The Prolonged Effects of a Low Cholesterol, High Carbohydrate Diet Upon the Serum Lipids in Diabetic Patients

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Vascular disease is the major complication of diabetes in the Western World. Increasing evidence from clinical, experimental and epidemiologic sources supports the belief in a correlation between diets rich in cholesterol and fat, and atherosclerosis. Because correlation does not imply cause and effect, there is a need for prolonged prospective studies designed to test the hypothesis that experimental diets will reduce the incidence of vascular complications in patients with diabetes mellitus.

Two years ago we started such a prospective study. We hope to continue it for at least eight more years. Our purpose is to determine the influence of an experimental diet on the serum lipids and on vascular, retinal, neurologic and renal complications in patients with diabetes. The experimental diet is restricted in cholesterol and fat. It contains much more carbohydrate than is usually prescribed for diabetic patients. This report describes our observations through April, 1962. The study is still in progress.

METHODS

All insulin-dependent diabetics attending the University Hospitals were considered for the study if they were more than sixteen or less than sixty years of age, and if they had had diabetes less than fifteen years. They were excluded if they had severe diabetic complications: cataracts with loss of vision; retinopathy with complete blindness in one eye; peripheral vascular occlusive disease which had caused rest pain, ulcers or gangrene; clinical evidence of coronary artery disease including angina pectoris, myocardial infarction, congestive heart failure or significant cardiac enlargement; diastolic blood pressure greater than 100; chronic pyelonephritis, diabetic nephropathy with blood urea nitrogen greater than 30 mg./100 ml.; peripheral neuropathy if associated with ulceration or Charcot joints. Patients were also excluded if they had other diseases which might limit life span to less than five years or alter serum lipid levels, if they weighed 20 per cent more than desirable body weight or if personality characteristics precluded their cooperation.

Patients who passed this initial selection were studied for a further baseline period. During this time, venous blood was collected after a fourteen-hour fast on at least three occasions each five days apart. After other detailed studies had been completed, patients were randomly assigned, within categories according to age and duration of diabetes, to the control or the experimental groups. Six diabetics with moderately elevated serum lipids were deliberately assigned to the experimental diet at the beginning of the study.

Apart from differences in diet and insulin dose, all patients were treated in exactly the same manner. Among our objectives were excellent diabetic regulation and precise dietary adherence. All patients received painstaking instruction about diabetes and their diet. After intensive study for one month, all patients returned after increasing intervals, eventually returning every three months. The control and experimental patients returned on different days for medical examination, investigations and re-instruction.

The control and experimental diets differed in their content of cholesterol, fat and carbohydrate. Table 1 details typical diets of 2,200 calories. The control diet was the exchange diet of the American Diabetes Association.[1] The experimental diet contained much less cholesterol, less fat but more carbohydrate than the control diet. The composition of fat in the two diets differed also. We designed nutritionally adequate experimental diets with a range of 1,200 to 3,200 calories. We arranged caloric intake to suit energy needs and to prevent change of weight.

The detailed and precise dietary information essential for this study was obtained by two dietitians. Patients were questioned about previous dietary prescriptions, adherence to present diet, food habits, exercise, family background, socio-economic status and social habits.

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TABLE 1

Composition of the control (ADA) diet and the experimental diet

	Control diet	Experimental diet
Calories	2,200	2,200
Protein	90 gm. (17%)*	82 gm. (16%)
Carbohydrate	220 gm. (41%)	358 gm. (64%)
Fat	100 gm. (42%)	49 gm. (20%)
Saturated fatty acids	51 gm. (22%)	11 gm. (4%)
Monounsaturated	41 gm. (17%)	22 gm. (9%)
Polyunsaturated	8 gm. (3%)	15 gm. (6%)
Iodine number	50	95
Cholesterol	800-1,000 mg.	100 mg.

*Per cent of total calories.

On each return visit, the dietitians took either a twenty-four-hour diet history or a three-day diet history, and discussed seasonal and social changes in eating habits. Recipes and new ideas were exchanged while previous suggestions were discussed. Between visits to the hospital, the patients sent the dietitians a report every two weeks. This report included an exact inventory of all food eaten on a specified day, of insulin needs and weight changes, and of any irregularity that may have occurred. These reports were discussed at the next hospital visit.

Diabetic control was evaluated by urine testing four times daily, supplemented by an occasional estimation of twenty-four-hour urinary glucose excretion[2] and by fasting and postprandial blood sugar estimations.[3] All blood specimens for lipid determination were drawn after an overnight fast and before insulin. The serum was analyzed for total cholesterol[4] and triglyceride.[5]

RESULTS

We report here preliminary information on the first twenty-five control and thirty-one experimental patients. Table 2 portrays clinical observations on these patients.

