Vascular Disease in Juvenile Diabetic Patients of Long Duration

A Preliminary Report

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The introduction of insulin to medical practice was followed by a remarkable improvement in the physical state of diabetic patients. However, it is obvious that with increased expectancy of life, they are prone to a greater incidence of vascular disorders compared to other members of the community. Furthermore, these changes differ from those seen in nondiabetics. It is disturbing, after more than three decades of insulin therapy, to realize that the reason for this is still unknown.

For many years the term "degenerative" has been applied to arteriosclerotic change, implying that blood vessels wear out in much the same way as a piece of hose. It is remarkable that little attention has been paid in recent years to studies of the arterial wall as a living tissue subject to the influence of humoral factors known to affect the metabolism of other bodily tissues.

Most of the attempts to explain the occurrence of premature vascular changes in diabetic patients have been related to clinical management and are concerned with observations on hyperglycemia and glycosuria. It must be obvious that any assessment of the successful management or "control" of patients of long duration can only be related to intermittent observations of the level of blood sugar or glycosuria. It is questionable whether such evidence can ever be sufficiently accurate to support the dogmatic conclusions which have been made.

No simple clinical test has yet been devised to provide an estimate of the daily control of protein or fat metabolism. Yet this information could be of equal importance in any long-term study of vascular disease. The advent of the sulfonylurea drugs and our lack of precise knowledge of their mode of action only serve to emphasize the difficulties of defining control of diabetic patients.

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It cannot be denied that failure to establish normoglycemia could be related to the lack of a perfect therapeutic preparation of insulin capable of exerting a true homeostatic effect on the disturbed metabolism of human patients. If this had been available vascular disease might have ceased to be a problem. However, it must not be forgotten that vascular changes occur in middle-aged diabetics whose diabetes seems capable of adequate control by dietary restriction alone.

In recent years, evidence has been presented which suggests that the vascular changes seen in patients inadequately controlled by conventional standards do not differ significantly from those found in patients considered to have been well controlled.[1,2] This has prompted an investigation into a group of juvenile diabetic patients of long duration in an attempt to determine whether any other factors might be responsible for premature vascular change.

MATERIAL AND METHODS

Forty-seven patients, all of whom developed diabetes mellitus before the age of twenty-one years and who have had diabetes for more than twenty years, have been studied for evidences of vascular change and an attempt has been made to relate its occurrence to control. Each was subjected to a complete physical examination. In addition to routine clinical examination of the cardiovascular system, screening of the heart was undertaken in any instance where doubt existed as to cardiac function. Electrocardiograms were taken from every patient and were considered independently by a cardiologist, Dr. J. M. Gardiner. The state of the peripheral circulation was assessed by examination of the peripheral pulses and by oscillometric readings on the leg vessels in every patient. Retinoscopy was performed on all patients by Mr. James Foster, a senior ophthalmologist. Urinalysis for the presence of albumin and for microscopic abnormalities was undertaken in all patients and renal function tests were performed in all doubtful cases. Biochemical estimations of serum lipids were made

in sixteen patients and electrophoretic studies of serum lipids were performed on the plasma from most patients in the series. The presence or absence of insulin inhibitors in the serum of twenty-two patients was determined by Dr. J. Bornstein.[3] The assistance of our colleagues in providing independent opinions has proved of value in obtaining an unbiased assessment of the present physical state of the patients in this group.

Almost all of these patients have been under the observation of one of us (E.D.) for many years and with few exceptions, records extending for more than twenty and in some instances more than thirty years were available for analysis. Each patient was assessed independently. A careful history was compiled from the patients' own experiences, from the evidence of parents and from a survey of medical records. Particular attention was paid to insulin requirements during the diabetic life, to episodes of ketosis or severe hypoglycemia, and to any other significant events during adolescence or early adult life. The family history of each patient was carefully investigated and the obstetrical history of each married female was recorded.

From the data obtained, an attempt was made to estimate the present state of the vascular system of each patient and to relate it to conventional criteria of control, to the diabetic age, to the daily insulin requirements and to the presence or absence of insulin inhibitory factors in the plasma.

From the commencement of this analysis two difficulties were apparent: The first was concerned with criteria of control and the means of expressing this; the second with criteria of vascular change. The expression of both of these involved clinical impressions and the use of abstractions such as "good," "fair," and "poor" can only be regarded as sincere approximations. Assessment of control of hyperglycemia and glycosuria over a period of twenty or thirty years presented considerable difficulty and the data on each patient were too massive to reduce to simple tabular form. The same difficulty was encountered in classifying the vascular changes. Apart from grouping retinal findings, which can be done with some certainty, attempts to describe the entire vascular state of any individual patient again involved the use of the words "good," "fair" and "poor."

