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Use of low fat diet in treatment of diabetic retinopathy

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THE USE OF LOW FAT DIET IN TREATMENT OF DIABETIC RETINOPATHY

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INTRODUCTION

Diabetes mellitus is probably the disease in which the most varied picture of ocular signs may be seen. These signs include retinopathy, cataract, lipemia retinalis, changes in refraction, optic neuritis, eye muscle palsies, rubeosis iridis and glaucoma.

Among the ocular lesions occuring in diabetics fundus changes are those seen most frequently. They form a characteristic ophthalmoscopic picture known as diabetic retinopathy.

Diabetic retinopathy is rapidly becoming the single most important cause of new blindness among the adult population of the United States. In New York State, the percentage of blindness due to diabetes in 1941 was 4.5%; in 1954 it was 12.7%; in 1955 it was 15.3%; in 1956 it was 14.4%; and in 1957 it was 16.6%. In Massachusetts, the rise was from 3.8% in 1941 to 17.2% in 1958. Similar increases in incidence have been reported from California, Pennsylvania, and England [1]. The National Society for the Prevention of Blindness now estimates the number of persons in whom blindness is due to diabetes in the United States as 29,000, or 8.4% of all blind persons.

Thus, in addition to the more familiar problems of diabetes, we have here a very pressing illness which deserves a more intensified plan of therapy to prevent a continued rise in the incidence of blindness.

Before the introduction of insulin in therapy in 1922, retinopathy was limited almost entirely to diabetics over the age of 40 years with mild, easily controlled diabetes. Juvenile diabetics did not develop retinopathy at that time as they did not live long enough. Until 1942, therefore, even in large series, only few cases were reported where diabetics under the age of 40 years developed a retinopathy [8].

Gradually, as time went on, more cases of retinopathy were reported in long-standing juvenile diabetes. In 1953, Lundbaek, as cited by Larsen [27], reported he found in long-term diabetes (duration from 15 to 25 years) retinopathy in 87% of his cases under the age of 40 years.

The incidence of diabetic retinopathy rises slowly during the first 5 years of the disease, but after that time there is a sudden rise in frequency. After a duration of about 10 years or more, the incidence of retinopathy is nearly equal in all age-groups. In diabetics under the age of 16 to 18 years,

however, retinopathy seldom occurs, no matter how long the disease has lasted [27].

It is clearly established that careful control is important in prevention of vascular complications [6], but this is inadequate. The presence of retinopathy is not related to the severity of diabetes, as measured by the insulin requirement, but good control of the diabetic decreases the incidence of retinopathy by 30% to 50% [3].

Early Dietary Approaches: As compared with the abundant literature on the influence of dietary and other factors upon serum lipids, very little attention has been given to the significance of dietary fats for diabetes mellitus and its complications. When investigators recognized early in the study of the disease that a disturbance in the utilization of carbohydrates was the main characteristic, they prescribed diets containing a minimum of carbohydrates; the caloric balance was formed by fats. When insulin became available a more liberal intake of carbohydrates was permitted, but fats still provided a considerable percentage of the daily food intake, and the average diabetic diet at present contains from 80 to 110 grams of fat daily.

It is observed clinically that atherosclerosis is more common in the diabetic than in the non-diabetic of the same age group [3]. Furthermore, it is known that in poorly controlled diabetics all the serum lipids are increased. Some authors, however, maintain that the serum lipids of properly controlled diabetics, in patients taking the usual amount of dietary fats, are normal. The majority of papers, as exemplified by Rabinowitch [4], show that one of the most constant characteristics of a high-carbohydrate, low-fat diet was an immediate and sustained decrease of plasma cholesterol. In consequence, he advocated that by placing a patient on a 50 gram fat diet one might be able to decrease the incidence of arteriosclerosis.

Singh [5] has advocated the use of a low-fat diet in treatment of diabetes since it was his belief that the low-fat diet minimized the diabetogenic stimulus. His paper, although impressive, made no reference to serum lipids or retinopathy.

Recent dietary trials have indicated an approach which may change drastically the rationale in the management of the diabetic.

DEVELOPMENT AND COURSE OF DIABETIC RETINOPATHY

To understand the rationale of the treatment we must first understand the pathological background.

