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Research Progress and Application of Lipid-Lowering Drugs and Pharmacogenomics in Managing Chronic Diseases in the Elderly

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Abstract: With the advent of an aging society in China, the elderly population is growing, and their health status and disease burden are also increasing. Cardiovascular and cerebrovascular diseases are the main killers that harm the health of the elderly. Dyslipidemia is one of the independent risk factors for the occurrence of cardiovascular and cerebrovascular diseases. Lipid-lowering drugs, as commonly used drugs to prevent cardiovascular events in clinical practice, are widely used in elderly patients. This article summarizes and categorizes several major types of drugs currently used for lipid-lowering therapy, combining the latest research progress in pharmacogenomics to provide references for lipid-lowering regimens in elderly patients.

Keywords: Elderly; Chronic disease management; Lipid-lowering drugs; Pharmacogenomics

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1. Introduction

With the improvement of living standards and the acceleration of population aging in China, patients' requirements for health care are also increasing. Especially among elderly patients with chronic diseases, due to the diverse and complex types of diseases and the association of many diseases with genes, more detailed classification and targeted intervention are required [1]. However, there are few studies on chronic diseases of the elderly in China. How to meet the needs of personalized diagnosis and treatment of chronic diseases, optimize drug treatment plans, and ensure long-term safety and effectiveness of patients are still key issues that need attention.

In recent years, with the development of pharmacogenomics, personalized diagnosis and treatment of lipid-lowering drugs have become possible. Through correlation analysis of gene polymorphism and drug efficacy, precise drug administration can be facilitated, thereby achieving better treatment effects and reducing toxic side

effects. In recent years, there have been many breakthroughs in research on lipid-lowering drugs based on pharmacogenomics. For example, studies have shown that gene polymorphisms of *SLCO1B1* are associated with statin-induced myopathy, and gene polymorphisms of *APOE* can also affect the lipid-lowering effect of statins [2,3]. Further research has found that variations in the *PCSK9* gene are related to the efficacy of PCSK9 inhibitors. These findings suggest that genetic testing is expected to provide individualized lipid-lowering treatment regimens for elderly patients, thereby optimizing treatment effects and reducing the occurrence of adverse reactions. However, despite significant progress in the field of lipid-lowering drugs in pharmacogenomics, their application in the management of chronic diseases in the elderly still faces many challenges. Elderly patients often have multiple chronic diseases and need to use multiple drugs simultaneously, which complicates drug interactions. This increases the difficulty of implementing individualized drug regimens based on genetic testing. In addition, the high cost of pharmacogenomic testing technology limits its widespread application in primary medical institutions and economically underdeveloped areas. At the same time, the varying levels of clinicians' and pharmacists' knowledge of pharmacogenomics also affect its promotion and application in clinical practice.

2. Overview of pharmacogenomics

Pharmacogenomics primarily studies the effects of drugs on individuals with different genotypes. Currently, multiple reference genomes are used to guide clinical drug administration, including the International HapMap Project, gene frequency distribution characteristics of the Chinese population, and common single-nucleotide polymorphisms (SNPs) in European and American populations. Among them, the genes closely related to cardiovascular diseases are *APOE*, apolipoprotein E, *PCSK9*, and acyl-CoA binding protein genes.

The *APOE* gene plays a crucial role in regulating high-density lipoprotein (HDL) levels, liver cholesterol metabolism, and the formation of atherosclerosis. The *APOE* gene can mediate the clearance of low-density lipoprotein (LDL) by the liver through its encoded apolipoprotein A2, allowing HDL to be enriched [4]. The *PCSK9* gene inhibits the degradation of LDL receptors in the liver, leading to a continuous increase in LDL-C and ultimately causing atherosclerotic lesions in arteries. The acyl-CoA binding protein gene is mainly involved in the body's lipid metabolism through its encoded acetyl-CoA carboxylase. Mutations or variations in these genes can increase the risk of cardiovascular and cerebrovascular diseases.

3. Types of lipid-lowering drugs and genomics

Cholesterol is an important lipid component of the cell membrane and exerts its physiological functions mainly through the action of intracellular β-lipoproteins and apolipoproteins (ApoB). There are a large number of cholesterol receptors on the cell surface that transport cholesterol to the endoplasmic reticulum membrane for storage or secretion into bile, liver, and adipose tissue. It is then released into the bloodstream in the form of very low-density lipoproteins. When the total serum cholesterol (TC) exceeds 10.3 mmol/L, it is considered hypercholesterolemia. Currently, commonly used lipid-lowering drugs in clinical practice include statins, nicotinic acid, fibrates, and resins.