Insulin requirements did not change in either group. The mean insulin dose was 41 units per day in the experimental group and 43 units per day in the control group. Diabetic regulation was good in nearly all patients and did not differ between groups. Good control implies the objective of normoglycemia and aglycosuria. In practical terms, this means to the authors the avoidance of more than minimal glycosuria, the avoidance of more than 10 gm. of glucose per twenty-four-hour specimen of urine and of more than one mild hypoglycemic episode every two weeks.

The clinical condition of patients in each group showed little change. We observed subjective and objective improvement in long-standing neuropathy in six experimental patients but in only one control patient. We cannot suggest at this time that this improvement was caused by the change of diet; we record it simply as an association. We shall report later after longer clinical observations.

TABLE 2

Description of patients included in study

	Control patients	Experimental patients
Number of patients	25	31
Duration of study after baseline period (months)	12.75	12.75
Mean age (years)	34	40
Mean duration of diabetes (years)	9.3	11.8
Mean weight on entry to study (pounds)	146	142
Mean change of weight (pounds) throughout study	+3	+1

Figure 1 portrays changes in serum lipids for all control patients. The mean initial serum cholesterol was 218 mg./100 ml.; the mean final serum cholesterol was 215 mg./100 ml. The mean initial serum triglyceride was 121 mg./100 ml.; the mean final serum triglyceride was 125 mg./100 ml.

The changes in serum lipids for all experimental patients are portrayed in figure 2. The mean initial serum cholesterol was 251 mg./100 ml.; the mean final serum total cholesterol was 199 mg./100 ml. The decline of 52 mg./100 ml., or 21 per cent, was statistically significant ($p < 0.001$). The mean initial serum triglyceride was 149 mg./100 ml.; the mean final serum triglyceride was 123 mg./100 ml. The decline of 26 mg./100 ml. has little significance ($p < 0.1$).

It should be pointed out that there is a difference in the mean serum lipid levels at baseline time in the control and experimental groups. This is partly because six diabetics with elevated serum lipid levels were deliberately assigned to the experimental diet at the beginning of the study. These patients had been observed for long periods before their change from the diet of the American Diabetes Association (ADA) to the experimental diet. During the time that they had been eating the exchange (ADA) diet, their serum lipids had remained stationary despite good diabetic control. In addition, the mean age of patients in the experimental group was somewhat older than that of the control group. We plan to continue to assign patients randomly to the two groups, and, as the study enlarges, we expect that this difference in baseline levels will decrease.

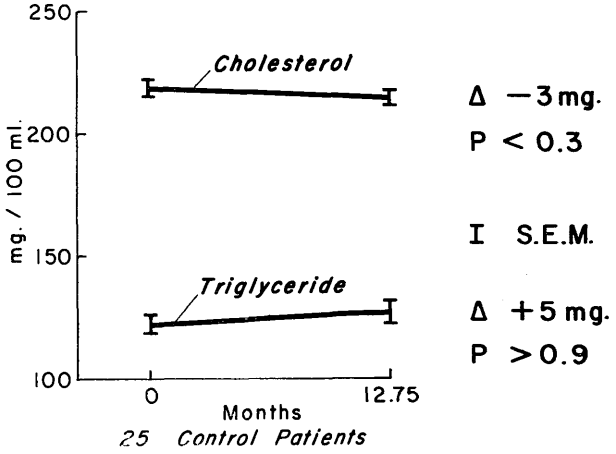

FIG. 1. Changes in mean serum lipids of control patients.

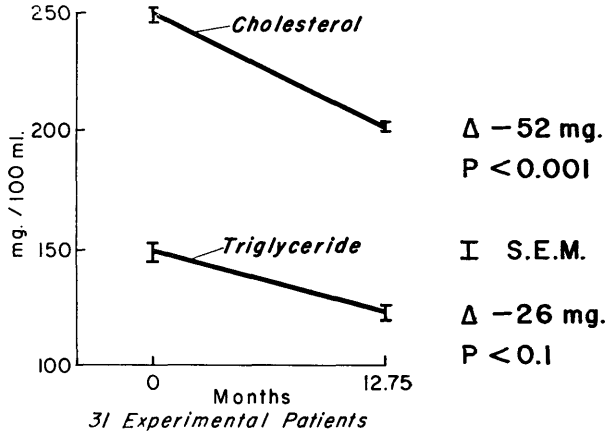

FIG. 2. Changes in mean serum lipids of experimental patients.

Figure 3 portrays serum lipid changes observed in one typical experimental patient. The patient was a man aged twenty-seven years who had had well-controlled insulin-dependent diabetes for five years. Detailed examination had not revealed any evidence of diabetic complications or other disease. His serum lipids changed little in the seven-month period of observation before he had been changed from the control to the experimental diet. At the time of the change of diet there occurred a sharp and sustained decrease in serum cholesterol. The serum triglyceride showed a transitory increase but then decreased over many months.

