

Conventional Concepts in Coronary Heart Disease and New Thoughts in its Prediction

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Abstract

Coronary heart disease (CHD) is the most leading cause of death worldwide. Risk factors of CHD include high blood pressure, smoking, obesity, diabetes, lack of exercise, poor diet, high blood triglycerides, cholesterol, low density lipoprotein (serum LDL), family history, hypertension and depression. Most previous investigations including biochemical as well as molecular markers were successfully predicted CHD. Studies indicated the importance and the benefits of lowering cholesterol and triglyceride blood levels to decrease the risk for developing cardiovascular disease. The present article aimed to discuss and identify nonconventional cardiovascular bio-markers as well as biochemical risk factors in early prediction of CHD.

Keywords: Coronary heart disease; Triglycerides; Cholesterol; Cardiovascular; Lipoprotein

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Introduction

Coronary heart disease (Atherosclerosis and Cardiovascular Diseases) is a disease where blood clots (mainly cholesterol) build up inside the coronary arteries. Clots narrow the coronary arteries and consequently reduce the flow of oxygen to the heart muscle. A large blood clot can completely block blood flow through a coronary artery causing a heart attack and without quick treatment; a heart attack may lead to death. Coronary artery disease (CAD) is the most common type of heart disease, which weakens the heart muscle, contributes to heart failure (where the heart can't pump enough blood to the rest of the body) causing death. In 2013 CAD caused 8.14 million deaths worldwide [1,2].

Risk Factors

Research indicated that risk factors of CHD include high blood pressure, smoking, obesity, diabetes, lack of exercise, poor diet, high blood triglycerides, lipoprotein and cholesterol, family history, hypertension and depression. It's estimated that one third of the U.S population has high triglycerides, a major risk factor for cardiovascular disease [3-6].

High density lipoprotein (HDL, Hyperalphalipoproteinemia) has a protective effect over development of coronary artery disease. HDL is associated with a decreased risk of coronary heart disease [7]. Furthermore, research result showed that high blood

triglyceride levels can predict cardiovascular disease, which causes high mortality in Western society [8]. CHD is one of the major causes of mortality in patients with essential hypertension and insulin resistance (a metabolic disorder that occurs when the body's cells cannot properly intake insulin) [9,10]. Changing lifestyle and medicines can help prevent coronary heart disease. Research showed that high levels of cholesterol and triglycerides can prevent vitamin E reaching the tissues that need it. This can be problematic because vitamin E is important in artery walls, for its antioxidant action, and it appears to play a major role in limiting the oxidation of LDL-cholesterol. When LDL is oxidized, it becomes chemically "stickier," in a sense, and this promotes its accumulation, as plaque, inside arteries. Research result also suggested that vitamin E may also prevent the thickening of blood-vessel walls thus permitting the free flow of blood and consequently favors a good cardiovascular health [11].

Plasma Lipids

Triglycerides and cholesterol are different types of lipids that circulate in the blood. Calories intake by person above needed are converted into triglycerides and stored as fat, which leads hypertriglyceridemia. High-density lipoprotein (HDL) helps remove fat from the body. On the other hand, low-density lipoprotein (LDL) plays in the buildup of plaque inside the arteries causing atherosclerosis. LDL cholesterol and HDL cholesterol are key factors in pathogenesis of atherosclerosis and coronary artery

disease. Increased LDL cholesterol levels and decreased HDL cholesterol levels are associated with increased risk for coronary heart disease. Using fish oil (omega-3-rich triglycerides), garlic, niacin, lavender, holy basil and lemongrass together with good diet and lifestyle changes can alleviate hypertriglyceridemia [12-16].

Moreover, hypertriglyceridemia is often observed in patients with type 2 diabetes as insulin plays a big role in the regulation of lipid homeostasis. When the body is resistant to insulin, the organs that are sensitive to insulin regulation, like the liver and skeletal muscle are unable to function properly [17].

