

Prevention of Vascular Disease in the Diabetic

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In view of the present state of our knowledge, the title of this paper is ambitious. I may begin with the unequivocal statement that neither my associates nor I have any magic formula which predictably will prevent vascular disease in the diabetic. However, I should like to consider with you some of the observations of others, and some observations of our own which bear upon this subject.

In our own thinking, diabetes mellitus is divided into two diseases: the form that occurs typically in middle age, which, from a functional standpoint, we consider as presenting essentially a problem in hypoinsulinism with associated metabolic abnormalities; and juvenile diabetes, which represents a combined problem of hyperpituitarism and hypoinsulinism.

In both groups one deals with two vascular problems. One, atherosclerosis, is identical with that which afflicts the average nondiabetic member of the American population, if he lives sufficiently long. Statistically, the onset of this vascular disease in the diabetic is earlier and the progress more rapid. The other is a rather specific disease, in which characteristic changes occur in the retinal and glomerular capillaries. This latter problem is most distressing in the juvenile diabetic, because of its occurrence at an early age.

ATHEROSCLEROSIS IN ASSOCIATION WITH DIABETES

With the possible exception of cancer, no field of clinical investigation is receiving more attention than that of degenerative vascular disease. Since atherosclerosis in the diabetic appears earlier and progresses more rapidly than in the nondiabetic, and since we have some knowledge of the endocrine and metabolic abnormalities which occur in diabetes and which, at least in part, are presumably related to the pathogenesis of the vascular disease, it seems logical to conclude that the answer to the over-all problem of atherosclerosis might very well

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be found more readily in the diabetic than in the non-diabetic population.

This is not the occasion for discussing all the divergent concepts regarding pathogenesis and management of atherosclerosis. Essentially there are three major points of view:

1. that dietary cholesterol is the most important factor in the production of atherosclerosis;
2. that dietary cholesterol is relatively unimportant, but that some disturbance in cholesterol metabolism is nonetheless the major abnormality in individuals who develop atherosclerosis;
3. that disorders of lipid metabolism are secondary, and that disorders of protein and/or other nonlipid metabolism are primary. There is disagreement as to the importance of nutritional factors among those who adhere to this concept.

It may be stated categorically that no individual or group knows the answer to the pathogenesis, the laboratory diagnosis, or the precise clinical management of atherosclerosis. If this is correct, does one have any reason to believe that there are available empirical procedures which, if adhered to, will lessen the incidence and/or the rate of progression of atherosclerosis in the diabetic subject? I believe the answer is a definite yes.

DIABETIC RETINOPATHY AND NEPHROPATHY

Kimmelsteil and Wilson¹ in 1936 described the intercapillary lesions in glomeruli of diabetic patients. Seven years later Ballantyne and Loewenstein^{2, 3} described the retinal capillary aneurysms in similar individuals. Since these reports appeared there has been increasing acceptance of the essential identity of the pathology in both these organs.^{4, 5} Aneurysmal dilation of capillaries has been seen in affected glomeruli, and no difference has been shown histochemically in the staining characteristics of the nodules in the kidneys and the hyalinized capillary aneurysms in the retinas.⁶ This form of vascular disease may occur in the middle-aged diabetic, but it occurs most characteristically in the juvenile diabetic. Its recognition and the emphasis which it has received in the last decade are largely due to the survival of juvenile diabetics, who without insulin and antibiotics would not have lived sufficiently long to develop any form of vascular disease.

RELATION OF CONTROL OF DIABETES TO THE DEVELOPMENT OF VASCULAR DISEASE

It is generally recognized that two major schools of thought exist in regard to management of the diabetic patient. The first is committed to the proposition that a goal of diabetic management is the maintenance at all times of a blood sugar within a normal range. The second school believes that the psychologic wear and tear attendant upon the maintenance of a physiologic norm in regard to blood sugar is not justified by the results achieved, and pays homage to something which is loosely called a "free diet."

One might fervently wish that the latter concept were correct, but it is only necessary to examine the literature objectively to be certain that it is not. In support of this statement are the numerous publications based upon the extensive experience of members of the Joslin Clinic.⁷⁻⁹ Their experience and concepts are supported by many other careful observers. The situation is well summarized by Engleson¹⁰ in a recent monograph. Specifically, a recent report by Dunlop¹¹ recounts "the straying from the straight and narrow path" of this investigator for a period of years, followed by a return to the principles of physiologic management. From his statistics and others like them, it is obvious that the incidence of complications is inversely proportional to the adequacy of control. The complications which are included are retinopathy, nephropathy, cardiovascular complications, tuberculosis and neuropathy.

