

Dietary Fat and Cholesterol Dilemma: Acute Vascular Events

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Abstract

Several studies have shown that elevated serum low-density lipoprotein cholesterol (LDL-C), with sedentary habits, is the driving force for development of subclinical atherosclerosis, and hardening of the arteries. Oxidized lipids, including fatty acids, and cholesterol, play a key role in the pathogenesis of atherosclerosis. Based on the results of earlier epidemiological studies, professional societies, funding agencies, and regulatory agencies, developed dietary guidelines to limit the intake of trans-fats, saturated fats, and cholesterol-rich foods such as eggs. Some experts feel, that this approach and aggressive implementation of such guidelines to some extent, is responsible for the rapid increase, in the incidence of obesity and type-2 diabetes. The reason for this kind of thinking is related, to the promotion of low-fat-high-carbohydrate diets in these recommendations. In recent years, there seems to be some shift in the thinking of experts. Currently, some of the restrictions have been relaxed, and modifications in the guidelines, and guidance statements, seem to be imminent. Having said that, we would like to inform the readers, to be cautious about what they read in the print, because contrary to the conclusions derived from such diet-heart studies, the data on blood cholesterol still shows, a key role for these lipids and their oxidized products, in the development of atherosclerosis, endothelial dysfunction, and acute vascular events. Recent studies have shown that LDL-C is an independent risk, for the development of subclinical atherosclerosis, and hardening of the arteries in middle-aged, asymptomatic adults. Aggressive lowering of LDL-C, seems to be associated with better outcome, in several clinical studies. Furthermore, in individuals on statin prophylaxis, addition of an antiinflammatory agent as complementary therapy, seems to offer better protection against CVD-events, suggesting a potential role for inflammation in the progress of the disease. The debate about the diet-heart is an age-old phenomenon, a complex topic, and it is too early to draw final conclusions. Furthermore, arterial thrombosis is a complex phenomenon, initiated and promoted by several cardiometabolic risks, and cluster of risks, and the story of thrombosis is not fully revealed as yet.

1. Introduction

Framingham Heart Study, initiated by the National Institutes of Health, USA, identified modifiable risk factors, which promote the development of cardiovascular diseases. Some of the major risks included, elevated cholesterol and triglycerides [1]. At the same time, long-term studies at the University of Minnesota, by Professor Ancel Keys and associates, developed a diet-heart hypothesis, based on the results of their one of a kind, seven countries epidemiological studies. In an overview,

summarizing the findings of this long-term studies, researchers concluded, “Interpreted in the light of experimental and clinical studies, the results of these cross-cultural analyses suggest, that dietary saturated and trans-fatty acids and dietary cholesterol are important determinants, of differences in population rates of coronary heart diseases death [2]. On the other hand, in North Karelia studies in Finland which was also a participant of the seven countries study, the focus of the overall program was, to reduce the serum cholesterol levels through dietary change, because of the presumed role in high CVD rates in Finland. This was accomplished, through widespread reductions in saturated fat intake, and concomitant increases in the consumption of vegetable and polyunsaturated fatty acids (PUFA). The intervention was originally designed, to be implemented throughout the community for five years, but eventually became a long-term prevention program. CVD risk factors under study over a 25-year follow-up (1972-1997), in both men and women, showed continued declines in serum cholesterol and systolic blood pressure levels [3]. According to Pekka Puska report, in the early 1970s, use of vegetable oil products was rare; now it is common. In 1972 about 90% of the population used mainly butter on their bread. Today less than 7%. The dietary changes have led to about 17% reduction in the mean serum cholesterol level in the population.

