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РОЛЬ ХОЛЕСТЕРИНА ЛПНП В АТЕРОСКЛЕРОЗЕ

Аннотация

Прошло более века с тех пор, как была впервые предложена липидная теория атеросклероза. Тем не менее, несколько авторов задавались вопросом, как гиперхолестеринемия способствует ее развитию. Многочисленные клинические, эпидемиологические и экспериментальные данные подтверждают эту связь. Основной причиной смерти в мире по-прежнему является атеросклеротическое сердечно-сосудистое заболевание. В этой статье собраны недавние генетические исследования по менделевской рандомизации и рандомизированные терапевтические испытания по снижению холестерина ЛПНП. Они категорически подтверждают идею о том, что холестерин ЛПНП играет роль в генезе атеросклероза.

Ключевые слова: холестерин ЛПНП; атеросклероз; липидная теория; менделевская рандомизация; клинические испытания.

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THE ROLE OF CHOLESTEROL LDL IN ATHEROSCLEROSIS

Annotation

Over a century has passed since the lipid theory of atherosclerosis was first proposed. Still, several writers have questioned how hypercholesterolemia contributes to its development.

Numerous clinical, epidemiological, and experimental findings support this connection. The world's leading cause of death is still atherosclerotic cardiovascular disease.

In this article, recent genetic research on Mendelian randomization and randomized therapeutic trials for lowering LDL cholesterol are compiled. They categorically support the idea that LDL cholesterol plays a part in the genesis of atherosclerosis.

Keywords: LDL cholesterol; Atherosclerosis; Lipid theory; Mendelian randomization; Clinical trials

Introduction

Despite the lipid hypothesis of arteriosclerosis being over a century old, the cycle of proving causation was not concluded until the end of the twentieth century due to the conclusive findings of numerous investigations on pharmaceutical interventions (2). Ironically, during the past few years, there have been multiple attempts by scientists to discredit the role of cholesterol in the development of arteriosclerosis (3) in the communication media and in certain forums. Luckily, the paper Intervention 2 (fig. 1) provides a strong foundation for the important role of cholesterol, and specifically the cholesterol transported by low-density lipoproteins (LDL-c) as a causative agent of arteriosclerosis, with epidemiological, genetic, experimental, and research pillars(1).

In the majority of individuals, 90% of circulating cholesterol is carried by LDL, which explains the strong link between total cholesterol and LDL-C levels: The Friedewald equation, which states that LDL cholesterol is a function linear of total cholesterol, is used to estimate LDL cholesterol levels in ordinary practice rather than actually measuring them(4). This is why total cholesterol and LDL calculations yield results that are nearly identical in many epidemiological studies.

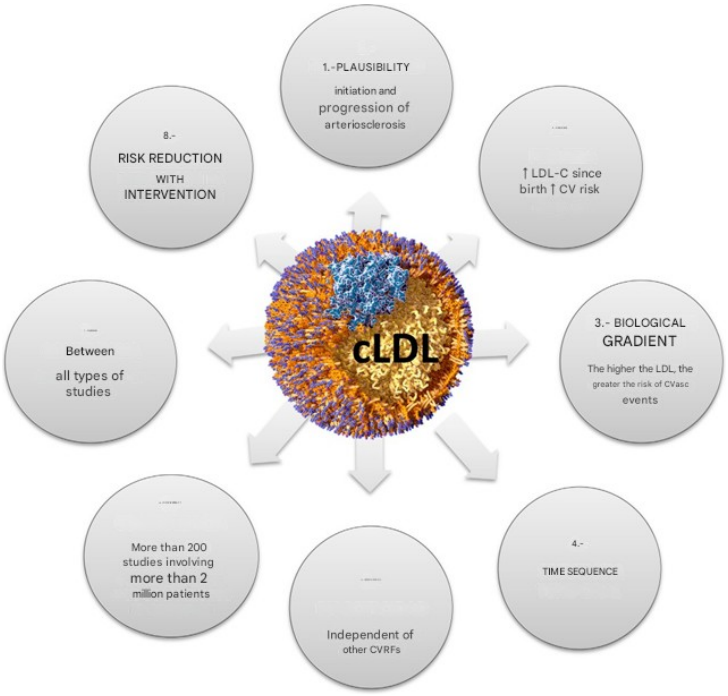

Figure 1 Criteria for causality: low-density lipoproteins (LDL) and arteriosclerosis. Adapted from Ference et al.2.

Materials and methods

Despite the robust, dose-dependent, and repeatable correlation between LDL-C, observational epidemiological studies lack randomized testing and are unable to prove causation due to a number of potential biases, including unknown reasons of confusion. A different kind of observational study known as "Mendelian randomization studies" has received a lot of interest lately (fig. 3)(5). The random distribution of both parents' genes during meiosis gives the cells' germinal emula 23 chromosomes, which is similar to the "assignment random" procedure of clinical trial treatments. Several gene variations have been identified as being linked to variations in c-LDL 10 levels.

