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Review

Apoprotein C-III: A review of its clinical implications

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ABSTRACT

Apoprotein C-III (apoC-III), originating from the apoA-I/C-III/A-IV gene cluster affected by multiple regulating factors, has been demonstrated to have a validated link with hypertriglyceridemia in humans. Following genome studies establishing the impact of apoC-III on both plasma triglyceride (TG) level and cardiovascular disease (CVD), apoC-III offers us a novel explanation attempting to resolve the long-existing confusion with regard to the atherogenic effect of TG. Notably, apoC-III exerts its atherogenic effect by means of not only intervening in the function and metabolism of various lipid molecules, but also accelerating pro-inflammatory effects between monocytes and endothelial cells. Data have suggested that diabetes, a common endocrine disease, also correlates closely with apoC-III in its apoptosis process of islet βcells. In fact, apoC-III genes, with various mutations among individuals, are also found to have relevance to other diseases, including fatty liver disease. Fortunately, besides present day therapeutic strategies, such as lifestyle changes and lipid-lowering drug treatments, a promising new antisense drug specifically targeting on apoC-III gene expression opens up new avenues. This article mainly summarizes the clinical implication of apoC-III and its future directions of treatment.

Contents

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1. Introduction

Lipid-lowering therapy plays an irreplaceable role in the prevention and treatment of cardiovascular disease (CVD). Among disorders in plasma lipid spectrum, low-density lipoprotein cholesterol (LDL-C) poses a risk for CVD. Statin therapy reduces plasma LDL-C levels and has a protective effect on CVD [1,2]. Clinical evidence has shown that a lipid-lowering strategy that merely focuses on LDL-C is insufficient [3,4]. Also, the risks of cardiovascular events still exist and are closely linked with plasma triglyceride (TG) levels, which is called *residual cardiovascular risk* [4].

It was in 1979 that Zilversmit first elucidated the atherogenic effect of TG [5]. According to the Copenhagen City Heart Study, postprandial TG-rich lipoprotein remnants (TRL-remnants) were considered to promote the development of atherosclerosis (AS, [6,7]). However, opinions about therapeutic strategy on plasma TG have long been controversial matter of debate. In the PROVE IT-TIMI 22 trial, achieving the therapeutic goal of TG < 150 mg/dl was independently associated with a lower risk of recurrent CVD events after acute coronary syndrome, providing evidence for the necessity of intervention on hypertriglyceridemia [8]. Interestingly, the combination of fenofibrate and simvastatin in the ACCORD study resulted in lower plasma TG levels, and had no clinical benefit [9]. In recent years, data have indicated that apoC-III plays an important role in the maintenance of plasma TG level [10]. Moreover, a large number of studies also confirmed that lower TG levels with less CVD risk could be caused by mutations of apoC-III genes [10,11]. In this condition, treatment for targeting TG in CVD seems to obtain its novel clinical application. In this review, we attempt at presenting a comprehensive summary of the clinical implications of apoC-III.

2. Molecular features of apoC-III

ApoC-III is encoded by a region on the long arm of chromosome 11q23 known as apoA-I/C-III/A-IV gene cluster [12]. The protein was first found by W. Virgil Brown in 1969 during analysis of the protein components of human plasma very low-density lipoprotein (VLDL, [13]). In fact, apoC-III, a molecular mass of 8.8 kDa, is initially synthesized as a 99-amino-acid peptide in the liver or intestine and matures after the removal of its 20-amino-acid-residue signal peptide [14]. ApoC-III mainly resides on apoB lipoproteins (chylomicrons and VLDL) and exchanges onto high-density lipoprotein (HDL) in the fasting state [15]. Currently, apoC-III is considered an independent risk factor of CVD, because of its close association with hypertriglyceridemia and other relevant disorders.