The individual fundus lesion seen in diabetics is not specific to diabetes [9]. Similar lesions may occur in several other diseases, such as retinal venous occlusion, thrombotic glaucoma, chronic glaucoma, chronic uveitis with secondary glaucoma, malignant hypertension, generalized arteriosclerosis, nephrosclerosis, nephritis, hypochromic anemia, pernicious anemia and sickle-cell anemia [10]. In diabetics the general ophthalmoscopic picture is so characteristic that the fundus changes can be considered as a clinical entity; diabetic retinopathy.

Diabetic retinopathy appears to proceed first with some dilatation of the retinal veins, with a few scattered microaneurysms, and punctate retinal hemorrhages. Later the microaneurysms and punctate hemorrhages tend to be more numerous and then are joined by small rounded hemorrhages and discrete, sharply outlined exudates. Retinopathy usually proceeds very slowly, but, in the course of time, the retinal hemorrhages will enlarge and the exudates are more extensive and confluent. It is only in a

smaller proportion of the patients that retinopathy proceeds to a proliferative stage with new-formed vessels, vitreous detachment, or vitreous hemorrhages, followed by fibrous tissue formation, retinal detachment, and loss of vision [27].

In older diabetics the ophthalmoscopic picture from the beginning is often dominated by sharply outlined exudates, either diffusely spread in the fundus or in a circunate arrangement around the macular area. Rounded retinal hemorrhages and microaneurysms are also seen, but microaneurysms are seldom so numerous as in juvenile or middle-aged diabetics. Besides these lesions, retinal changes due to arteriosclerosis and hypertension are often found in older diabetics.

In juvenile diabetics, the development of retinopathy may follow one of three different courses. The first is the ordinary course as described above. In the second, retinopathy proceeds directly into the proliferative state, generally of fine, newly formed vessels from the papillary tissue, partly on to the adjoining retinal surface, partly into the vitreous, followed by the development of sparse, slightly blurred connective tissue around the vessels. In some cases, however, it is found that the prolifera-

tive stage is preceded by pre-retinal, subhyaloid hemorrhages, degenerative changes in the hyaloid membrane, and vitreous detachment. In the third course retinopathy develops very slowly. Only a few microaneurysms, punctate and rounded retinal hemorrhages, and few discrete, sharply outlined exudates are seen for many years, but after 20 to 30 years duration of the disease several arteriosclerotic changes are seen in the fundus.

Normally, retinopathy develops slowly, but at times rapid progression may be seen to follow, as in infections or from unknown causes. To begin with, retinopathy may be found in only one eye, but fundus changes are usually found in both eyes later on, although the severity of the lesions may differ in each eye. The development of retinopathy may stop at any stage. In some cases the lesions may diminish again, and in a few not so advanced cases, the fundus changes may disappear completely.

As long as the fundus lesions are limited to venous dilatation, microaneurysms, retinal hemorrhages and exudates, the condition is often called simple retinopathy. When new formed vessels or fibrous tissue develop in the fundus, the retinopathy is termed proliferative [27].

If the retinal lesions are not localized in and around the macula, vision may remain unaltered for many years [12]. In cases dominated by confluent exudates in the macular area, vision is often reduced at an early stage. When retinopathy proceeds into the preproliferative and proliferative state, reduced vision or loss of vision will follow. It is therefore difficult to evaluate the visual prognosis in the individual cases, but generally the prognosis seems to be better in the older age group than in the other age groups.

There appear to be three theories in the pathogenesis of the microaneurysms. Ashton [13] postulated that the microaneurysms were in essence a neovascularization, and that something was occurring in the entire thickness of the vessel wall in which there was an attempt toward proliferation of new vessels. As this occurred, a U-shaped structure was formed which was abnormal in its physiology, allowing the vessel walls to become porous to the proteins which in turn formed hyalin. The center portion of the hyalin would disappear, and ultimately there was formed an aneurysm.

The second theory, as proposed by Bloodworth [11], is that the aneurysm may be a weakening in the vessel

wall, an outpouching not always unidirectional, but sometimes fusiform, with deposition of materials which are PAS stained. He suggests that this substance may be fibrin, although there is no clear-cut evidence one way or another.