3.1. Statins

As an important class of lipid-lowering drugs, statins primarily work by inhibiting the activity of

3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, thereby reducing endogenous cholesterol synthesis and effectively lowering low-density lipoprotein cholesterol (LDL-C) levels. At the same time, they can also slightly increase high-density lipoprotein cholesterol (HDL-C) and lower triglycerides (TG) [5]. Numerous clinical studies have confirmed that statins can effectively reduce the incidence of ASCVD and are considered cornerstone drugs for lipid-lowering therapy. In genomics, genetic variations in the *SLCO1B1* gene have a significant relationship with the plasma concentration and adverse effects of statins.

The gene encodes the organic anion transporting polypeptide 1B1 (OATP1B1), which is involved in the transport of statins from the blood to the liver [6]. Individuals carrying the *SLCO1B1*5* allele have reduced OATP1B1 transport function, leading to increased blood concentrations of statins and a significantly increased risk of muscle toxicity, such as a higher probability of developing rhabdomyolysis [7]. Additionally, polymorphisms in genes such as *ABCC2* and *CYP3A4* can also affect the pharmacokinetics and pharmacodynamics of statins, resulting in differences in efficacy and safety among individuals.

3.2. Fibrate drugs

Fibrate lipid-lowering drugs are divided into two major categories: niacin and fenofibrate. Fenofibrate can reduce cholesterol formation by inhibiting the activity of HMG-CoA reductase, a rate-limiting enzyme in cholesterol synthesis, and is a commonly used drug for the treatment of mild to moderate hypercholesterolemia. Niacin, on the other hand, is a vitamin with lipid-lowering effects that can increase HDL and regulate the lipid profile, making it a safer drug for the treatment of myopathy and renal failure.

Fibrate drugs primarily work by activating peroxisome proliferator-activated receptor alpha (PPARα), regulating the expression of genes involved in lipid metabolism, promoting the catabolism of triglycerides (TG), significantly reducing TG levels, and moderately increasing HDL-C and decreasing LDL-C. They are suitable for patients with primarily high TG hyperlipidemia or mixed dyslipidemia, and they play a role in reducing the risk of ASCVD while lowering TG-rich lipoprotein levels.

Genomic studies have found that polymorphisms in the *PPARA* gene can affect the efficacy of fibrate drugs. For example, the rs4253778 polymorphism in the *PPARA* gene is associated with the effect of fibrate drugs on reducing TG, and there are differences in drug response among patients with different genotypes [8]. Additionally, polymorphisms in the *APOC3* gene, which encodes a protein that inhibits lipoprotein lipase activity, can also influence the lipid-lowering effect of fibrate drugs, potentially altering their regulatory effect on TG metabolism.

3.3. Resin drugs

Resin drugs, also known as bile acid sequestrants, mainly include bile acid derivatives, polyunsaturated fatty acids, and monoamine oxidase inhibitors. Bile acid derivatives primarily work by competitively binding to cholesterol transporters on the surface of liver cells, thereby promoting the excretion of cholesterol from the body. Polyunsaturated fatty acids mainly reduce blood cholesterol concentrations by promoting the reverse transport of endogenous cholesterol and increasing the excretion of free cholesterol. However, long-term use may increase the risk of arterial hardening and cardiovascular events. Monoamine oxidase inhibitors lower blood cholesterol levels by inhibiting the action of methylmalonyl-CoA oxidase in the polyamine metabolic pathway.

In the field of genomics, there are relatively few studies on resin drugs. However, some research suggests that

polymorphisms in the *ABCG5/ABCG8* genes may affect the regulatory role of resin drugs on cholesterol metabolism. The ABCG5 and ABCG8 proteins are involved in intestinal cholesterol absorption and biliary cholesterol secretion, and variations in these genes may alter the intestine's ability to process cholesterol, thereby influencing the lipid-lowering effects of resin drugs [9].

3.4. Ezetimibe

Ezetimibe selectively inhibits the absorption of intestinal cholesterol by targeting the Niemann-Pick C1-Like 1 (NPC1L1) protein at the brush border of the small intestine, thereby lowering blood cholesterol levels. Ezetimibe can be used in combination with statins to synergistically reduce LDL-C levels. This combination therapy has been shown to be more effective in lipid lowering than monotherapy and has a good safety profile [10].