It has been more than four decades, since the US Federal Government first recommended, that except young children all others should opt, for low-fat or nonfat dairy products, over high-fat dairy products, as a part of an overall goal, to reduce saturated fat intake in general population [4]. This created a formidable dairy industry in the USA, which produced more low-fat and skim milk, than whole milk. Furthermore, the Healthy, Hunger-Free Kids Act, required that schools follow dietary guidelines, and replace whole milk, with nonfat or low-fat milk. Now after decades of advocacy of such guidelines, there seems to be a sudden change of mind. Dr Dariush Mozaffarian, the Dean of Friedman School of Nutrition Science at Tufts University says, that there is not much of evidence to recommend low-fat dairy. According to Dr Frank Hu, Chair of Nutrition, Harvard University Nutrition Department, “this is a very complicated area, because dairy is not a homogenous food.” One of the largest studies, conducted to examine the association between the dairy and cardiovascular disease (CVD), is the Prospective Urban Rural Epidemiology (PURE) Study, involving 163,384 subjects [5-8]. Surprising findings of this study was, that intake of dairy (more than two servings), was associated with a lower risk of death or a major cardiovascular event. Whole-fat dairy products, seem to be more protective than nonfat or low-fat food. According to Professor P.A. Loannidis, at the Stanford University Research Prevention Center, epidemiological nutrition studies could lead to “implausible estimates of benefits or risk associated with diet.” In spite of the fact, that the US dietary guidelines recommend 3 servings a day, less than 20% of the population consumes this recommended intake. Dr Hu, who serves on the panel that develops US guidelines, in a review concludes, “Do not get over stressed about just one thing. Overall dietary pattern is very important, and dairy is only one of many food items on our plate.” The debate on good fat versus bad fat, is going on for many years. However, there are some recent studies, suggesting that milk, cheese, yogurt, and even egg may be more beneficial than harmful.

Another dietary food that came into limelight, during the same period as dairy products, was consumption of eggs. The recommended daily limit for dietary cholesterol was 300 mg for healthy individuals and 200 mg for patients at risk for CVD [9-12]. In a recent study, researchers at the University of Massachusetts have demonstrated that the consumption of 12 eggs per week for one year does not significantly alter fasting serum lipids, lipoprotein cholesterol, or other biomarkers of CVD in older adults [12]. Furthermore, researchers from China and the United Kingdom, have reported their data on studies done on, more than half a million subjects, who consumed at least one egg a day [13]. Researchers found that daily consumption of

egg was associated with a lower risk of CVD, compared with those who never took egg or just rarely consumed eggs. They also noted that daily egg consumers had a 26% lower risk for hemorrhagic stroke and 18% lower risk for CVD death. The egg/cholesterol controversy, started when the American Heart Association recommended, that everyone reduce dietary cholesterol to less than 300 mg per day, and eats no more than three whole eggs per week. According to a review by McNamara, in 2015 dietary cholesterol and egg restriction have been dropped by most health promotion agencies worldwide, and recommended to be dropped from the 2015 Dietary Guidelines for Americans as well [14].

Several studies have shown an association, between trans fatty acid consumption and increased risk for CVD events [15]. This increased risk seems to be related to the fact that trans-fat increases the ratio between LDL-cholesterol (Bad-cholesterol) to HDL-cholesterol (Good-cholesterol). Philadelphia researchers in a recent article, concluded, “While dairy fat (milk, cheese) is associated with a slightly lower CVD risk compared to meat, dairy fat results in a significantly greater CVD risk, relative to unsaturated fatty acids [16].” Therefore, debate about the good fat and bad fat is still going on. Traditionally, nutrition research has focused on single nutrients. Having said that, it is now very well recognized, that the total diet must be considered, because of the interdependent relationships among dietary components.

2. Discussion

Now that we have discussed briefly, the association between the dietary trans-fat, saturated fat, cholesterol and the risk for cardiovascular disease and acute vascular events, let us see what the clinical outcome studies; have to say on these controversial topics. In a study focused on identifying “at risk” individuals, Valentin Fuster, Professor and Chief, the Division of Cardiology, Icahn School of Medicine, Mount Sinai Hospital, New York, sought to identify predictors of subclinical atherosclerosis, in the absence of cardiovascular risk factors (CVRFs). These researchers concluded, from their studies, that many CVRF-free middle-aged individuals have atherosclerosis with hardening of the arteries. LDL-Cholesterol, even at levels currently considered normal, is independently associated with the presence and extent of early systematic atherosclerosis, in the absence of major CVRFs. These studies support and recommend more effective lowering of LDL-C for ‘primordial prevention’, even in individuals conventionally considered at optimal risk [17]. Subclinical atherosclerosis underlies most cardiovascular events, and its detection can improve risk stratification. Prof. Fuster and associates identified subclinical atherosclerosis in nearly 60% of middle-aged individuals classified at low risk; according to traditional risk scale. They found a linear correlation between the increase in LDL-Cholesterol levels and significant increase in the prevalence of atherosclerosis.