The third theory cited, but not necessarily supported, by Bloodworth, is that there may be an increase in the pressure of the vessels of the retina[11].

PATHOGENESIS OF ASSOCIATED VASCULAR COMPLICATIONS

It is agreed that, in addition to a defect in glucose metabolism, the diabetic is also subject to a separate, degenerative vascular disease of the glomerulus and retina that probably involves a defect in the metabolism of complex lipoprotein-carbohydrate molecules, generally known as mucoids or glycoproteins [14].

The specific nodular lesion of the glomerulus of the diabetic has distinctive properties that allow it to be identified histochemically by phase microscopy, and by its ultra-violet absorption spectrum. It is positively correlated with the duration of diabetes and the presence of retinopathy [15]. In addition to the nodular lesion, a diffuse glomerulosclerosis and an exudative glomerular lesion also occur frequently in diabetes. The diffuse form has been produced experimentally in animals by alloxan and by pancreatectomy. The exudative lesion has been produced in man and animals by steroid administration. As of now, no one has succeeded in producing the specific nodular lesion of diabetes under experimental conditions.

All of the blood vessels of the diabetic appear to be susceptible to premature aging and degeneration, and this is reflected in the fact that among diabetics the death rate from cardiovascular and renal disease is twice that of the general population [16].

There is a highly characteristic subendothelial accumulation of hyalin in the afferent and efferent glomerular arterioles of the diabetic. Ashton has described a similar change in the wall of the retinal arterioles in diabetes [12].

The levels of glycoproteins are usually reported to be higher in the diabetic than in the nondiabetic, and higher in the diabetic with retinopathy than in the diabetic without retinopathy [17]. Because of the many variables in the techniques of collection, storage, extraction, assay, and interpretation, many conflictive reports are common, and even when a fraction is thought to be elevated, it is impossible to say whether this is the cause or result of the diabetic condition.

The various lipid fractions are usually found elevated in the diabetic, and abnormal lipids have been identified in the urine of the diabetic patient. As is the case with the glycoproteins, the specifi-

city of these findings is in doubt, and it is uncertain whether they represent cause or effect [18].

Although there is a considerable amount of clinical and pathological evidence to suggest that adrenal cortical function is implicated in the pathogenesis of diabetic vascular disease, recent improvements in the methods of study of urinary and plasma steroids have revealed no evidence of abnormal adrenal function in patients with uncomplicated diabetes, diabetic retinopathy, or diabetic nephropathy [19].

DIETS IN DIABETICS

Early in the study of diabetes it was established that there was a disturbance in the utilization of carbohydrates, and, as a result, the patient was placed on a low carbohydrate diet. As soon as insulin was made available the diets became more liberal in carbohydrates, and fats provided a considerable percentage of the calories.

It has been clearly established that the diabetic is highly subject to hyperlipemia [2], yet little attention has been given, until very recently, to the significance of dietary fats and their role in the disorder.

However, evidence accumulated regarding the use of low-fat diet and its effect in depressing blood lipids [20], and it was only a matter of time until low-fat diets were attempted to see what effect there would be on the diabetic.

Kempner [21], in 1945, made a study on the effect of a "rice diet" in hypertensive disease. Among his subjects were some diabetics, two of whom he described in detail, including the retinopathy. He noticed that in one patient, the serum cholesterol dropped from 315 mg/100cc to 230 mg/100cc, along with a marked

improvement of the retinopathy. In the other patient, he made no mention of the serum lipids; however, he did again mention marked improvement of the retinopathy.

In 1958, Kempner [25] followed one hundred consecutive diabetic patients with hypertension over a period of twenty-two months. These patients were placed on a rice diet, which consisted of 565 to 570 gm. of carbohydrate, 20 to 25 gm. of protein, and less than 5 gm. of fat. These were mainly the maturity onset type of diabetics, ages ranging from nineteen to seventy-one years, with the average age of fifty-one. The average insulin dose was 25 units per day. The specific diabetic retinopathy, even retinitis proliferans, was found to be improved in 25 percent of the cases. The insulin requirement did not increase with this high carbohydrate regimen, and it actually decreased in forty-two out of the seventy-two insulin treated patients.