Genomic studies have revealed that polymorphisms in the *NPC1L1* gene significantly affect the efficacy of ezetimibe. Individuals carrying specific *NPC1L1* gene variations may experience a reduced inhibitory effect on intestinal cholesterol absorption, leading to a decreased lipid-lowering response to ezetimibe. Additionally, polymorphisms in the *ABCG5/ABCG8* genes may indirectly influence the efficacy of ezetimibe by affecting intestinal cholesterol transport and metabolism [11].

4. Drug targets in genomics and prediction methods

Identifying the key genes that affect drug efficacy and toxicity is a critical step in pharmacogenomics, as part of the study of different genetic factors. Reports have shown that gene variations, including ApoE, Lp(a), and PCSK9, can reduce patient responsiveness to statins, while having no significant impact on other lipid-lowering drugs such as ezetimibe and fibrates.

Therefore, it is speculated that this is related to whether the above gene variations lead to changes in the expression level of drug-metabolizing enzymes. For example, increased CYP3A4 activity, elevated CYP substrate specificity, and an increase in CYP degradation products have been observed in patients with *APOE* gene mutations. Meanwhile, the CYP2C19rs7265048 locus is also associated with statin metabolism. Polymorphism at this locus is positively correlated with the therapeutic effect of statins, meaning that individuals carrying this polymorphism show a more significant increase in plasma drug concentration and better drug efficacy after administration. Additionally, mutations in the *LpA* gene or decreased LpA protein levels can affect the beta-oxidation process of fatty acids in the liver, leading to increased cholesterol synthesis and ultimately causing dyslipidemia [12].

Currently, it is known that multiple drugs have potential interactions. For instance, clopidogrel interacts with liver enzyme inducers (LTP), limiting its clinical application. Dipyridamole can interact with rifaximin, simvastatin, fluvastatin, etc., potentially causing an increase in transaminase levels. When fenofibrate is used in combination with hypoglycemic drugs or anticoagulants, it may lead to poor glycemic control due to antagonistic effects.

Some scholars have proposed methods to predict drug mechanisms using bioinformatics tools, employing techniques such as bibliometric analysis, machine learning, and correlation analysis for data processing and mining. A series of mathematical models have been established to evaluate the relationship between specific gene variations and drug responses, providing an important basis for guiding individualized medication. Recently, researchers have selected a large number of differentially expressed genes (DEGs) from vast genetic datasets and constructed a new deep learning-based prediction model based on these DEGs. This model can effectively distinguish changes in

individual gene expression levels and their underlying causal effects, thereby predicting the potential mechanisms of multiple drugs or therapies. This will significantly accelerate the speed of targeted drug development and improve drug development efficiency.

5. Summary and outlook

The acceleration of population aging has made dyslipidemia a common chronic disease among the elderly. Compared to the general population, elderly individuals with high cholesterol tend to have faster disease progression and higher mortality rates. Commonly used lipid-lowering drugs include statins, fibrates, and niacin. In recent years, pharmacogenomics-based research methods have enabled the analysis of the mechanism of action of potential drugs and assisted clinicians in selecting the most suitable medications for patients, thus achieving personalized medication. However, current pharmacogenomics research suffers from a limited sample size and a lack of large-scale clinical trials for validation. Larger, multicenter clinical studies are needed to confirm these findings. Additionally, individual differences in drug response, metabolic enzyme polymorphisms, and genetic instability can significantly impact drug efficacy, making it challenging to conduct precise individualized drug screening based on a single target or pathway. Therefore, it is essential to comprehensively analyze existing research results based on patients' individual characteristics and establish a more comprehensive and efficient pharmacogenomic database through correlation studies across multiple databases. On this foundation, by combining genomics technology with artificial intelligence techniques, a drug-gene interaction network based on machine learning can be constructed. This network can then be used to automatically recommend medication regimens through predictive models, representing a significant direction for future pharmacogenomics research. With the continuous development of pharmacogenomics-related technologies, it is believed that they will provide strong support for rational drug use in clinical settings, allowing elderly patients to benefit from safer and more effective drug treatments [13].

Disclosure statement

The author declares no conflict of interest.

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