With these reservations, it is desirable to define these terms as applied to the patients under consideration. "Good control" has been applied to patients who, apart from episodes of incidental ketosis due to infection or other circumstances outside the individual's control, were known to be careful and regular in habit, to cooperate closely in treatment and to be regular in attendance for supervision. In addition, records of urinalysis and of blood sugar analysis indicated that over the years these patients had been noted as aglycosuric and normoglycemic. "Fair control" was applied to those who, because of difficulty in maintaining stability of diabetes or through carelessness or temperament, had experienced unnecessary episodes of ketosis, and whose urine tests and blood sugar estimations indicated the existence of glycosuria and hyperglycemia at intervals throughout the years of observation. "Poor control" has been applied to those patients who, apart from continuing a daily dose of insulin, paid scant regard to dietary care or to urine examinations, who have been irregular in their medical supervision and who have frequently been hyperglycemic and glycosuric.

In assessment of vascular change the term "good" has been applied to those patients who have no evidence of cardiac disease, a normal electrocardiogram, normal blood pressure, normal oscillometric readings, no evidence of renal disease and whose optic fundi revealed no abnormality or at most an isolated microaneurysm. The term "fair" has been applied to those whose optic fundi showed minor changes on retinoscopy or a minor degree of hypertension or a slight intermittent albuminuria. More than one such abnormality designated the patient as "poor," as did severe retinopathy, marked hypertension or definite evidence of renal impairment.

RESULTS

The relationship between diabetic control and clinical evidences of vascular change, of retinopathy and of nephropathy in the forty-seven patients investigated is summarized in table 1. The relationship between the duration of diabetes and of the daily insulin dosage to the vascular state of these patients is shown in tables 2 and 3. From the data presented there seems to be no reason to assume that any direct connection exists between vascular disease and control, duration of diabetes or the daily insulin dosage.

The relationship between the presence of detectable insulin inhibitory substances in the plasma and vascular change in a random sample of the patients examined is shown in table 4. Table 5 shows a comparison between the findings of insulin inhibitory substances and the average daily insulin dosage of these patients. It is apparent that insulin inhibition as demonstrated in vitro by estimation of glucose uptake by the isolated rat diaphragm bears no relation to the insulin requirements of these patients.

There is, however, one significant difference between the patients with clinical evidence of vascular damage

TABLE 1

Relation between diabetic control and vascular state, retinopathy and nephropathy

Patients	Control	Cardiovascular assessment		Retinal change				Albuminuria	
		Normal	Abnormal	Nil	*	†	‡	Nil	Present
17	Good	8	9	10	4	2	1	13	4
23	Fair	10	13	14	6	2	1	19	4
7	Poor	2	5	4	0	1	2	3	4

* Isolated microaneurysm.
† Retinal exudate or hemorrhage.
‡ Extensive retinitis, detachment or retinitis proliferans.

TABLE 2

Relation of vascular state to duration of diabetes mellitus

Patients	Diabetes (years)	Vascular state		
		Good	Fair	Poor
13	30	8	5	0
34	20-30	12	17	5

TABLE 3

Relation of vascular state to average daily insulin dose

Patients	Insulin dose per day	Vascular state		
		Good	Fair	Poor
16	>60	9	6	1
23	40-60	9	12	2
8	<40	2	4	2

TABLE 4

Relation of vascular state to presence of insulin inhibitors in plasma

Patients	Inhibitors in plasma	Vascular state		
		Good	Fair	Poor
8	Nil	8	0	0
14	Present	2	7	5

TABLE 5

Relation of insulin inhibitors in plasma to average daily dosage of insulin

Patients	Inhibitors in plasma	Average insulin dose U./day		
		>60	40-60	<40
8	Nil	3	4	1
14	Present	6	5	3

and those who showed minimal or no vascular change. In the former group insulin inhibitory substances were present in the plasma of twelve patients with vascular change and also in two with no clinical evidence thereof. In the remaining eight patients with no evidence of vascular damage insulin inhibitory substances were not demonstrated in the plasma.

Electrophoretic and lipid studies were made on the serum from over thirty patients in the series, all of whom were suitably prepared by abstention from fat before the tests were undertaken. The results of the lipid analyses showed no significant difference between the patients with no evidence of vascular change and those with early evidence thereof. All the patients with obvious vascular damage showed the usual pattern of increase in β lipoprotein, cholesterol, fatty acids and total lipids. No significant difference was found in the electrophoretic patterns of the patients with good vascular state and those classified as fair.

Two incidental observations were made during the course of this study. The first was the finding of an unusually high incidence of a family history of diabetes. Thirty-two of the forty-seven patients gave a history of diabetes in some member of an earlier generation, an incidence of approximately 69 per cent. The second was concerned with the obstetrical histories of the women in this series. In tables 6 and 7 the numbers of stillborn and living children are related to the vascular state and to an assessment of the diabetic control of the mothers. With very few exceptions all these patients were under the care of one obstetrical service throughout their pregnancies.