Since Kempner's original work was published, others have had similar results with the low-fat diet [22]. Watson and Wharton [23] studied 27 trained diabetics of various grades of severity. By using various diets and the necessary amounts of insulin

to maintain control, they found that a high-fat, low-carbohydrate diet caused a decrease in the daily requirement of insulin; however, the amount of insulin required was greater in proportion to the amount of carbohydrate in the diet. In other words, they stated that this diet tended to cause a decline in the carbohydrate tolerance and to favor ketonuria. They showed that, on the contrary, many patients could tolerate a high carbohydrate diet, providing the fat intake was kept low. Raising the carbohydrate intake did not require an increased insulin dose; in other words, high-carbohydrate, low-fat diet caused an improvement of the tolerance. They found that from the patient's standpoint, the most acceptable diet was a liberal carbohydrate allowance with about 100 grams of fat per day. It was their impression that the higher carbohydrate diet further promoted a state of physical well-being and, therefore, more cooperation on the part of the patient. The blood cholesterol with their diets did not vary.

Van Eck [24], in 1959, was more strict in his study, and his diet consisted of 20 grams of fat per day, 80 grams of protein per day, and the balance of the caloric equilibrium was maintained with carbohydrates.

He was particularly interested in what effects could be obtained on retinopathy and serum lipids by giving a low-fat diet. All subjects had diabetes with retinopathy. Some were taking insulin; in others the disease was controlled by diet alone. All had been properly controlled, with infrequent slight glycosuria and no ketonuria for prolonged periods. With the strict low-fat diet, it meant, in most cases, the replacement of 80 to 110 grams of fat by carbohydrates. All patients were conscientiously observed to make sure that they followed the diet or to detect those who did not. Three admitted not having followed the diet as prescribed: one patient was seen to consume butter, eggs and milk freely, and he was dropped from the series; another admitted having neglected her diet; in the third case, a private physician obtained this information although the patient had previously denied it. Although it was realized that the diet might interfere with the normal intake and absorption of fat-soluable vitamins, no dietary supplements of any kind were given.

In reporting his results, complete blood counts, hematocrit, urine, renal function (serum non-protein nitrogen, phenolsulphonphthalein excretion), serum electrolytes, serum proteins and liver function tests

were performed at intervals during the study. Color photographs of the fundi were made of each patient before dietary treatment began and at three-month intervals. Total fatty acids were determined, and free and total cholesterol were also noted.

Van Eck's results were in close agreement with the incidental findings of Kempner's rice diet-hypertension studies, later corroborated by Watkin and colleagues. A striking increase in the glucose tolerance of these patients was observed, which made it possible to increase the carbohydrates to at least 135 grams per day without increase of the insulin requirement. Patients who were controlled by diet alone did not require insulin after the transition to the low fat diet, despite the increased carbohydrate intake. Of the eleven patients who followed the diet, lowering of the serum lipids was obtained in ten. This effect was maintained during the entire observation period of one to two years. Of the ten patients who presented exudates in their fundi, marked decreases or disappearance was noticed in five; discrete but convincing reduction in three others. In two patients, whose exudates were minimal to start with, the changes were less convincing. In no patient who followed the low-fat diet did new large exudates

develop during the observation period. Although Van Eck's paper did not mention changes in visual acuity, he did state at the Conference of Diabetic Retinopathy in Haddonfield, New Jersey, that he had several patients who were not able to read headlines in newspapers, and who later on read the newspaper itself or watched television. He had one patient in that category who later on could thread a needle. There was no notation made of a change of refraction in any of the patients observed. It was his opinion that it seems justifiable to consider a strict low-fat diet in diabetic patients who present elevated serum lipids and distinct retinopathy.

In discussing the use of fats in the diabetic diet, Pollack [26], in 1960, stated that the substitution of the polyunsaturated fatty acids in the diet for the more saturated fats and oils, offered the possibility of controlling the levels of circulating blood cholesterol without having to resort to supplementary medication or unusual dietary practices. He advocated the use of the vegetable oils, nuts, chicken, and fish, and maintained that much better control of the glycosuria and glycemia could be obtained with diets relatively high in fat content than with diets whose carbohydrate content is high. He advocated the

use of comparatively fat-rich diet for the diabetic patient, providing it includes adequate quantities of the vegetable oils, such as cottonseed or corn oils, which have a high content of poly-unsaturated fatty acids.

