through the inhibition of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase activity by monacolins, which corresponds to the mechanism of statins [19,20]. Currently, the long-term safety of regular use of RYR products has not been definitively established. Some preparations available on the market have been found to contain contaminants, and similar adverse effects to those seen with statin therapy have been reported [21]. Clinically significant

reductions in cholesterol levels (up to 20%) can be observed during treatment with RYR products containing 2.5-10 mg of monacolin K per day [22].

Dietary Fiber (β-Glucan)

According to current medical knowledge, β-glucan, a soluble dietary fiber found in oats and barley, has a beneficial impact on reducing total cholesterol and LDL cholesterol levels. Patients generally tolerate dietary supplements and foods enriched with this fiber well, making their use recommended for lowering LDL cholesterol levels [23]. To achieve a clinically significant reduction in cholesterol levels (about 3-5%), the recommended intake of β-glucan ranges from 2 to 10 grams per day [24].

Soy Protein

The reduction in cholesterol levels attributed to soy is due to the presence of isoflavones and phytoestrogens. It's important to note that the concentration of these compounds gradually decreases with increased processing of soy products. Studies have shown that replacing animal protein products with soy-based products has a modest effect on lowering LDL cholesterol levels [24,25].

Omega-3 Polyunsaturated Fatty Acids

Research has demonstrated that consuming plant-based foods rich in omega-3 fatty acids and fish (twice a week) reduces the risk of cardiovascular-related death and stroke [26-30].

3. PHARMACOLOGICAL TREATMENT

STATINS

In the pharmacological management of hypercholesterolemia, statins are considered the first-line medications. The most commonly prescribed statins include formulations containing atorvastatin and rosuvastatin, which are known for their potent cholesterol-lowering effects within this class of drugs. Statins work by competitively inhibiting the enzyme HMG-CoA reductase in the liver, which plays a crucial role in cholesterol synthesis. By reducing the synthesis of cholesterol, statins lead to a decrease in intracellular cholesterol levels. This, in

turn, upregulates the expression of LDL receptors on hepatocytes (liver cells). Increased LDL receptor activity enhances the uptake of LDL cholesterol from the bloodstream, thereby lowering LDL cholesterol levels in circulation [31]. In therapy, it is valuable to apply the principles of "the lower, the better" and "the earlier, the better" [32,33].

Statin-based pharmacotherapy of hypercholesterolemia is divided into 3 categories of intensity:

- High-intensity, aiming for at least a 50% reduction in cholesterol LDL.
  Examples: Atorvastatin 40–80 mg daily, Rosuvastatin 20–40 mg daily.
- Moderate-intensity, aiming at a 30% to 49% reduction in cholesterol LDL.
- Examples: Atorvastatin 10–20 mg, Rosuvastatin 5–10 mg
- Low-intensity, aiming at a cholesterol LDL reduction of less than 30% [34-37].

In many patients, statin therapy allows achieving target LDL cholesterol levels in the blood. However, in some cases, monotherapy may not be sufficient to achieve the desired therapeutic effect. For patients at high or very high risk of cardiovascular diseases, additional lipid-lowering medications are recommended. Statistics from studies such as Da Vinci demonstrate that up to 82% of very high-risk patients did not achieve therapeutic goals with statin monotherapy, similar to findings from the EUROASPIRE-V study where 71% of high-risk patients faced similar challenges [38-40]. In such cases, combination therapy is justified as soon as possible. According to current medical knowledge, adding ezetimibe (after 4-6 weeks) is recommended for individuals at high and very high risk of cardiovascular diseases who have not achieved therapeutic goals with maximal statin monotherapy. If target cholesterol levels are still not reached despite adding a second agent, the addition of a PCSK9 inhibitor (after another 4-6 weeks) is recommended [41,37]. When managing hypercholesterolemia pharmacotherapy, it is crucial to consider the patient's individual tolerance to statins. Monitoring for adverse effects such as elevated serum ALT and AST levels, muscle pains, or myopathies is essential. If adverse effects occur, physicians should adjust the dose or frequency, switch to a different statin, or combine statin therapy with non-statin treatment. If symptoms persist despite these measures, non-statin therapies should be considered [1,31].

NONSTATIN DRUGS

Recent randomized clinical trials found that the nonstatin LDL-lowering drugs (such as ezetimibe and PCSK9 inhibitors) can be added to statin therapy with noted improvement in cardiovascular outcomes in patients with atherosclerotic cardiovascular disease [34-37]. The mechanism of action of ezetimibe involves inhibiting the absorption of cholesterol from food and bile at the brush border of the small intestine. It does not affect the absorption of fat-soluble nutrients. By reducing the amount of cholesterol reaching the liver, ezetimibe decreases LDL cholesterol levels in the blood by approximately 20%. Studies have shown that adding ezetimibe to moderate-intensity statin therapy reduces cardiovascular risk over a 7-year follow-up period in patients with recent acute coronary syndromes [34,35,42]. PCSK9 inhibitors act on the PCSK9 protein, which plays a role in controlling LDL receptor levels [43]. PCSK9 binds to LDL receptors, leading to their lysosomal degradation and reduced LDL receptor expression when PCSK9 levels are elevated. Consequently, this results in increased LDL cholesterol levels in the blood. PCSK9 inhibitors reduce PCSK9 levels and activity, thereby lowering LDL cholesterol levels in the bloodstream [44]. Currently, the only registered PCSK9 inhibitors are two fully human monoclonal antibodies: alirocumab and evolocumab. Statin therapy increases circulating PCSK9 levels in the blood. Therefore, combining statins with these monoclonal antibodies allows for optimal therapeutic effects [45]. Despite the effectiveness of statins in treating hypercholesterolemia, they have faced unwarranted negative perceptions, leading to increased patient reluctance to take this class of medications. Consequently, there has been a growing trend of non-adherence to treatment recommendations and self-discontinuation of therapy by patients [32,46].

4. SUMMARY

Based on the information provided above, we can conclude that the treatment of hypercholesterolemia and prevention of its complications is a complex and multifactorial process. This phenomenon requires a holistic approach to patient care. The most appropriate course of action appears to be a combination of non-pharmacological methods, such as maintaining a balanced diet and regular physical activity, along with timely initiation of pharmacotherapy when necessary. However, it is crucial to consider the patient's adherence to the recommendations and their level of awareness regarding the implications of hypercholesterolemia.

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