If one accepts, then, the statement that good diabetic control results in a much lower incidence of vascular complications than "free" diabetic management, in terms both of time of onset and of rate of progression, a number of questions arise, among which are the following:

1. Can vascular disease be completely prevented in the diabetic by a program of optimal diabetic control? Is optimal control possible in all diabetics?
2. What are the quantitative and qualitative factors which enter into optimal control?
3. If a "free diet" is synonymous with relatively early onset and rapid progression of vascular disease, what are the known or probable factors which bring about such a relationship?

On the basis of my experience and that recorded by others, one may say that increased incidence of vascular disease in the relatively benign diabetes of middle age can be prevented by optimal diabetic control, in terms of our present conception of the term. Insofar as juvenile diabetes is concerned, Joslin's "Quarter-Century Victory Medal" patients indicate that the onset of vascular dis-

ease in such patients may be postponed for a long period. Dr. Joslin¹² has written us that as of mid-September 1954 the patients who have received the medal numbered fifty-four. In our experience, however, there are a certain number of juvenile diabetics whose disease is so severe as to make excellent or even good control a clinical impossibility. Representative of this is the blood sugar chart of a patient followed on the metabolic ward for a prolonged period of time (figure 1). This patient, even under conditions of chemically constant dietary intake, required insulin every six hours or oftener in order to maintain a blood sugar level within the normal range.

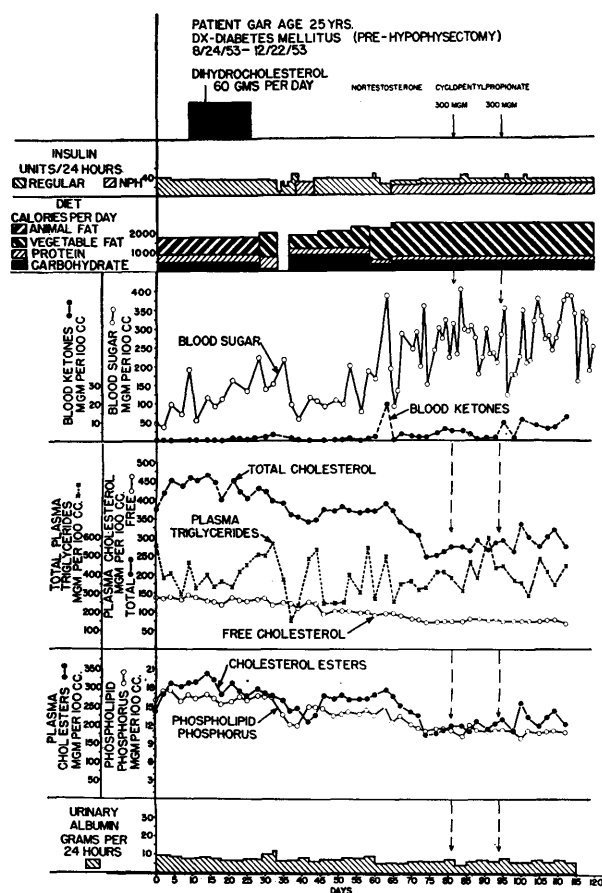


FIG. 1. Only the administration of "regular" insulin every six hours resulted in maintenance of normal blood sugar levels in this severe diabetic.

One must approach the answer to the second question most cautiously. Obviously the maintenance of a normal blood sugar is not the only essential criterion, since it is theoretically and clinically possible to maintain such control in many diabetics on diets grossly deficient in

protein, electrolytes, and/or vitamins. In the light of our present knowledge (or ignorance), perhaps the following definition will do: a diet containing protein adequate in amount and in biologic quality to permit of normal growth and repair; sufficient carbohydrate and fat to produce an optimal weight-height relationship, and thereafter to maintain caloric equilibrium; a qualitative and quantitative balance between insulin and carbohydrate to permit of maintenance of a true blood sugar between 60 and 160 mg. per 100 cc. throughout the twenty-four hours; sufficient carbohydrate combustion to prevent hyperketonemia; and an intake of essential vitamins, unsaturated fatty acids, and minerals sufficient to provide for growth and repair of all tissues.

