REVIEWING THE ROLE OF DIETARY LIPIDS IN CORONARY HEART DISEASE

Klodiola DHAMO
Universiteti Aldent
Rezarta SHKRELI
Universiteti Aldent
Amilda BALLATA
Fakulteti i Shkencave të Natyrës

ABSTRACT

It has been shown that coronary heart disease (CHD) is related to high serum total cholesterol (TC) levels. In all the urban population compared with the rural population is showed a rise of serum TC. This is reflected in the trend of CHD morbidity and mortality as well. In spite of a declining trend in serum TC level, CHD morbidity and mortality are still high year after year. In general, there is still a rising trend in serum TC level and in CHD mortality in many countries. However it may be controlled and managed. This may be attributed to a better control of other CHD risk factors such as hypertension and smoking. More than a century of laboratory and human findings cholesterol levels with a propensity to develop atherosclerosis. Low-density lipoprotein (LDL) is the major atherogenic lipoprotein, and numerous clinical trials have shown the efficacy of lowering LDL-cholesterol (LDL-C) for reducing CHD

risk. The rising trend in serum TC level remains a cause for concern, as this will emerge as a major problem for CHD morbidity and mortality in the future.

Keywords *Lipids, Coronary heart disease, Total cholesterol, Morbidity*

INTRODUCTION

It is not in doubt that coronary heart disease (CHD) represents a major, often the major, cause of death and ill-health in developed industrialized countries. (WHO 1990) In the U.K, CHD accounts for about one third of male and a quarter of female deaths. While the peak age of death from CHD is 70-74 for men and 75-79 for women, particular concern has been expressed that it is principally a cause of premature death especially in middle aged men, with grave social and economic consequences. (DHSS 1984) Consensus regards environmental factors as more important, although the variety of factors that has been suggested to be involved is bewildering. (Hopkins *et al.* 2001) Of these, diet, smoking habits and physical activity have received most attention as being potentially subject to modification. It is probably true to say that smoking and dietary modification aimed at controlling plasma lipid concentrations, have been the major targets of public education campaigns. This review is concerned only with dietary lipids but the reader is entreated to keep in mind three cautions that set dietary lipids in context. First, diet is but one of many environmental factors that might be targeted and there is controversy about its relative importance; (Stehbens *et al* 1990) second, dietary fat is one of many dietary factors that might be implicated in the development of CHD; (Hopkins *et al.* 2001, Stehbens *et al* 1990) Plasma lipids, although having been given overwhelming emphasis in the formulation of

public policy, are not the only predictors of CHD that might be influenced by dietary lipids. (Senti *et al*. 1998). Moreover, there are very large regional differences even within a country with a small land area, as well as substantial differences between ethnic groups that are independent of geographical location. CHD prevalence is dependent on latitude, altitude and climate. The term "CHD" covers a complex set of contributory conditions. (Beaglehole 1990) Failure to find a satisfactory all-embracing explanation may in part be due to failure to realize that any environmental factors being considered, for example, dietary fatty acids, influence these different aspects of the disease in different ways.

THE LIPID HYPOTHESIS OF CORONARY HEART DISEASE

A combination of factors may influence the likelihood of thrombus formation, including: alterations in the character of the blood and of particular blood proteins; disturbances in blood flow (particularly the development of turbulence) and damage to, or alteration in, function of the endothelial cells. The turbulent blood flow itself, and sometimes alterations to the composition of the blood, may cause actual injury to the epithelium.(Flynn *et al*. 2013) Increased numbers of platelets and increased concentrations of activated aggregation and coagulation factors are found in places where blood flow separates and forms vortices. Fast flowing blood will dislodge platelets from the surface of the thrombus and the aggregator factors will be diluted so that, unless flow is slowed or arrested in these vessels, the likelihood of the formation of a thrombus big enough to block an artery is reduced. Connective tissue is important in the

initiation of thrombi in injured and healthy arteries. (Senti 1998) Rupture of atherosclerotic plaque frequently leads to formation of an occlusive thrombus in a coronary artery. (Falk 1983) Modem concepts of the development of atherosclerosis and thrombosis postulate a degree of interrelationship between the two processes. Blood lipids and tissue lipids are involved in several ways.