DISCUSSION

The aim of this prospective study is to reduce the high incidence of vascular complications observed in diabetics whose diets traditionally have been rich in

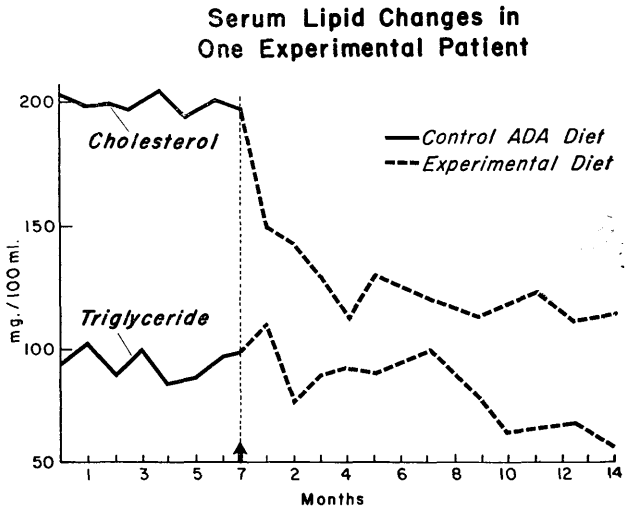

FIG. 3. Serum lipid changes in one experimental patient.

cholesterol and fat. Diets rich in cholesterol and fat, consumed over the human lifetime, are associated with pronounced elevation of the serum lipid levels.[6,7]

In the pre-insulin era, an effective treatment for patients with severe diabetes was the use of diets high in fat and cholesterol but severely restricted in carbohydrate.[8,9] After the introduction of insulin, some investigators suggested that an isocaloric change of diet (with an increase of carbohydrate and a reduction of fat) did not increase the insulin requirements of many diabetics.[10-17] Most of these diets had a carbohydrate content of 150-200 gm., not high by contemporary standards. A few investigators[10] had used higher carbohydrate diets, usually for short periods.[13] The introduction of higher carbohydrate diets into clinical practice caused controversy, however, for many physicians believed that such diets would cause an increase in blood sugar, in glycosuria and in insulin requirements. The practice of restricting carbohydrate has continued. It has recently been stated again that a carbohydrate intake of more than 250 gm. daily tends to make diabetic regulation more difficult with the insulins currently available.[18]

The lack of change of insulin requirements in our experimental patients is especially significant in view of their greatly increased carbohydrate intake. Diabetic regulation was good in both control and experimental patients. Eleven of the experimental patients consumed more than 350 gm. of carbohydrate daily. One experimental patient, a man aged twenty-six, had been well regulated with 62 units of insulin when eating the control (ADA) diet. When he was changed to the experimental diet his carbohydrate intake was

increased to 525 gm. daily. Two years later he remained excellently regulated without increase of insulin requirements.

The typical diabetic diet, rich in fat and cholesterol, is associated with, and may be the direct cause of, the strikingly high incidence of occlusive atherosclerotic disease in diabetic patients. There is an historical precedent for this suggestion. Joslin, in 1928, suspected that high fat, high-cholesterol diets might favor atherosclerosis.[19] He wrote: "Can it be that the prevalence of arteriosclerosis in diabetes is to be attributed to the high fat diets we have prescribed and more especially to these diets having been rich in cholesterol? I suspect this may be the case. At any rate it is reasonable to maintain the cholesterol in the blood of our patients at a normal level and that I shall strive to do. This may result in the limitation of eggs, each one of which contains about 0.38 gm. of cholesterol. . . . This therapeutic procedure is adaptable for experimental investigation and should not require long for solution." Obviously, his prediction has not yet been realized.

Our experimental diet was designed with three objectives: First, it should effectively reduce the level of serum cholesterol in man. Secondly, since it is not known that a reduction of the level of serum cholesterol in hypercholesterolemic Americans will postpone or prevent atherosclerosis, the design of the diet should receive support from the evidence derived from experimental animals and from epidemiologic studies. Thirdly, the diet should be acceptable and nutritionally adequate.

The decrease in the mean serum cholesterol level resulting from the consumption of the experimental diet was as great or greater than the results reported by others using different diets designed to lower the serum lipids in outpatients.[20-23] The hypocholesterolemic effect of our experimental diet might be attributed to any of the following: the pronounced reduction in the intake of dietary cholesterol; the moderate reduction in dietary fat; the change in fatty acid composition; or the increase in the carbohydrate intake. We know of no evidence which suggests that mixed carbohydrates per se are hypocholesterolemic and will confine the discussion to consideration of cholesterol and fat in the diet.