Because of the almost hysterical emphasis upon the dangers of dietary fat and cholesterol in recent medical and lay literature, there has been a tendency to curtail dietary fat intake in diabetics, with a consequent increase in concentrated carbohydrates. Such a program makes for maximal fluctuations in blood sugar, particularly if a single-dose insulin regimen is utilized. A report by Johnson and Rynearson¹³ of the Mayo Clinic makes untenable the concept of a mandatory relationship between atherosclerosis and high fat-high cholesterol intake. The patient referred to in this report had for twenty-nine years adhered rigidly to a diet containing 254 gm. of fat, 50 gm. of protein, and 46 gm. of carbohydrate. His blood pressure and ophthalmoscopic and neurologic findings were normal. There was no clinical evidence of peripheral vascular disease. The blood lipids were normal, and the urine examination revealed no abnormality.

The answers to the third question must for the present remain purely conjectural. Our own working hypothesis is as follows:

1. The most important abnormality which causes diabetics to be more susceptible to vascular disease than nondiabetics is broad fluctuation in blood sugar levels.
2. Such fluctuations over a period of months and years, because of disturbed intracellular and extracellular osmotic relationships, bring about functional abnormalities and finally structural cellular change. Prominent among such changes are those in the vascular intima.
3. Damage to endothelium having occurred, abnormal deposition of lipids and other material occurs in the damaged cells. Any factors, endogenous or exogenous, which tend to produce an elevation of plasma cholesterol will probably aid this process.

SPECIFIC DIETARY FACTORS

For present purposes, I shall dismiss the important aspect of vitamins in relation to diabetes and diabetic

vascular disease with the statement that the problem is complex. In addition to using diets which are well balanced, our own approach is, in adult patients to provide vitamin supplementation insofar as the B complex group of vitamins is concerned, and in growing children to provide in addition supplementation with the fat-soluble vitamins.

Protein. Dietary protein has frequently received rather offhand treatment in the calculation of diabetic diets. A magical figure of "one gram of protein per kilogram of body weight" seems to be firmly implanted in the minds of most physicians. Assuming that the protein is of good biologic quality, this is a perfectly adequate figure for an adult diabetic whose disease is well controlled, that is, who is not wasting sugar, and whose diet is adequate in other respects. It may not be adequate for a poorly controlled adult diabetic, and most emphatically is not adequate for any diabetic who is still in a period of active growth.

Carbohydrate. If a major part of optimal diabetic management is the maintenance of a blood sugar within a normal range, and if one attempts to maintain most of his patients on one, or at the most two, doses of insulin daily, it follows that concentrated carbohydrate must be used sparingly or not at all. In other words, essentially all of the dietary carbohydrate must be derived from sources containing less than 15 per cent of carbohydrate. This in turn means a diet which is potentially unpleasantly bulky. Consequently, the total dietary carbohydrate will rarely exceed 160 gm. per day, and a considerable portion of the caloric requirement must be obtained from fat.

Fat. The metabolism of lipids is less well understood than that of either protein or carbohydrate. Because of the finding of lipid deposits in vascular lesions, dietary fat has been viewed with alarm. The case report cited by Johnson and Rynearson¹³ is, therefore, reassuring.

Until recently the source of fat was considered to be of little importance insofar as relationship to blood lipid content was concerned. Observations from our own laboratory during the past few years, however, indicate that the source of dietary fat is of major importance in this regard.¹⁴⁻¹⁹ Specifically, the administration of large amounts of vegetable fat, with complete exclusion of animal fats in the diet, has resulted in a striking decrease in the level of cholesterol and phospholipids in the plasma in all individuals studied, regardless of whether their initial plasma lipids were high, normal, or low. In some juvenile diabetics with hypercholesterolemia in association with advanced vascular disease, including retinal disease, the decrease in plasma lipids

associated with such dietary intake has been associated with major subjective and objective improvement in the retinal condition. This statement is made cautiously, inasmuch as at least a portion of the clinical improvement may be attributable to better diabetic control in some of these patients. Representative of the changes in serum lipids which may be achieved with a high vegetable lipid regimen, in figure 2 are shown the changes in plasma lipids in one of our recently studied diabetic patients with marked hypercholesterolemia.