DESCRIPTION OF THE LIPID HYPOTHESIS

The lipid hypothesis had its origins in the early part of this century in attempts to reproduce some of the pathology of atherosclerosis in animals given diets rich in cholesterol. (Antisci-iow *et al*. 1913) Among the observations were that the animals developed high concentrations of plasma lipids. It was a wide interest grew in the effects of different dietary fats on plasma cholesterol in experimental animals and man. Much of this early work is reviewed by Mc Gandy and Hegsted (Marmot *et al*. 1987) but the interested reader is encouraged to go back to some of the original classical papers. (Ahrens *et al* 1957, Trenchard 1978). Keys and his colleagues were engaged in the classic epidemiological investigations of the Seven Countries Study that produced cross-cultural evidence for associations between dietary saturated fatty acids (SFA), plasma cholesterol and CHD mortality. (Hopkins *et al*. 2001). The lipid hypothesis is based in four tenets: (1) Diets containing a high fat/saturated fatty acid/cholesterol content lead to high concentrations of cholesterol (particularly LDL-cholesterol) in plasma. (2) A high plasma cholesterol (particularly high LDL-cholesterol) presents a high risk for coronary heart

disease (CHD) and leads to a high CHD morbidity and mortality. (3) Reducing the amount of fat/saturated fatty acids/cholesterol in the diet will result in a reduced concentration of cholesterol (particularly LDL-cholesterol) in plasma. (4) Reducing the concentration of cholesterol (particularly LDL-cholesterol) in plasma will result in a lower risk of CHD and eventually a lower morbidity and mortality. Different authors pose the lipid hypothesis in different ways. Some concentrate on the effects of dietary lipids on blood cholesterol; of these, some will emphasize total fat, others saturated fatty acids and still others cholesterol. Others will emphasize the relationship between high blood lipids and coronary disease, irrespective of the etiology of the high blood lipids. The four tenets set out above give little hint of the complex relationships between blood lipids and total dietary fat, saturated, monounsaturated, trans and polyunsaturated fatty acids and dietary cholesterol. (Trenchard 1978) They do not consider whether it is the absolute intake of these dietary components that is important, the ratio between the different fat components, or between fat and other energy-providing constituents of the diet. Neither do they make sufficient distinction between the types of plasma lipoproteins, of which cholesterol is a constituent. (Hopkins *et al.* 2001) Finally, the concepts embodied in the lipid hypothesis date from an era when attention was concentrated almost entirely on the atherosclerotic component of CHD and the role of lipids in contributing to atherosclerosis. It did not consider whether lipids might play a role in the thrombotic episode.

DIETARY CHOLESTEROL

Addition of cholesterol to the diets of many species of experimental animals elicits a rise in plasma cholesterol concentration. Rabbits are particularly sensitive and so are many types of monkeys while rats are relatively insensitive. (Beznen *et al* 1987) The relevance of these animal experiments to an understanding of human physiology is highly questionable. The influence of dietary cholesterol on plasma concentration in man is in general less pronounced than in other primates. Many carefully supervised experiments with subjects in metabolic wards have demonstrated small but significant rises in plasma cholesterol in response to dietary cholesterol. In contrast, studies with "free-living" subjects seem to have shown little or no effect, (Grundy *et al* 2015). Pure cholesterol added to diets had no influence on human plasma cholesterol concentration in man. (Cortese *et al* 1993) Experimenters have subsequently relied on supplementing the diet with eggs because of their very high content of cholesterol (about 270 mg per egg). (Davms *et al*. 1987) While some experiments conducted under well controlled conditions showed modest (10-20%) rises with one or two eggs when compared with a controlled diet of low cholesterol content, others (Grundy *et al* 1990) found rises of less than 10%. Yet others (Senti *et al*. 1998) found similar plasma cholesterol concentrations in men ingesting as many as 11 or as few as 2 eggs per week. Certain individuals respond strongly and others weakly to dietary cholesterol (hyper and hypo-responders). This phenomenon is seen in a variety of animals and in humans. Mc Namara (Keys *et al*. 2012) has analyzed the results of 68 clinical trials representing 1490 subjects. It should be stressed that such meta-analyses gives mean results for a large number of individuals and that

predictive formulae, such as those of Keys *et al* (2012). Hold only for group or population means, not for individuals. Some epidemiological observations also suggest that there is a linear association between dietary and plasma cholesterol. (Hopkins *et al.* 2001). However, because foods that are rich in cholesterol also tend to have a high proportion of saturated to unsaturated fatty acids, it is difficult to distinguish clearly between the two influences.