Lipoprotein Lipase

Biologists and clinicians have studied lipoprotein lipase (LPL) for a long time. LPL is an enzyme that hydrolyzes triglyceride (TG) into free fatty acids and glycerol. LPL is the main enzyme that removes triglyceride from the bloodstream. Severe mutations that cause LPL deficiency resulted in type I hyperlipoproteinemia, while less extreme mutations in LPL are linked to many disorders of lipoprotein metabolism. Recent studies also indicated that LPL stimulates selective uptake of lipids from HDL and LDL. Furthermore, LPL stimulates selective uptake of cholesteryl esters from LDL, and this process also occurs *in vivo* in tissues where abundant LPL is present [18-20]

Genetic Variations

Results of research indicated that plasma lipid-lipoprotein levels are under genetic control. Genome-wide association studies have showed that plasma lipids under control of multi-loci (polygenic inheritance). However, most of the identified loci have small effect and explain only one third of phenotypic variations in lipid level. Genes with major roles in lipoprotein metabolism are excellent biomarkers for among individual variations in susceptibility to CHD. Several polymorphisms have been identified in the LPL gene. Three of the polymorphic can alter the protein sequence of LPL, namely D9N, N291S, and S447X. These polymorphic can play role in plasma lipoproteins metabolism and CHD risk. The D9N and N291S alleles were associated with lower levels of HDL. Contrary to that the S447X allele was associated with higher levels of HDL, decreased triglycerides, and reduced CHD risk [21-24]. Many studies showed that LPL is central to TG metabolism. D9N is associated with high TG, lowered HDL concentrations and increase risk of coronary artery disease. LPL was able to completely hydrolyze the retinyl ester to retinol and facilitate uptake of retinoid by adipocytes. Furthermore, LPL hydrolyzes chylomicron and very low density lipoprotein triglycerides to provide fatty acids to tissues. Recent studies also indicated that LPL stimulates selective uptake of lipids from HDL and very low density lipoprotein. Moreover, LPL stimulates selective uptake of cholesteryl esters from LDL via pathways that are distinct from SR-BI. This process also occurs *in vivo* in tissues where abundant LPL is present [25]. Research results also indicated that out of 12 genes studied in a stepwise regression multivariate risk analysis, uncoupling protein 2 (UCP2), apolipoprotein E (APOE), LPL, and apolipoprotein AIV (APOA4) were significantly considered risk factors of CHD. It was found that incorporating conventional risk factors of CRF and

genotypes were more effective than that used conventional risk factors alone [26]. Moreover, the interaction of genetics and environment factors is considered vital issues for health and disease. Using techniques of molecular biology has been shown that genetic factors were detrimental in susceptibility to disease and that environmental factors were detrimental in which genetically susceptible individuals will be affected. Nutrition is considered an environmental risk factor of major importance. Using the tools of molecular genetics, researchers defined the mechanisms by which genes influence nutrient absorption and metabolism, as well as the mechanisms by which nutrients influence gene expression. The precise molecular mechanisms that lead to coronary artery disease (CAD) and myocardial infarction (MI) are not understood yet. CAD and MI are complex genetic diseases; neither the environment alone nor a single gene cause disease, but the interaction between environmental and genetic factors lead to atherosclerosis of the coronary arteries. Progress in sequencing and mapping of the human genome and efforts to identify all of the expected one million single nucleotide polymorphisms (SNPs) expected to allow new approaches for early diagnosis of CAD and MI compared to the traditional pathophysiological approaches. Except for certain polymorphisms in lipid genes (i.e., apolipoprotein E, apo E), which have causal effects on both the LDL level in plasma and the clinical phenotypes (CAD/MI), although the role of most gene polymorphisms is controversial or unknown. In addition to an unfavorable lipid profile, an increase in the thrombotic risk was identified in some populations. Effect of the APO AI-CIII genes was observed in triglyceride levels. Apolipoprotein CIII was found *in vivo* to inhibit the lipoprotein and hepatic lipases, reducing hydrolysis of triglycerides. The genes that regulate the expression of apolipoproteins AI and CIII are very closely located in a gene complex in the long arm of human chromosome 11 [27,28].

Conventional Treatment for High Triglycerides

The two most common treatments for high triglycerides (hypertriglyceridemia) are statins and fibrates. Statins is used raise low HDL and reduce high LDL. Studies showed that in patients with cardiovascular disease, modestly elevated triglyceride levels and low HDL cholesterol levels, fibrates have been shown to decrease the risk of cardiovascular events. Furthermore, research results showed that there are several ways to lower cholesterol and triglyceride levels naturally. Among these ways are diet (via cut back on calories), lifestyle changes, reduce alcohol, and exercise regularly. According to researchers, long-chain omega-3 fatty acids are effective for reducing plasma triglyceride levels. Furthermore, niacin (vitamin B3), lipoic acid, garlic, lavender and holy basil significantly reduces LDL cholesterol and triglyceride, while increasing HDL [29].