SUMMARY

With the apparent increase of blindness due to diabetes mellitus, the subject of diabetic retinopathy is of major importance today. The increased life span of the diabetic, made possible by the control of the defect of carbohydrate metabolism, has brought about a steady increase in the incidence of vascular complications in these patients. This is shown by the fact that the death rate of diabetics from cardiovascular and renal disease is twice that of the general population, and by the increase in the rate of new blindness in adults due to diabetic retinopathy. Most of the cardiovascular changes are those of aging and senility, and, except for their premature onset in the diabetic, are not different from lesions seen in the general public. The peculiar capillary degenerations of the retina and of the glomerulus, however, are highly characteristic of diabetes and appear to be due to a complex disturbance in lipoprotein and mucopolysaccharide metabolism.

The duration of diabetes is important in the incidence of vascular degeneration, but there is now adequate clinical evidence that early case finding and strict control will delay the onset of vascular

complications and minimize their severity.

In general, retinopathy develops slowly in the course of several years. Some dilatation of the retinal veins, a few microaneurysms of punctate retinal hemorrhages are the first signs of retinopathy. Later, the number of microaneurysms increases, the deep retinal hemorrhages enlarge, and sharply outlined retinal exudates appear, enlarge, and tend to be confluent. In most cases, the development of retinopathy stops here or before the exudates enlarge. In a smaller number of patients retinopathy proceeds to a proliferative stage, with successive formation of new-formed vessels, pre-retinal and vitreous hemorrhages, degeneration of the hyaloid membrane, vitreous detachment, fibrous tissue formation, retinal detachment and sometimes rubeosis iridis and hemorrhagic glaucoma.

In older diabetics, the retinopathy mostly behaves as previously mentioned, but it is characteristic for this group, however, that sharply outlined retinal exudates often appear early in retinopathy.

In juvenile and middle-aged diabetics, the course is often the same, but in some juveniles retinopathy sometimes either proceeds from the stage with venous dilatation directly to a proliferative stage, or

develops very slowly. When retinopathy develops slowly, it is predominantly characterized by severe arteriosclerotic changes.

The theories of the development of the micro-aneurysms are (1) an attempt to neovascularization, (2) a weakening of the vessel wall with a resulting out-pouching, or (3) an increase in the pressure of the vessels of the retina.

In addition to the defect in glucose metabolism, the diabetic is subject to various degenerative diseases of the kidneys, blood vessels, and retina. All vessels appear to be susceptable to premature aging and degeneration as is evidenced by the increased death rate from cardiovascular disease among diabetics.

CONCLUSIONS

Although little has been published to date on the effect of low-fat diets and their effect on diabetic retinopathy, one cannot overlook the apparent improvement in the retinopathy, and the decreased serum lipids after following such a diet. It is also note-worthy that by reducing the amount of fat ingested one can increase the amount of carbohydrate in the diet without increasing the amount of insulin required. To the contrary, it is frequently possible to reduce the amount of insulin needed, and in a few cases, eliminate insulin altogether. The mechanism of this is not understood, but it is believed to be due to diminished fat deposition in the liver and improved glucose oxidation. Improvement in the retinopathy has been obtained by diets consisting of 20 grams of fat up to 100 grams of fat, the greatest improvement seen at the lower figure. Since one must consider the established eating habits of man and his unwillingness to cooperate in any diet, it would appear that great improvement could be obtained by utilizing a diet consisting of 50 grams of fat, 80 to 100 grams of protein and the balance of the caloric requirement in the form of carbohydrates. This would

especially hold true if the patient presents himself with elevated serum lipids and distinct retinopathy.

The question of types of fats to be used or avoided have only been mentioned briefly in this paper as it is highly controversial, and much more work is needed before any definite statement can be made. It may be that once this question has been answered, the diabetic diet can be altered accordingly.

The field of diabetic retinopathy and its relationship to low-fat diets is still in its infancy and much more study is needed, especially as to (1) its prevention or development of retinopathy, and (2) what effect it has in the improvement in visual acuity of the patient with diabetic retinopathy.

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