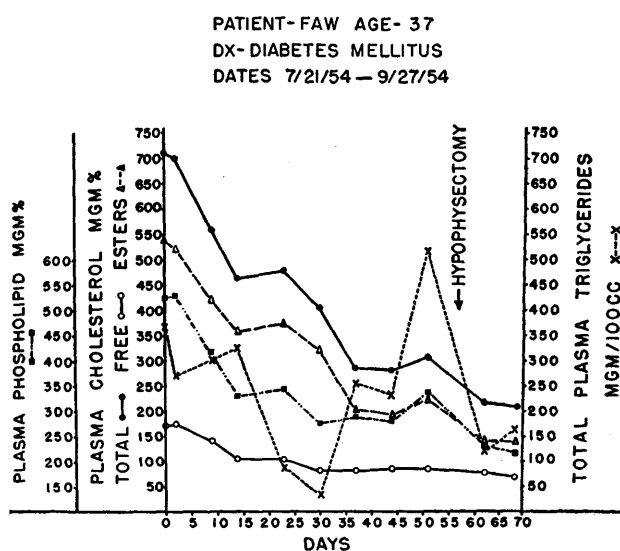


FIG. 2. A mixed diet high in vegetable fat, corrected hypercholesterolemia in this patient within a period of approximately one month.

The mechanism of the above effects is by no means clear. Conceivably the effect could be negative, that is, merely attributable to absence of cholesterol and related materials in the vegetable fat. Equally conceivably it could be positive, that is, attributable to some positive factor in the vegetable lipid which produced the changes in plasma cholesterol and phospholipid. In our hands to date, no fat derivative has produced changes of the constancy or of the magnitude noted with the high vegetable lipid diet. The same statement so far seems to apply to diets from which *all* lipids have been excluded.

In our clinic, diabetics are maintained on diets which contain from 100 to 150 gm. of protein (unless renal insufficiency is present), which are nearly or completely free of concentrated carbohydrate, and which consequently are high in fat. Except in patients with demonstrable vascular disease and/or hypercholesterolemia, the fat is of mixed vegetable and animal origin.

THE RELATIONSHIP OF ENDOCRINE FACTORS TO VASCULAR DISEASE IN THE DIABETIC

Directly or indirectly, the pituitary and the adrenal cortex appear to be implicated in diabetic retinopathy and nephropathy. Lukens and Dohan²⁰ reported renal lesions in a dog made diabetic by injections of anterior pituitary material. These lesions were similar to those described by Kimmelsteil and Wilson. Becker²¹ noted no characteristic retinal or renal lesions in alloxan-diabetic rabbits, but was able to produce both when cortisone was administered. Corticotropin produced similar lesions. Rich, Berthrong and Bennett²² reported glomerular nodules in nondiabetic rabbits receiving cortisone for three weeks.

Increased production of corticoids during pregnancy is only one small part of the increased endocrine activity which occurs, but whatever the reason, the aggravation of existing diabetic vascular disease during pregnancy is well documented, as well as its regression following the termination of pregnancy.^{21, 23, 24} Retinal capillary aneurysms have been observed in nondiabetic and diabetic individuals during the administration of corticotropin.²⁵

Conversely, improvement in diabetic retinopathy has been reported following bilateral adrenalectomy and following the superimposition of Sheehan's syndrome upon pre-existing diabetes.²⁶⁻²⁸

In our limited experience, unequivocal improvement in retinopathy and probable improvement in nephropathy appear to follow hypophysectomy in diabetic patients with advanced vascular disease.²⁹ Hypophysectomy invariably transforms a severe diabetes into a mild one.

Certainly neither adrenalectomy, hypophysectomy, nor any other form of surgery represents the final answer, even if it should prove to be a reasonably efficient answer, to the prevention of diabetic vascular disease.

EXERCISE IN RELATION TO DIABETIC CONTROL AND VASCULAR DISEASE

Assuming good diabetic management both at home and in camp, the insulin requirement of the average juvenile diabetic who goes to camp decreases by more than 40 per cent.³⁰ Factors other than exercise may play some part in this rather remarkable change, but it seems reasonable to assume that increased physical activity is the major factor which is responsible.

