DIET, SERUM CHLOESTEROL AND CORONARY DISEASES

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ABSTRACT

The probable sequence of events leading to atherosclerotic disease of the coronary artery and heart attack are briefly described. Blood cholesterol as a causal agent in atherosclerosis and how blood cholesterol can be modified are discussed. The effects of various dietary components particularly quality and quantity of fat and protein on the blood cholesterol concentration are discussed and it is emphasised that more work needs to be done to ascertain the role of individual components of the diet and their relative importance in atherogenesis.

Introduction

The coronary disease is one of the major health problems in most of the highly industrialised countries of the world and it has been reported that the incidence of this disease is on the increase in India. Amongst various forms of coronary disease atherosclerotic disease of the coronary artery is the prime killer. There are about 1·5 million deaths in United States due to coronary disease and 9 out of 10 are caused by atherosclerosis.

Atherosclerosis and Coronary Disease

What is atheroclerosis and how it leads to coronary disease? Broadly speaking atherosclerosis may be considered as a mixture of various degenerative and reparative processes which lead to increased rigidity, decreased elasticity and very often to narrowing of blood vessels. These reactions in blood vessels are associated with deposition of excessive quantities of lipids or fats in general and cholesterol in particular. The initial stage is the formation of atheroma which starts as a yellow streak of fibrous cells. These cells are extended and laden with lipids and cholesterol. These initial atheromatous plaques undergo degenerative and reparative changes and project into the lumen of the artery. They vary in size from 1 mm. to several mm. in diameter and are of irregular shapes. Excessive formation of atherosclerotic plaques may occur in any blood vessel but they occur most frequently in coronary and cerebral arteries.

A plaque may be so large as to reduce the lumen of the artery to such an extent that the blood supply of the tissue is diminished appreciably. The tissue beyond this block and supplied by this artery dies for want of adequate oxygen and is said to be infarcated.

The presence of atherosclerotic plaques produces pressure on the surrounding cells and increased irritability results. Hemorrhage into these plaques may

result in swelling and this may occasionally lead to obliteration or occlusion of the artery. Further the roughened surface of these plaques form ready sites for the formation of clot or thrombus. If this happens in a coronary artery it is called coronary thrombosis. The blood supply, thus, is completely cut off—coronary occlusion due to coronary thrombosis. The heart muscle supplied by the artery, consequently, dies—coronary infaraction. The person is said to have heart attack. The degree or severity of heart attack depends upon how much portion of the heart muscle is involved. An infarct involvng a large portion of the heart muscle is immediately fatal. The muscle cells involved in the infarct cannot be regenerated, but the dead cells are slowly replaced by fibrous tissue on healing and thus leave a permanent scar on the heart's muscle or myocardium.

Blood Cholesterol and Atherosclerosis

The exact etiology of atheroselerosis, or how these lipids-cholesterol get deposited on the blood vessel is not known with certainty. However, hypercholesteremia either of dietary or metabolic origin is generally asscciated with this disease. A number of theories have been advanced regarding atherogenesis, but the concept that atherosclerosis is the result of a defect(s) in lipid metabolism or transport or both particularly that in cholesterol, is currently favoured most.

Evidence that atherosclerosis represents a metabolic disorder involving cholesterol is based on clinical and experimental support. There is higher incidence of atherosclerosis in conditions associated with abnormally high serum cholesterol concentrations as in familial hypercholesteremia, myxedema, nephrosis, and Cushing's syndrome. On the other hand, clinically low cholesteremia states in prolonged consuming diseases, cirrohsis of the liver, and hyperthyroidism are associated with low incidence of atherosclerosis. Further population groups with low serum cholesterol levels have low incidence of atherosclerosis.

Hypercholesteremia or a defect in cholesterol or lipid metabolism is, thus, primarily or secondarily involved in atherogenesis. Body cholesterol can arise from endogenous synthesis or dietary cholesterol. Cholesterol is synthesised in almost all the tissues of the body, however liver is the main regulator for blood cholesterol. The synthesis of cholesterol in the body is influenced by the dietary cholesterol. Ingestion of large quantities of cholesterol reduces the synthesis of cholesterol in the body. Further, it is now well-recognised that lipid metabolism including cholesterol can be modified by dietary means. Also some of the dietary components may greatly alter the absorption of dietary cholesterol.