New Thoughts and Future Directions for Prediction of CHD

Although biochemists, molecular biologists and clinicians have many standards CAD biochemicals risk factors as well as molecular

markers to predict CHD. Most previous investigations were successfully predicting CHD. Several studies support the benefits of lowering cholesterol and triglyceride levels to decrease the risk for developing cardiovascular disease. LDL cholesterol and HDL cholesterol are key factors in pathogenesis of atherosclerosis and coronary artery disease. Increased LDL cholesterol levels and decreased HDL cholesterol levels are associated with increased risk for coronary heart disease. Increased levels of triglycerides are not a risk factor on their own. However, there is evidence that the triglyceride is a synergistic coronary artery disease risk factor. High triglyceride levels along with high LDL levels and low HDL levels suggest some underlying pathologic process, which indicates a high risk for coronary artery disease.

As science and research are dynamic processes further techniques must be continuously developed to early detect CHD. This can be useful tools in the future for early speculate the susceptibility and consequently the occurrence of CHD, where precaution, therapy, and cure can be more effective. Before discussing these new methodologies, following questions need to be discussed and that should be investigated thoroughly:

- 1- What is the repeatability of CHD biochemical risk factors (total cholesterol, HDL and LDL)? These are considered the classical biochemical risk factors for symptoms of coronary artery disease. The repeatability estimate, which will reflect biochemical homeostasis (stability) of the risk factors and consequently will be providing a good impression of no future sign of CHD. Repeatability estimate also reflect upper limit of the genetic variance of the biochemical risk factors.

Approach

To estimate repeatability 6 bimonthly (one year) biochemical risk factors should be tested on the same individual who want to estimate his/her biochemical homeostasis. A total of at least 500 persons should be included in the trial. The theoretical repeatability estimate will be ranged from 0 – 100. The higher the values of the repeatability estimate the higher stability (low coefficient of variation) of biochemical risk factors. Thus indicate low risk factors for CHD and vice versa. Nevertheless, age of individual should be taking into consideration.

Is there any role of sebaceous glands (as far as number and level of secretion and composition of contents), to the homeostasis of blood lipids profile? If so, are there any genetic variations among individuals, families and population? What is the percentage of such genetic variance compared to total phenotypic variation (the heritability)? It is suggested that number of sebaceous per unit area, level of secretion and composition of contents reflect the metabolic rate of blood lipid. Sebaceous glands are small oil-producing glands and release a fatty substance into the follicular duct and thence to the surface of the skin. The sebaceous glands secrete a mixture of fats (triglycerides, wax esters, squalene,

sebum and cholesterol). They are as many as 900 glands/cm² on the face. The Sebaceous glands receive their lipids from circulating blood lipids. The sebaceous gland provides an interesting model to study lipid expelling from the blood [30].

Approach

To investigate the potential and effectiveness of sebaceous glands to expel all types of body lipids, this considered playing role and causing CHD. The trial should be carried out on at least 500 individuals. Number of sebaceous glands per unit area (cm²) in at least 3 locations in the body should be secured in single test. Estimate of the quantities of the secretion of lipids for 4 times during experimental period for one year (in different seasons) is vital. It is expected that the higher the values of the lipids production estimate of an individual the lower the risk factors for CHD. It is recommended to have simultaneously CHD biochemical risk factors (total cholesterol, HDL cholesterol and LDL cholesterol) in order to investigate the associations among these parameters.

- 1- Are there any genetic variations among individuals, families and population in blood lipids profile (total cholesterol, HDL cholesterol and LDL cholesterol)? Similarly, are there any genetic variations among individuals, families and population in lipase, insulin levels and adrenaline hormone? If so, at what person's age be the highest? Where molecular biologists and clinicians can be more precise in early detecting CHD. It is well known that both of genetics and environment factors contributed to manifest of diseases including CHD. Some genes only express a given phenotype in certain environmental conditions. Genotypic expression of the CHD depends on risk factors. The genotype by environment interaction indicates the different response of different genotypes (manifestation of CHD) to different risk factors.

Approach

Investigating the mechanisms by which CHD genes influence lipid digestion, absorption, metabolism and excretion. Classical biochemical risk factors tests (4 tests) for CHD should be carried out on at least 200 healthy families (no symptoms of CHD), each with 4-5 full sibs together with at least 200 families with CHD and each with 4-5 full sibs. Statistical analysis will be performed to figure out variations within full sibs among individuals as well as among groups. Genetic variations will be secured from the foregoing statistical analysis. If the genetic variations will be high (above 50% out the total phenotypic variations), this indicate genetic factors play a big role in CHD. In this case, researchers should focus on molecular genetics profile rather than biochemical risk factors and vice versa. Once such genetic parameter secured, biochemists, molecular biologists and/or clinicians can guide and recommends the right approach for each person or family to avoid CHD.

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