One of my friends, presently aged forty-seven, is a diabetic of twenty-nine years' duration. Having observed his habits in regard to the intake of food and drink over a period of some years, I would rate his diabetic control

as poor by any criteria. If one looked no further than this portion of his history, he could be pointed to triumphantly by proponents of the "free diet" philosophy, since prior to six months ago his vascular status was such as to qualify him for one of Dr. Joslin's victory medals. His program, year in and year out, includes strenuous tennis. One case proves nothing, but we suspect strongly that but for tennis this man's vascular status would be very different. If this assumption be correct, daily strenuous physical activity should be as much a part of the juvenile diabetic regimen as constant diet and insulin. Whether such a program can consistently counteract the deleterious effects of a "free diet," one may only guess at the present time. This question impresses us as well worth careful evaluation.

SUMMARY AND CONCLUSIONS

Vascular disease in the diabetic appears to be the resultant of exogenous and endogenous factors. For present purposes, it is probably permissible to oversimplify the problem and to arrive at a few conclusions.

1. The incidence of atherosclerosis is higher and the age of onset earlier in the diabetic than in the non-diabetic population.

2. Kimmelsteil-Wilson nephropathy and associated retinopathy appear to be essentially identical processes from a pathologic standpoint, and to be peculiar to diabetics.

3. Assuming a diet adequate in other respects, the maintenance of a blood sugar within a physiologic range will significantly decrease the incidence and severity of vascular disease in the diabetic. This is equivalent to stating that a "free diet" is unphysiologic and predisposes to vascular complications.

4. Because of the production, directly or indirectly, by the pituitary of excessive amounts of "anti-insulin factors," optimal control is clinically impossible in some diabetics. In patients in this category in whom vascular disease is progressing rapidly, hypophysectomy (and possibly adrenalectomy) may decelerate or halt the progress of the vascular disease. Conceivably, strenuous exercise begun early in the course of the diabetes, and taken regularly may have some prophylactic value.

5. The evidence is lacking that a high fat diet in a nonobese patient in itself predisposes to vascular disease. A case has been cited in which a diabetic was maintained on an ultra-high fat diet for twenty-nine years with no demonstrable vascular disease. In diabetics with vascular disease in association with hypercholesterolemia, the administration of a diet high in fat, exclusively of vegetable origin, will predictably result

in a fall of cholesterol and other lipids to a normal range. Under these circumstances, such a diet may have therapeutic value.

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SUMMARIO E CONCLUSIONES IN INTERLINGUA

Prevention de Morbo Vascolar in Diabeticos

Morbo vascolar in diabeticos pare esser le resultante de factores exogene e endogene. In le presente contexto il es probabilemente permittite simplificar le problema e formular le sequente conclusiones:

1. Inter diabeticos, comparate con le population nondiabetic, le frequentia de atherosclerosis es plus alte e le declaration del morbo occurre a etates plus juvene.

2. Nephropathia de Kimmelsteil-Wilson e le retinopathia associate con illo pare esser processos identic in essentia ab le puncto de vista pathologic. Illos pare occurrer solmente in casos de diabete.

3. Providite que le dieta es adequate in altere respectos, le mantententia del sucro sanguinee intra limites physiologic va servir a significativamente reducer le frequentia e severitate de morbo vascolar in diabeticos. Iste assertion significa que un "dieta libere" es aphysiologic e predispone a complicationes vascolar.

4. In certe patientes le glandula pituitari produce, directe- o indirectemente, quantitates excessive de "fac-

tores anti-insulinic." In tal casos le optime regulation del morbo es clinicamente impossibile. Si patientes de iste typo exhibi un rapide progresso del morbo vascolar, le execution de hypophysectomia (e forsan de adrenalectomia) pote servir a decelerar le processo. Il es possibile que strenue exercitios, initiate promptemente in le curso del diabete e continuate regularmente, ha alicun valor prophylactic.

5. Il non existe datos a supportar le conception que, in patientes nonobese, dietas ric in grassia suffice a establir un predisposition a morbo vascolar. Nos cita un caso in que un diabetico se manteneva super un dieta ultraric in grassia durante un periodo de 29 annos sin ulle demonstrabile signo de morbo vascolar. In diabeticos con morbo vascolar in association con hypercholesterolemia, le administration de un dieta ric in grassia de origine exclusivamente vegetal va resultar predicibilemente in un reduction del contento de cholesterol e de altere lipidos a valores normal. Sub tal conditiones, un dieta del typo mentionate pote esser de valor therapeutic.