According to a recent report in the NEJM (Nov 2018), patients who have had acute coronary syndrome, remain at high risk for recurrent ischemic cardiovascular events. This residual risk is attributable to elevated levels of low-density lipoprotein (LDL) cholesterol, and other atherogenic lipoproteins [18]. As a part of the OSYSSEY OUTCOMES Clinical Trials, the researchers found, that among patients who had previous acute coronary syndrome and who were receiving high-intensity statin therapy, the risk of recurrent ischemic cardiovascular event was higher among those who received placebo. Proprotein convertase subtilisin-kexin type 9 (PCSK9), promotes degradation of LDL receptors, thereby diminishing the clearance of LDL-C, from the circulation. Contrary to what PESA study showed, a meta-analysis and meta-regression, conducted by a multinational group demonstrated, that more intensive compared with less intensive LDL-cholesterol lowering, was associated with a greater reduction in risks of total and cardiovascular mortality, in trial of patients with higher baseline LDL-

C levels [19]. Most recent Cholesterol Guidelines published by the joint efforts of several professional societies including American Heart Association (2018) by Grundy SM and associates, states very clearly, “In patients with clinical atherosclerotic cardiovascular disease (ASCVD), reduce low-density lipoprotein cholesterol (LDL-C), with high intensity statin therapy or maximally tolerated statin therapy. The more LDL-C is reduced on statin therapy, the greater will be subsequent reduction. Use a maximally tolerated statin to lower LDL-C levels by >50% (20). Readers are urged to consult the “Top 10 take-home messages to reduce risk of atherosclerotic disease through cholesterol management [20].”

Month of September is considered National Cholesterol Education Month. In their news release, Center for Disease Control (CDC) and Prevention, USA, has the following introductory paragraph, “Ever since Nikolai N. Anitschkow first discovered the part, cholesterol plays in atherosclerosis back in 1913, researchers have been trying to find a way to effectively treat this disease with some success. Yet, this disease is still responsible for high rates of morbidity and mortality in the United States and Internationally [21].” According to the latest statistics, 75 million adults (>30%) in the United States alone, have high low-density lipoprotein (LDL) or “bad” cholesterol. Added to this observation, fewer than one out of 3 adults (29%) with high LDL cholesterol, has the condition under control. We have been discussing all aspects of LDL-C, without explaining the basic mechanisms, by which it induces the damage to the coronary arteries. Studies have demonstrated the presence of oxidized forms of cholesterol, -oxysterols – in the vascular lesions of the arteries [22]. In addition, it has been presumed that these molecules possess pro-atherosclerotic properties. Having said that, it is not known, as to how exactly oxysterols induce the observed arterial vascular lesions. Researchers have reported that the formation of oxysterols in the atherosclerotic lesions, as a result of LDL oxidation, is due to the inflammatory response of cells and mechanical stress. How does this mechanical stress occur? This question brings us to the role of oscillating shear stress, and the endothelial dysfunction. Looks like there are multiple players in this process of arterial vessel damage,- oxidation of LDL, inflammation, shear stress, mechanical damage of the endothelium, and endothelial dysfunction. When considering various risks for acute vascular events, like heart attack and stroke, we can add a few more risks, such as, intima media thickness (IMT), degree of vessel narrowing, atherosclerotic plaque, (plaque morphology; volume, composition, and consistency), level of activation of platelets and coagulation proteins (thrombotic state of the blood).

Oxidized metabolites of Linoleic acid (LA), including bioactive 9-and 13-hydroxy-octadienoic acid and 9-and 13-oxo-octadecadienoic acid, exert several pro-inflammatory and pro-atherogenic properties [23]. Some studies have demonstrated that higher plasma phospholipid n-6PUFAs were associated with increased arterial stiffness as measured by carotid-femoral pulse wave velocity [24]. There is considerable evidence from randomized trials, that replacement of dietary saturated fatty acids by LA, significantly lowers serum total cholesterol (mostly by reducing low-density lipoprotein cholesterol), but does not support the hypothesis, that this translates to a lower risk of death from CAD, or decreased all-cause mortality [23]. This kind of evidence supports the hypothesis, that in addition to lowering LDL-C, it is essential to lower the systemic inflammation. In an interview, during the European Society of Cardiology Congress-2017, Dr. Paul Ridker, Professor of cardiology at Harvard Medical School, summarized the CNATOS trial results as follows: Lowering Inflammation, not LDL-C to reduce CVD. He further elaborated his ideas, “If we think of preventive cardiology, the first era was mom and pop and apple pie. There was diet, exercise, and smoking cessation. The second era began, I think in 1994 with the 4S Trial. We said, “Wow -statins really work. We need to think about the expansion of that, ultimately leading to the PCSK9 inhibitors.” He concluded the interview by saying, “What we have really learned from the CANTOS is that inflammation reduction, in the