The cholesterol content of the experimental diet was 100 mg., an amount one eighth or less than the usual intake of cholesterol. During the past four years we have reported three different studies[24-26] showing that the removal of cholesterol from the diet caused a great lowering of the serum cholesterol levels both in nondiabetics and in diabetics. In these studies the amount of fat and its composition were carefully controlled. Steiner et al. have reported similar observations in nondiabetics.[27] Beveridge et al. have also found that dietary cholesterol influences the serum lipids.[28,29] Experimentally, cholesterol is the most significant component in the diets of all animals—including primates—in whom hypercholesterolemia, atherosclerosis and myocardial infarction have been produced.[6,7,30-32] It should be emphasized that atherosclerotic lesions closely resembling advanced human lesions have occurred in the arteries of experimental animals.[33] Epidemiologically, there is a close correlation between dietary cholesterol intake and the mortality from coronary heart disease.[34]

This experimental diet contained only about one half of the fat content of the usual American diet, yet this amount, 20 per cent of the total calories, provided enough fat to give the diet palatability and acceptability. Undoubtedly, some of its hypocholesterolemic effect was derived from its reduced fat content. Even in previous studies showing the hypocholesterolemic effect of low-fat diets, however, the amount of cholesterol in the diet was also restricted.[35] Fat facilitates the absorption of dietary cholesterol by the gastrointestinal tract. In man, as in experimental animals, restriction of dietary fat tends to reduce serum cholesterol levels.[36]

It might be suggested that the experimental diet reduced the level of serum cholesterol because of its change of fatty acid composition. Many investigators have clearly documented that the dietary substitution of 40 to 50 gm. of polyunsaturated for saturated fat will effectively reduce the level of serum cholesterol.[37-41] The amount of polyunsaturated fat in our experimental diet, however, was increased only from 8 gm. to 15 gm., or from 3 per cent to 6 per cent of total calories. The increase of polyunsaturated fat of 3 per cent of total calories would have a negligible effect upon the level of serum cholesterol.[35] The two other types of dietary fatty acids, saturated and monounsaturated, were greatly altered during the change from the control to the experimental diet. At a diet of 2,200 calories, for instance, the intake of saturated fat was reduced by 40 gm., and of monounsaturated fat by 19 gm. Thus any hypocholesterolemic effect from lowering of the fat content of the experimental diet was probably attributable to the reduction of saturated and monounsaturated fat.

The patients reported in this paper did not demonstrate an increase of serum triglyceride levels when they changed from the control (ADA) to the experimental diet. This requires special comment, for Albrink and other authors[42-45] have suggested that there

is a close correlation between elevated serum triglyceride levels and the incidence of coronary heart disease. Others have reported that high-carbohydrate, low-fat diets have induced hypertriglyceridemia in a wide variety of patients[46–53] and Bierman and Hamlin reported *carbohydrate induced hyperlipemia in diabetics.*[54]

All these investigators, however, used diets extremely low in fat. In fact, Bierman and Hamlin used a formula which consisted of 15 per cent protein, 85 per cent carbohydrate and no fat. Horlick demonstrated that there was little rise of triglyceride with a 14 per cent intake, and no significant rise with a 24 per cent fat intake.[55] Horlick also suggested that hypertriglyceridemia tended to regress with time. Antonis and Bersohn observed adaptation to a 15 per cent fat intake with a decline of serum triglyceride after three to six months.[56] In our experience, the amount of fat in the diet need not exceed 20 per cent of total calories in order to prevent elevation of the level of serum triglycerides.

SUMMARY

We report the preliminary results of a prolonged prospective study of the influence of an experimental diet in patients with diabetes. This diet is restricted in cholesterol to 100 mg. daily and in fat to 20 per cent of the total calories. Its carbohydrate content is relatively high (64 per cent of the total calories). Suitably instructed patients adhered to the diet. Despite the large intake of carbohydrate, insulin requirements did not increase. Diabetic regulation was good or excellent. This experimental diet effectively reduced serum cholesterol levels and did not increase the concentration of serum triglyceride.

SUMMARIO IN INTERLINGUA

Le Effectos del Ingestion Prolongate de Dietas a Basse Contento de Cholesterol e a Alte Contento de Hydratos de Carbon Super le Lipidos Seral de Patientes con Diabete

Nos reporta le resultatos preliminari de un studio prospective a longe vista in re le influentia de un dieta experimental in patientes con diabete. Iste dieta es restringite in cholesterol a 100 mg per die e in grassia a 20 pro cento del contento total de calorias. Le contento de hydratos de carbon es relativemente alte (64 pro cento del contento total de calorias). Le intelligentemente pre-instruite patientes observava le regulas del dieta. In despecto del grande ingestion de hydrato de carbon, le requirimentos de insulina non cresceva. Le regulation del diabete esseva bon o excellente. Iste dieta experimental reduceva efficacemente le nivellos de cholesterol del sero e non augmentava le concentration de triglycerido in le sero.

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