Diet and Blood Cholesterol

A number of dietary factors have been implicated in atherogenesis or in the regulation of blood cholesterol levels. Among the various dietary factors which have been mentioned in this connection are: the total calorie content of the diet, the quality and quantity of dietary fat, the amount and nature of dietary protein, and some specified amino acids; the type of carbohydrate in the diet, the plant sterol content of the diet; deficiency of certain vitamins and excess of others; certain minerals and intake of cholesterol itself. It is not possible to include all these nutritional factors involved, in a short review like

this, however an attempt will be made to summarize briefly and critically the available evidence concerning the roles of three major constituents of the diet, *i.e.*, fats, proteins and carbohydrates in influencing blood cholesterol levels or in atherogenesis.

Role of Dietary fat

(*a*) *Amount of Dietary fat:* Ancel Keys and his school, in particular, have stressed that the total quantity of fat in the diet, more than anything else, influences the serum cholesterol level and development of atherosclerosis. There is abundance of data which support this hypothesis, but there are large number of observations which cannot be reconciled with this hypothesis. Moreover the effect of decreases or increases in dietary fat intake cannot be dissociated from changes in other dietary constituents particularly the caloric intake. Excessive caloric intake and resulting obesity may lead to hypercholesteremia and development of atherosclerosis. Postmortem examinations have revealed that atherosclerosis is commonly associated with obesity. Further the physical state of the persons consuming a high fat diet or excessive calories may also be important. It has been reported that the serum cholesterol levels of young adult males consuming high animal fat diet with high calorie content, did not increase as long as appreciable weight increase was prevented by severe exercise. On the other hand, severe caloric restriction has been reported to increase hypercholesteremia and atherosclerosis in some experimental situations. Thus the role of quantity of fat in the diet and caloric intake and their relative importance in atherogenesis remains still unsolved.

(*b*) *Animal fat* vs *vegetable fat and the role of essential fatty acids (EFA):* The ingestion of certain vegetable oils, under certain controlled conditions, was shown to be associated with a reduction in serum cholesterol concentration. This observation has been repeatedly confirmed both in human and experimental animals, and now it is generally agreed that certain fats typically reduce while others typically elevate the serum cholesterol concentration. Since this discovery, attempts have been made to identify and separate the factors or components responsible for cholesterol-lowering or cholesterol-elevating in various fats. Surprisingly, though there is remarkable agreement between the results, the interpretation of these results is subject to wide disagreements regarding the component(s) of the fat responsible for cholesterol-lowering or cholesterol-elevating effect. The cholesterol-lowering activity of vegetable oils has been attributed to: (i) the sitosterol content of these vegetable fats and some unidentified factor present in them, (ii) to the total unsaturation of these fats in terms of iodine value and their solvent action, (iii) removal of some hypercholesteremic component along with the removal of animal fats, (iv) and essential fatty acid content of these fats. Also the cholesterol elevation caused by animal fats is attributed to: (i) some hypercholesteremic component present, (ii) relative lack of essential fatty acid and abundance of saturated fatty acids, (iii) presence of excess of short chain fatty acids.

The vegetable fats are rich in plant sterols and it has been shown that plant sterol have cholesterol lowering activity and this is related to their effect on their absorption of cholesterol. It has, therefore, been suggested that cholesterol-lowering activity of corn oil, and presumably of other vegetable oils, is

related to its content of plant sterols. However the sterol content of corn oil could not account for the entire activity of corn oil and it was suggested that these sterols may be acting synergistically with some unidentified component in corn oil.

The observation that tung oil with an iodine number of 191 entrances cholesteremia also cast doubt on the relationship between iodine value or total unsaturation of a fat and its cholesterol-lowering effect.

The most attractive hypothesis is that atherosclerosis is the result of chronic essential fatty acid (EFA) (*e.g.*, seasame, mustard, ground nut) deficiency and the vegetable oils supply these EFA. According to this hypothesis cholesterol in the body is normally esterified with EFA and when there is deficiency of EFA, cholesterol is esterified with abnormal saturated fatty acids and these abnormal cholesterol esters are not easily metabolised and get deposited in the tissues. It has been suggested that the production of atherosclerosis in pyridoxine deficient monkeys may be the result of EFA deficiency brought about by pyridoxine-deficiency and thus lack of conversion of linoleic to arachidonic acid. It has been suggested that this EFA deficiency in human diet may arise by the use of high extraction flour, use of improvers and increased use of saturated or hydrogenated fats.