SATURATED FATTY ACIDS

Athough early research did indicate that not all saturated fatty acids were equivalent in their cholesterol-raising effects, the use of a single all-embracing term for saturates in the Keys (Keys *et al.* 2012) equation has tended to obscure this fact and it is only recently that serious attention has been given to these differential effects. Early work indicated that fatty acids with chain lengths up to and including 10 carbon atoms (short- and medium-chain fatty acids) do not influence plasma cholesterol (Grundy *et al.* 1990) because they are absorbed directly into the blood supplying the liver and rapidly metabolized in that organ, unlike the longer chain acids which are absorbed as "chylomicrons". (Dreon *et al.* 1990) Lauric (12:0), myristic (14:0) and palmitic (1 6:0) acids have generally been regarded as the three "cholesterol-raising" fatty acids and the major plasma lipoprotein fraction affected is LDL. Palmitic is quantitatively the most significant since it is the principal saturated fatty acid in most diets, occurring widely in animal and plant fats. Cross-cultural epidemiological studies have generally demonstrated correlations between the average consumption of

saturated fatty acids and the mean plasma total cholesterol concentration. Thus, the Seven Countries Study of Keys *et al.* (2012) indicated a high correlation between the percentage of total calories from saturated fatty acids and plasma total cholesterol. The finding that weak or absent correlations between individual dietary intakes, plasma lipoprotein concentrations and CHD risk within populations is explained by Blackburn (*et al* 2018) as being mainly due to the weak and variable measures with which we attempt to characterize an individual's diet, and to the vagaries in blood lipoprotein levels and their measurement.

MONOUNSATURATED FATTY

Keys *et al.* (2012) found that monounsaturates were "neutral" in their effect on plasma cholesterol and did not include a term for them in their equation. Recently, this question has been re-evaluated. Broadly, two types of experiments have been conducted. In the first type, diets of equal (and relatively high) fat content have been compared, differing only in the fatty acid composition, with either saturates, monounsaturates or n-6 polyunsaturates predominating. (Dreon *et al.* 1990) In the second type, carbohydrates have been substituted with fat rich in monounsaturates so that a high fat monounsaturated diet has been compared with a low fat diet. While not all studies were well controlled, (Trenchard 1978) most found that monounsaturates, when substituted for saturates, lowered plasma total cholesterol concentration as effectively as n-6 polyunsaturates, (Grundy *et al.* 1990) although the findings were not entirely consistently The lowering was almost entirely associated with the

LDL fraction. When substituted for carbohydrates, they resulted in a similarly low plasma cholesterol (LDL) but did not elicit the rise in VLDL (and, therefore, triacylglycerol's) often seen with high carbohydrate diets.

POLYUNSATURATED FATTY ACIDS

Just as the term "saturates" embraces a wide range of structures each with different physiological activities, so the term "polyunsaturates" is equally broad and non-specific. An enormous number of studies has left little doubt that a major effect of consuming n-6 polyunsaturated fatty acids, in substitution for saturated fatty acids, is a lowering of plasma cholesterol, principally the LDL fraction. There is little effect on HDL-cholesterol provided that the contribution of linoleic acid is not much more than 12% of dietary energy or the ratio of polyunsaturated to saturated fatty acids (P/S) is not much more than 1.0 (Hopkins *et al* 2001, Beaglehole 1990) These conditions are unlikely to occur in most self-selected diets in developed countries. There is also little effect of exchanging n-6 PUFA for SFA on VLDL. The fact that these effects are similar to those obtained by substituting monounsaturated for saturated fatty acids suggests that the effect may be due more to a reduction in saturates intake than an increase in unsaturates. (Blacburn *et al*. 2018, Beynen *et al*. 1987) In contrast, the effect of dietary n-3 fatty acids is to reduce the concentration of VLDL and since the major lipid component of these lipoproteins is triacylglycerol, the chief response is a lowering of plasma triacylglycerol concentrations. (Muller *et al*. 2014) Only at very high intakes of fish oils is there a lowering of LDL or total cholesterol. The effect seems mainly confined to the very long-chain n-3 PUFA since linseed oil, which has a

high content of 18:3 n-3, is ineffective at similar doses. (Vergroesen *et al* 1995) Just as there are wide differences in individual responses to dietary cholesterol, so there are hyper and hypo responders to dietary fatty acids. It is apparent that one can find subjects with consistently high or low responses but that total insensitivity is rare.

INFLUENCE OF TRIACYLGLYCEROL STRUCTURE

Natural fats are characterized by a stereospecific distribution of fatty acids on the three positions of the glycerol backbone rather than a random distribution. The way in which fatty acids are distributed may influence plasma cholesterol irrespective of the overall composition of the fatty acids. (Grundy *et al*. 1988) Thus linoleic acid is more hypocholesterolaemic and saturates more hypercholesterolaemic (Stehbens *et al*. 1990) when present at position 2 than in positions 1 or 3. The fact that stearic acid is normally esterified at position 1, rarely at position 2, may in part explain the neutral effect of this fatty acid on blood cholesterol. Butter is much less hypercholesterolaemic when the positions of its fatty acids are randomized by interesterification. (Christophe *et al* 1998)