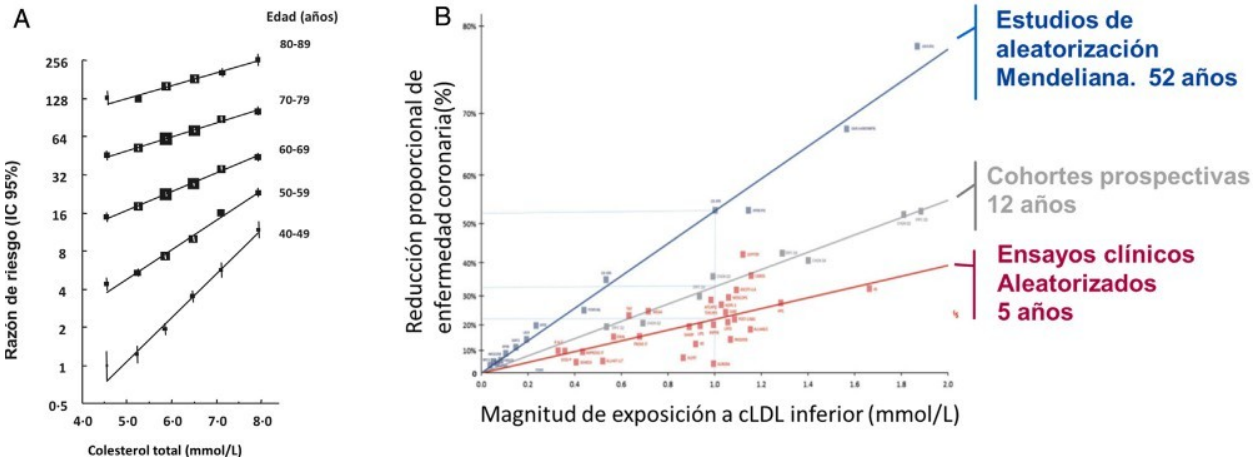

Figure 2 shows the association between coronary heart disease mortality and cholesterol in traditional epidemiological studies (A), randomized Mendelian and Essays clinicians (TO and B). For all cholesterol ranks and age groups, epidemiological classics show a correlation between changes in cholesterol levels and coronary heart disease mortality. Based on Lewington et al. (8).

Changes in cardiovascular morbidity and cholesterol exhibit the same log-linear connection in classic cohort studies(6), Mendelian randomization studies, and interventionist essays. The effects on morbidity depend largely on changes in cholesterol levels during a shorter period of time: five years in intervention studies, twelve years in cohort studies, and more than fifty years in Mendelian randomization studies. From Ference et al. (2) with adaptation.

Results and Discussion

All of the previously discussed evidence is crucial for confirming the causal relationship between c-LDL and atherosclerosis, but it is particularly important to show that lowering c-LDL HE levels is linked to a regression in the size of atherosclerosis plates or a decrease in cardiovascular events(9). Great transcendence 2 turns out to be the case. In this regard, it is crucial to emphasize the data from primary and secondary prevention studies showing that a decrease in the rates of cardiovascular events in the elderly is linked to a reduction in c-LDL levels in the elderly that is accomplished with statins and other treatments.

The strongest evidence in this area comes from statin-induced inhibition of HMG-CoA reductase. This contained information from 26 clinical trials with 170,000 individual participants. I show that, over a median of five years, the risk relative of major cardiovascular events decreases by 22-23% with statin treatment for every mmol/l

(about 39 mg/dl) decrease in c-LDL levels(7). This advantage was minimal in the first year of follow-up, but it was irrespective of the baseline level of c-LDL and grew during the course of treatment years. Furthermore, when HE reaches levels of c-LDL of 70 mg/dL 22, studies using ultrasonography intravascular of the coronary atheromatous plaque have clearly shown that treatment with high-intensity statins stabilizes the progression or even recovers the volume of the plate atherosclerotic(10).

Not only does this affect heart disease ischemic and coronary arteries, but numerous studies have demonstrated that intensive statin treatment lowers the risk of ischemic stroke and the advancement of arteriosclerosis in the carotid arteries, which is also correlated with the degree of c-LDL 23 reduction.

But statins are not the only factor responsible for these positive effects of lowering LDL-C levels. Other therapies have also been demonstrated to lower the incidence of cardiovascular events by lowering c-LDL without blocking HMG-CoA reductase.

In conclusion

In the development of atherosclerosis, c-LDL plays a role that is either etiological or causative. The targets (HMG-coA reductase, NPC1L1, and PCSK9) that were identified from a genetic perspective using Mendelian randomization studies have been validated in intervention studies, which demonstrate that lowering LDL-c levels through procedures or medication treatments is associated with a regression of atheroma plates and a decrease in cardiovascular events linked to atherosclerosis.

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