If atherosclerosis is the result of EFA deficiency, this deficiency should be reflected in the EFA content of blood of normals and patients with coronary disease. However, in a recent report no such differences were observed between linoleic and arachidonic acid content of normals and patients. The oleic acid content of patients was found to be higher. Further it has been observed that EFA content of atheromatous tissue was no lower in cases of deaths from coronary thrombosis than in cases of deaths from other causes.

However, the results have to be interpreted within the limitation of the methods for the determination of individual fatty acids. Further the observation that feeding of cholesterol to experimental animal enhances the symptoms of EFA deficiency lends support to the role of EFA in cholesterol metabolism. This naturally brings to mind the effect of continuous use of hydrogenated fats in our diets. Hydrogenation of the oils reduces the unsaturated fatty acids or EFA content, and also leads to the formation of transisomers of these fatty acids. These transisomers not only have no EFA activity but some of them also enhance EFA deficiency. Because of this it may be possible that continuous use of these fats over prolonged periods may produce relative lack of EFA in the body and thus disturb cholesterol metabolism. Further the use of the hydrogenated fats must also be viewed from another angle. Recently there has been some evidence, based on animal experiments, that use of hydrogenated oils without adequate EFA leads to disturbances of reproductive systems both in female and male. Though there is no direct evidence in humans, the continuous and increasing use of hydrogenated oils in human diet over prolonged period of time may have some adverse effects.

(*c*) *Dietary Cholesterol*: Although faulty lipid cholesterol metabolism is generally associated with atherosclerosis and although feeding of cholesterol has been consistently used in the production of atherosclerosis in susceptible animals, the nature of the role of dietary cholesterol in the regulation of cholesteremia and in the development of atherosclerosis in man has not been generally

agreed upon. It has been stressed, on the basis of exerperiments and surveys with humans that the dietary intake of cholesterol in natural foods does not significantly alter the serum cholesterol concentration in man and thus may not play any important role in the development of atherosclerosis. This concept is based on the following arguments. The amount of dietary cholesterol to produce hypercholesteremia and atherosclerosis in experiments on susceptible species is beyond the level found in any natural food. Further, man unlike some experimental animals, is far better able to regulate his blood cholesterol level independently of the cholesterol in the diet. Even the feeding of high dozes of cholesterol without additional fat was shown to have a trivial effect on the blood cholesterol concentration. However, one must keep in mind that atherosclerosis in man is a slow process which develops over a number of years. Short term experiments with humans, therefore, may not show any relationship between cholesterol in the blood and that in diet. This does not necessarily mean that increased dietary intake of cholesterol over a number of years does not influence cholesterol metabolism in the body or does not influence atherogenesis. Furthermore, the consistent production of hypercholesteremia by feeding small amounts of cholesterol over longer periods in some experimental animals invalidates criticism against some role of dietary cholesterol in the development of atherosclerosis. The effect of dietary cholesterol may also be influenced by its absorption since the addition of egg yolk to the diet increases serum cholesterol concentration more effectively than the addition of pure cholesterol in comparable amounts.

Role of Dietary Protein

Dietary Protein was implicated in atherogenesis as early as 1921, when it was claimed that a high protein intake induced atherosclerosis in the rabbit. The protein supplied was either in the form of milk or casein or mechanically defatted dried beef powder. It was further noted that the amount of vascular injury was proportional to the duration of high protein feeding and this effect was not due to the cholesterol consumed along with these poteins. Later it was shown that high protein diet containing alfa alfa, soyabean and gluten flour had no such effect on the rabbit. This brought in the question of animal and vegetable protein in the process of atherosclerosis.

Recently the role of dietary protein in the regulation of hypercholesteremia and development of atherosclerosis, has received great attention. It has been reported that high protein diet have beneficial effects on the blood cholesterol of some experimental animal under certain controlled conditions. This beneficial effect of the high or optimum level of dietary protein may vary with the type of diet used and that increase in the dietary level beyond the optimum may actually lead to adverse effects.

Also vegetable proteins (soyabean) low in sulphur amino acid have been shown to increase hypercholesteremia and lead to atherosclerosis in monkeys. This effect of vegetable proteins can be prevented by substituting soyabean protein with casein or supplementing the diet with sulphur amino acids, such as methionine, cystine, cysteine. It has been possible to show that most of the effect of high levels of casein in the diet in lowering serum cholesterol can be accounted for by the higher sulphur amino acid intake accompanying protein intake.