3. Regulating factors of apoC-III

A considerable number of studies on regulation of apoC-III gene expression have validated that multiple factors affect the transcription process in either positive or negative ways. It has been suggested that insulin treatment for mouse models with insulin-dependent diabetes mellitus induces a dose-dependent negative regulation of apoC-III mRNA levels through up-regulating hepatic forkhead box O1 (FoxO1, [16,17]). On the contrary, glucose promotes apoC-III transcription by positively regulating hepatic nuclear factor-4 (HNF-4, [18]). Transfection of Rev-erb in apoC-III expressing human hepatic HepG2 cells also leads to repressed apoC-III gene promoter activity [19]. Similar effect was mirrored in farnesoid X receptor (FXR). Interestingly, it has been proved in in vitro studies that treatment of FXR agonist represses liver apoC-III gene expression [20]. Moreover, peroxisome proliferator-activated receptor (PPAR) α suppresses the expression of apoC-III gene by down-regulating HNF-4 and removing the promoter region of apoC-III gene [21]. This mechanism may also explain the effect of lowering plasma apoC-III for some lipid-lowering drugs such as fibrates. In addition, PPARγ coactivator-1β (PGC-1β) is a transcriptional co-activator regulated by plasma free fatty acids. Data also showed that PGC-1β could result in hypertriglyceridemia through stimulating apoC-III gene expression, and by inhibiting hepatic PGC-1β the therapeutic effect of nicotinic acid is achieved [22].

4. ApoC-III and atherosclerotic cardiovascular disease (ASCVD)

4.1. Role of apoC-III genes in ASCVD risk

With more in-depth studies conducted on apoC-III, the impact of apoC-III on the risk of ASCVD has also been demonstrated in genome studies. Available data indicated that the polymorphism of apoC-III genes caused both pathogenic and protective effects. In fact, Sst I polymorphism was the first polymorphism discovered in the apoC-III gene in the 3′ untranslated region (UTR). It was confirmed that this polymorphism was relevant to higher apoC-III levels. It has also been shown in some studies that this polymorphism is associated with both higher risks of CVD and hypertriglyceridemia. Also, a series of mutations on apoC-III have been found [23,24]. Studies on a group of Ashkenazi Jewish people have illustrated that the -641C allele in the apoC-III gene promoter is associated with lower levels of plasma apoC-III, contributing to their lower risk of ASCVD and higher insulin sensitivity [25,26]. In the Exome Sequencing Project, four typical mutations were first systematically described, including three loss-of-function mutations: a nonsense mutation (R19X) and two splice-site mutations (IVS2 + 1G → A and IVS3 + 1G → T), and a missense mutation (A43T, [10]). Although only an extremely small proportion (1 in 150 persons) carried some of these mutations, the risk of ASCVD in the carriers was 40% lower than risk of non-carriers [10]. Correspondingly, another study, including a cohort of 75,725 individuals, also reported that loss-of-function mutations in APOC-III genes caused 44% reduction in non-fasting triglyceride levels and 36% reduction in ischemic heart disease [11].

4.2. Role of apoC-III in lipid metabolism and function

ApoC-III was initially found to have an impact on the metabolism of TGs by uncompetitively inhibiting lipoprotein lipase (LPL) in in vitro studies [27–29]. Subsequently, the specific mechanism was demonstrated as replacing LPL molecules from TRLs and further accelerating its inactivation conversion from dimer to monomer by angiopoietin-like protein 4 (ANGPTL4, [30,31]). In addition, apoC-III also weakens the elimination process of TRL-remnants in the liver [32], and it stimulates recruitment of extra TG onto apoB-100 scaffolds during the synthesis process of TG-rich VLDL in the liver [33]. Interestingly, a recent study suggested that overexpression of apoC-III decreased secretion of dietary TG into lymph, thus causing accumulation of TG in the intestinal lumen, setting a basis for its gastrointestinal regulation pathway [34].

HDL is traditionally defined as a beneficial factor for its protective effect on circulation system against AS [35,36]. In two prospective studies within the Nurses' Health Studies (NHS) and the Health Professionals Follow-Up Studies (HFPS), the anti-atherogenic effect of HDL was redefined. In those two parallel studies, HDL-C was divided into two different subgroups (with or without apoC-III), and HDL particles facilitated with apoC-III were revealed to induce a higher risk of CVD [37]. Proteomic analyses and functional characterizations of HDL isolated from patients with stable coronary artery disease, acute coronary syndrome, and healthy subjects also validated the altered function of HDL particles caused by apoC-III content. In this study, HDL particles with apoC-III content actually stimulated potential endothelial proapoptotic pathways rather than blocking them [38]. These are likely to define the protective and atherogenic subgroups of HDL in another aspect. Hence, apoC-III, a small protein binding on the surface of HDL particles, attenuated the protective effect of HDL. The current evidence of HDL subgroups possibly offers us a reasonable explanation of the fact that drugs that simply target raising plasma HDL levels failed to provide cardiovascular benefits.