absence of lipid reduction, still lowers vascular event rates.” The researchers have highlighted the results of CANTOS trial, and elaborated on the role of inflammation in cardiovascular disease in their recent article, in which they report that directly reducing inflammation with Canakinumab, an interleukin (IL)-1 β neutralizing monoclonal antibody, could also reduce acute cardiovascular events [25,26].

According to a web page of the Famous Cleveland Clinic, USA, High levels of “bad” cholesterol in the blood, which have been linked to heart disease, are still a health problem. What has changed in recent years is, that many researchers and clinicians now believe that eating cholesterol-rich foods such as eggs, may not affect the cholesterol in your blood. However, people with certain health problems, such as diabetes, should continue to avoid cholesterol-rich foods. Having said that, we would like to inform the readers that the current guidelines, still call for a daily limit of 300 mgs of dietary cholesterol. Cholesterol story is complicated as is the story of “diet and heart” and arterial thrombosis. In addition, current research is showing that your genetic makeup-not diet- is the driving force, behind blood cholesterol levels. Therefore, ‘one size fits all’ approach will not work. In addition to dietary cholesterol, some tropical oils such as palm oil, palm kernel oil, and coconut oil, can also trigger your liver to make more cholesterol, according to an American Heart Association advisory.

3. Conclusions

Numerous epidemiological studies and clinical trials, including Framingham Heart Study, Seven Countries Study, Pritikin diet studies, Ornish LifeStyle Heart trail, Omni heart trail, Portfolio diet, Mediterranean diet, Ketogenic diet, and Atkin’s diet, have clearly established the relationship between diet, serum lipids, inflammation, endothelial dysfunction, subclinical atherosclerosis, and CVD. Based on some of the earlier studies, Professor Keys, at the University of Minnesota, developed diet-heart hypothesis, which has been controversial for over 100 years [27]. In fact, there is some speculation among experts, that low-fat-high-carbohydrate diet, recommended by the National Cholesterol Program of the NIH, American Heart Association and U.S. Department of Agriculture, may have played an unintended, unanticipated role, in the current diabetes and obesity epidemic. According to Hooper and associates, “Despite decades of effort, and many thousands of randomized studies, there is still limited and inconclusive evidence, of the effects of modification of total, saturated, mono-unsaturated or poly-unsaturated fats, on cardiovascular mortality and morbidity [28-30]. In spite of this observed controversies, results of the North Karelia Prevention Project, stands out, as an outstanding success of the recognition, of the role played by lifestyle-related risk factors, in driving up chronic metabolic diseases. According to Dr. Pekka Puska, the annual age standardized mortality rate for CVD in North Karelia, Finland, in 2006 was 80% lower than during the period between 1969-1971; nationally, the reduction was around 80%.

Despite the controversies surrounding various dietary studies, there seems to be a strong supportive role for the risk of CVD-events, with the increasing levels of blood cholesterol. Studies by Prof. Fuster and associates, clearly demonstrates the role of LDL-C as an independent risk for the development of subclinical atherosclerosis, and hardening of the arteries, in middle-aged asymptomatic adults. Importance of the benefits of aggressive lowering of LDL-C, on the final clinical outcome, has been reported in several clinical studies. Further evidence for the benefit of LDL-C lowering, comes from studies with PCSK9 inhibitors, which prevent LDL-C receptor clearing. Studies from Professor Paul Ridker’s group has demonstrated that not only LDL-C, but the inflammation associated with this pathology, is also partially responsible the development of acute vascular events. The CANTOS trial for the first time, demonstrated the role of inflammation in the CVD-related acute

events. It should be noted, that none of the known modifiable risk factors, alone precipitate acute vascular events leading to heart attacks and stroke. Ultimate CVD-event is precipitated by concerted action of multiple cardiometabolic risks, or cluster of risks, and the presence of a prothrombotic state.

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