The protection offered by high levels of some vegetable proteins against hypercholesteremia or atherosclerosis may be due to some lipid material associated with these proteins. The cholesterol lowering activity of wheat gluten has been found to be associated with lipid material present in it. Some preliminary studies also indicate that some other so-called vegetable proteins also contain appreciable quantities of lipids in them, which might explain some of the discrepancies reported in literature about the effect of animal and vegetable proteins. Vegetable proteins freed of lipids, actually cause higher degree of hypercholesteremia than that produced by animal proteins such as casein. As most of the effect of high level of casein can be accounted for by sulphur amino acid, the greater hypercholesteremia with some vegetable proteins raise the question of the availability of sone amino acid, particularly those containing sulphur in the vegetable proteins.

The role of dietary protein in human atherosclerosis is a subject of considerable controversy. A. Keys and co-workers on the basis of limited experiments have indicated that the quantity of dietary protein has no effect on the serum cholesterol concentration of man. However in their experiments entire range of protein studied was high. R.E. Olson and co-workers at the University of Pittsburgh on the other hand, reported that low protein diet, have beneficial effects in lowering serum cholesterol concentration. However, they used animal proteins in high protein diets and vegetable protein from cereals and legumes for low protein diets. The association of lipid material possessing cholesterol-lowering actively with vegetable proteins must be kept in mind. Further the two diets differed in the quantity of choline supplied which make it hard to attribute the results only to low dietary protein. Furthermore, atherosclerosis in man is a slow process which develops over a number of years. Experiments of short duration with human subjects may not reflect the true state of affairs. These experiments in humans, if they are to be meaningful, have to be carried over a long period of time. The cholesteremic response to a particular dietary constituent may be modified by the presence of other dietary components. Thus it has been reported that either the level or nature of dietary fat has effect on the serum cholesterol concentration of chicks fed high protein diets. On the other hand, there is also evidence that high level of dietary casein does not influence the serum cholesterol concentration of rats fed abundance of lipid mixture containing high percentage of polyunsaturated fatty acids.

Role of Carbohydrate and other Dietary factors

The effects of alteration in the carbohydrate or other constituents of the diet have not been much studied. However some recent reports implicate the nature of the carbohydrate in cholesterol metabolism and cholesteremia. It has been reported that the serum cholesterol level of rats was higher when sucrose was the carbohydrate than when starch was the carbohydrate. This effect has been attributed to greater excretion of cholic acid (an excretory product of cholesterol) on starch diet. However this observation has not been confirmed or rigorously proven. Lactose (milk sugar) and glucose have also been implicated; while the effect of lactose may be the result of greater cholesterol absorption, the cholesterol-lowering attributed to glucose is not confirmed. Further, in evaluating the role of these carbohydrates, the purity and possibility of some contaminant present must be kept in mind.

Vitamins play an important role in lipid metabolism, their role in atherogenesis has received little attention. Large dozes of nicotinic acid have been shown to reduce serum cholesterol concentration in humans and rabbits. These large dozes of nicotinic acid are accompanied by stress reactions as "flushes" in humans. The effects of large dozes of nicotinic acid appear to be pharmacological rather than physiological. Further, possibility of some adverse side effects of large amount of nicotinic when administered for long periods, must be kept in mind.

Pyridoxine (vitamin B6) deficiency has been used to produce hypercholesteremia and atherosclerosis in monkeys and had been shown to lead to greater degrees of hypercholesteremia in rats. It has been suggested that vitamin B6 may be involved in cholesterol metabolism through essential fatty acids, since vitamin B6 is involved in the conversion of linoleic to arachidonic acid.

Some other vitamins as ascorbic acid (vitamin C), vitamin D, vitamin E, and other components as niositol, choline, magnesium have also been mentioned in this connection. However, information about these components is so meagre that no definite conclusion can be drawn.

Conclusion

It is definite that more work needs to be done to ascertain the role of various dietary constituents and their relative importance in the process of atherogenesis.

"There is not enough evidence available to permit a rigid stand on what the relationship is between nutrition, particularly the fat content of the diet, and atherosclerosis and coronary disease. We are certain of one thing, the evidence now in existence justifies the most thorough investigation. This should be done soon, thoroughly, and uncompromisingly."