Invited commentary

Dietary fatty acids and atherosclerosis regression

Atherosclerotic cardiovascular disease is the leading cause of death in most Western industrialized countries. Atherosclerosis is a multistep process that begins with the development of fatty streaks in lesion-prone regions of the aorta and coronary arteries. Fatty streaks can be found in most young adults (Rainwater *et al.* 1999) and are characterized by an accumulation of cholesteryl ester-loaded foam cells in the subendothelial space. Foam cell formation occurs when cholesterol influx into the arterial wall from apoB-containing lipoproteins exceeds cholesterol efflux. Increased influx of LDL into the subendothelial space is accompanied by an increased influx of monocyte/macrophages that take up oxidized and aggregated LDL and store the cholesterol as esters. Fatty streaks may progress to more advanced lesions that consist of necrotic foam cells and extracellular lipid covered by a fibrous cap containing smooth muscle cells and collagen. Not all fatty streaks progress to complex arteriosclerotic lesions. What determines whether a fatty streak progresses is not known, but the same risk factors that predict the presence of fatty streaks also predict the presence of advanced lesions (Rainwater *et al.* 1999). Finally, plaques may rupture resulting in thrombosis, arterial occlusion and myocardial infarction.

Dietary factors play an important role in atherogenesis mainly, although not exclusively, through effects on serum lipoprotein concentrations. Western diets high in saturated fat and cholesterol raise serum total and LDL-cholesterol concentrations and are associated with a high prevalence of coronary heart disease. Diet modification is usually recommended as the initial approach for the large segment of the population with undesirably high serum cholesterol concentrations. Support for this approach comes from recent randomized controlled trials demonstrating that diet modification can reduce coronary events (de Lorgeril *et al.* 1999) and improve coronary anatomy relative to a Western diet (Watts *et al.* 1992). Exactly how diets should be modified apart from reducing saturated fat and cholesterol intake is controversial. Epidemiological evidence can be found to support low-fat diets or diets rich in monounsaturated fats or marine lipids. The effect of these diets on serum lipoprotein levels is well documented but there have been no human trials to compare the effects of diets rich in polyunsaturated fat (*n*-3 or *n*-6), monounsaturated fat or carbohydrate on coronary anatomy, coronary events or overall mortality.

Much of the information that forms the basis for our understanding of atherosclerosis comes from studies in animals. Numerous animal models have been used to study the pathogenesis of atherosclerosis and to evaluate potential treatments. In most models, atherosclerosis is induced by feeding an atherogenic diet that is high in cholesterol and saturated fat. In a few models, for example the WHHL rabbit and the apoE knockout mouse, atherosclerosis develops spontaneously on a low-cholesterol, low-fat diet. Non-human primates (such as the rhesus monkey, the African green monkey and the baboon) are seemingly the most relevant models of human atherosclerosis. When placed on diets rich in cholesterol and saturated fat, these primate models develop lesions that remarkably resemble human atherosclerotic plaques in terms of their distribution, morphology and clinical complications. Studies in non-human primates clearly demonstrate that substantial regression of advanced atherosclerotic plaque can occur after prolonged reduction of serum total and LDL-cholesterol concentrations (usually achieved by removing saturated fat and cholesterol from the diet) (Wissler & Vesselinovitch, 1990). Significant regression of coronary atherosclerosis requires a reduction in serum cholesterol concentrations to about 20 g/l or less (Clarkson *et al.* 1981). The role of dietary fatty acids in atherogenesis has been evaluated in African green monkeys (Rudel *et al.* 1998). It was found that for a given intake of cholesterol, coronary atherosclerosis was less in animals fed on triacylglycerols rich in *n*-6 or *n*-3 polyunsaturated fatty acids than in animals fed on triacylglycerols rich in saturated or monounsaturated fatty acids. Thus when compared with saturated fatty acids, polyunsaturated fatty acids (*n*-3 or *n*-6) protected against atherosclerosis whereas monounsaturated fatty acids did not, even though monounsaturated fat produced favorable effects on serum lipoprotein concentrations and on the susceptibility of LDL to oxidation. Despite their apparent relevance to human disease, the use of non-human primates in atherosclerosis research is limited by availability, the expense involved in purchasing and maintaining the animals, and the long time-frame for atherosclerosis induction and regression. The pig is frequently used as an alternative model for atherosclerosis research. Pigs and humans are quite similar in terms of lipoprotein metabolism and the pattern of atherosclerosis that develops in response to an atherogenic diet. Pigs are widely available but studies are relatively expensive because of the size of the animals and the length of time required for atherosclerosis induction and regression. Rabbits have been used extensively in atherosclerosis research. However, when fed on an atherogenic diet rabbits develop a cholesterol storage disease with massive accumulation of cholesterol in the liver and RE system that makes studies of atherosclerosis regression difficult. Over the past decade a large number of induced mutant mouse lines have been generated and used to evaluate genetic factors that control lipoprotein metabolism and influence atherosclerosis. Some of these mouse models have also been used to study the influence of nutritional factors on atherogenesis.

The Syrian hamster has recently emerged as another small animal model for atherosclerosis research. Syrian hamsters are readily available, easy to handle, and are more humanlike in their response to diet modification than most other rodents. Atherosclerosis can be induced in the Syrian hamster by feeding a diet enriched with cholesterol and saturated fat. After about 1 month on an atherogenic diet, Oil Red O-stainable deposits develop (initially localized along the inner curvature of the aortic arch), which are composed of subendothelial foam cells, the precursor of the fatty streak. With continued exposure to an atherogenic diet, lesions can progress into complex plaques resembling human lesions (Nistor *et al.* 1987). The effect of dietary cholesterol and fatty acids on lipoprotein transport and whole body sterol balance has been well characterized in the hamster (Spady *et al.* 1993; Woollett *et al.* 1997). On a low-fat, low-cholesterol diet the hamster has a relatively low serum LDL-cholesterol concentration (about 0·7 mM); however, in response to an atherogenic diet, serum LDL concentrations rise into the range commonly seen in Western humans. Unlike most humans, the hamster also accumulates large amounts of VLDL/IDL in response to an atherogenic diet. In addition, the hamster has an anomalous response to *n*-3 polyunsaturated fatty acids characterized by a marked reduction in serum HDL levels and a variable increase in lower density lipoproteins (Spady *et al.* 1995).

In this issue, Mangiapane *et al.* (1999) have used the hamster model to address the question of how different dietary fatty acids affect atherosclerosis regression. Early atherosclerosis was induced with a diet enriched with cholesterol and coconut oil. Animals were than placed on low-cholesterol diets enriched with either coconut oil or olive oil. Overall, little evidence for regression was seen in the coconut oil group even though saturated fat (without cholesterol) does not induce atherosclerosis in the hamster. It is possible that regression would eventually occur since plasma cholesterol levels were still falling by the end of the study. Compared with animals fed on coconut oil, animals fed on olive oil had significantly less atherosclerosis at the end of the regression period. Differences in regression were highly correlated with differences in serum non-HDL cholesterol concentrations. The question remains as to whether experimental animal models that have as their endpoint the surface area stained by Oil Red O can adequately predict the arterial wall changes that may occur in humans. Nevertheless, while there is no one perfect animal model that completely replicates all stages of human atherosclerosis, the hamster promises to be a very useful small-animal model for exploring the effects of nutritional factors on the genesis and regression of atherosclerosis.

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