MECHANISMS

Differences between individuals in their responses to dietary cholesterol might be accounted for by differences in: absorption of dietary cholesterol; cholesterol biosynthesis; output of LDL by the liver or in the receptor-mediated clearance of LDL from plasma; sterol and bile acid excretion from the body or the accumulation of cholesterol in body tissues, *(*Grundy

et al. 1990) Differences between individuals in cholesterol absorption and in the capacity to regulate cholesterol biosynthesis to compensate for dietary intake clearly exist. (Flynn *et al* 2013) The apo-B receptor plays a major role in regulating the rate of removal of LDL as well as its rate of synthesis from VLDL. Hepatic receptors for apo-B account for most of the capacity to remove LDL. The binding capacity of the apo-B receptor is genetically determined but the number of receptors expressed is influenced by dietary and hormonal factors. Grundy *et al.* (*1990)* discuss a model in which an increase in absorbed cholesterol reduces the activity of LDL-receptors which, in turn, retards the uptake of LDL and VLDL remnants. An increased conversion of VLDL remnants into LDL as well as a reduced uptake of LDL results in increased plasma concentrations of LDL. The influence of the non-specific endocytosis and scavenger pathways remains uncertain. Likewise, several mechanisms by which specific saturated fatty acids raise LDL cholesterol while specific unsaturated fatty acids either lower it or restrict the rise, have been discussed. *(*Grundy *et al. 1990)* Dietary fatty acid composition may influence: (1) the excretion of bile acids that occurs at each passage of the entero-hepatic circulation; (2) the production of cholesterol and of apo-B-containing lipoproteins; (3) the catabolism of LDL; (4) the .cholesterol ester content of each LDL particle in the plasma. The "hypercholesterolaemic" SFA appear to suppress the receptor-mediated clearance of LDL from plasma. (Grundy *et al.* 1988, Baggio *et al* 1988)) The reduced activity of the LDL receptors reduces the rate of catabolism of LDL as well as enhancing the rate of conversion of VLDL remnants to LDL. Caution has to be exercised in extrapolating results from experimental animals to man. LDL receptor activity may be low in man

compared with other animals. Consequently, LDL cholesterol concentrations could be primarily determined by rates of LDL synthesis rather than by rates of removal. Using radioactively labelled apo lipoproteins to follow the kinetics of LDL synthesis in human subjects, several laboratories have demonstrated a marked reduction in LDL synthetic rates when linoleic acid replaced saturated fatty acids in the diet (Cortese *et al.* 1993, Vergoesen *et al* 1995) and a slight rise in fractional catabolic rate. (Hopkins *et al.* 2001)

CONCLUSION

There can be no doubt that lipids are involved in the progression of CHD both in its atherosclerotic and thrombotic phases. There is also evidence for lipid involvement in other components of heart disease, such as cardiac arrhythmias. (Abeywardena *et al.* 1988) The points of contention are (1) whether plasma LDL has a causal role (Falk 1983) as distinct from an exacerbating role; and (2) whether dietary lipids have a primary role in either causation or exacerbation of the disease. The hemodynamic stress can induce atherosclerosis in vessels of animals with very low LDL concentrations, (Bronsgeest *et al* 1979) suggesting that a high concentration of LDL is not a prerequisite for its development. It is a stronger predictor of CHD risk than LDL and may provide an important link between the atherosclerotic and thrombotic phases of the disease. (Davms 1987, Antisci 1913) Research so far has revealed little influence of diet on its concentration in plasma but this is clearly an area where more investigation is needed. Emphasis has shifted in recent years away from the atherogenic potential of LDL itself toward an understanding of the

role of modified LDL and its uptake by the scavenger receptors of macrophages to form foam cells. (Buzzard *et al.* 1982) LDL may be modified by a number of mechanisms. Thus, Gey *et al.* (2014) studied 16 populations in Europe representing regions of high (Finland, Scotland), medium (Denmark, Northern Ireland, Israel) and low (Switzerland, Southern Italy, Southern France, Catalonia, Spain) CHD incidence. There was an 8-fold difference in CHD mortality between Glasgow, Scotland and Catalonia, Spain but no difference in mean plasma cholesterol (Ahrens *et al.* 1957) Cholesterol could not, therefore, explain the difference. Dietary intervention studies are needed to clarify this point. If subsequent studies confirm the role of antioxidant nutrients in the diet, the emphasis in dietary guidelines may need to shift away from emphasis on the modification of fat towards an emphasis on the consumption of fruit and vegetables rich in antioxidant nutrients. This does not in any way mean that advice to modify fat may not be beneficial for many individuals, especially those with clinical problems of overweight, diabetes mellitus or very severe hyperlipoproteinaemia.

There can be no argument that eating too much of any dietary component--and fat is a good example--is not conducive to good health. The message is that dietary fat reduction or modification may be beneficial for some individuals. The fact is that over 50% of CHD mortality is unexplained by any of the frequently described environmental factors.

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