DISCUSSION

In selecting a group of juvenile patients for investigation it was felt that an assessment of patients in earlier age groups when vascular disease is seldom seen in non-diabetic subjects would disclose evidence of vascular change more clearly than in later periods of life.

A vast literature has been developed to support the doctrine that strict control prevents or delays the onset of vascular change and this view is firmly held in

TABLE 6

Relation of vascular state to outcome of pregnancy

Patients	Vascular state	Pregnancy	
		Living	Stillborn
7	Good	9	5
11	Fair	3	10
1	Poor	1	0

TABLE 7

Relation of control to outcome of pregnancy

Patients	Control	Pregnancy	
		Living	Stillborn
7	Good	5	6
10	Fair	9	8
2	Poor	2	0

many clinics throughout the world. It is only recently that contrary views have been expressed as has been emphasized by Danowski:[4] "Perhaps the most pernicious effect of the view that strict regimentation prevents the vascular complications of juvenile or other long-term diabetes is the distraction of the interest of clinicians and investigators from studies of alternative views." Both Gerritzen[5] and Jackson[6] have postulated that vascular disease and diabetes may stem from a common cause. They suggest that the development of vascular disorders bears no relation to the clinical management of diabetes as practiced today. Larsson, Lichtenstein and Ploman[1] have stated that clinical control had no influence upon the development of vascular changes in a large group of juvenile diabetics under their care for many years. The studies of Aarseth[7] and of Lundbaek[8] are in agreement with this view. Danowski's survey of a group of children with diabetes of ten to twenty years' duration also supports the idea that other factors are concerned. The rare instances of spontaneous improvement or disappearance of vascular lesions, and the benefit which sometimes follows hypophysectomy, emphasize the need for a fresh approach to the problem.

The material presented in this study provides no support for the view that control has any influence on the presence or absence of vascular lesions. It is quite striking that several patients who have had diabetes for over thirty years with no signs whatever of vascular change must be classified as among the worst-behaved when judged by conventional standards. No significant relationship has been found between the duration of diabetes, the range of insulin dosage or the electrophoretic pattern of the plasma and the occurrence of vascular disease. While the greatest incidence of change has been observed in the retinal patterns of these patients this may merely reflect the fact that this is the one area of the body which readily presents blood vessels for direct inspection.

It is neither possible nor desirable to make dogmatic statements on a limited experience with a small number of patients. The number of cases classified as poorly controlled seems remarkably small. It could be that some, who treated their complaint with contempt, are now dead because of their own neglect or from lack of adequate supervision during the war years. The failure to establish a clear relationship to control and the difference which apparently exists in the presence of insulin inhibitory substances in our patients may be of significance. Observations are proceeding in a similar age group on patients who have arterial disease of nondiabetic origin. In addition a group of elderly diabetic and nondiabetic patients is being investigated in an attempt to determine the importance of this finding.

While the benefits of insulin therapy are universally recognized, its use in clinical practice cannot be regarded as similar to the exhibition of thyroid extract in cases of thyroid deficiency. If diabetes mellitus and its vascular complications are solely concerned with insulin deficiency, both should be capable of correction indefinitely by substitution therapy. It seems that there must be other unknown factors which are responsible for the vascular change.

A possible relationship between insulin inhibitory substances and vascular disease has been observed. While the importance of this observation is not clear, it has prompted further studies to determine whether these substances are related to the development of vascular changes or whether they are merely a consequence of an etiologic factor as yet unknown.

SUMMARY

Forty-seven diabetic patients, all of whom developed diabetes before the age of twenty years and who had histories of more than twenty years, have been examined in an attempt to ascertain the relationship between control of diabetes and the development of vascular sequelae.

No relationship has been established between the presence of vascular damage and the adequacy of control, the insulin dosage, or the duration of diabetes.

A relationship seems to exist between the occurrence of vascular disease and the presence of insulin inhibitory substances in the serum of these patients.

The significance of this finding is unknown. Studies are proceeding and the hope is expressed that they may

provide a new approach to the problem of diabetic vascular disease.

SUMMARIO IN INTERLINGUA

Morbo Vascular in Patientes con Diabete Juvenil de Longe Duration—Un Reporto Preliminari

Quaranta-septe patientes diabetic—omnes con diabete depost ante lor vintesime anno e omnes vivente con ille condition depost plus que vinti annos—esseva examinate con le objectivo de determinar le relation inter le "stabilisation" de diabete e le disveloppamento de sequellas vascular.

Nulle correlation esseva constatate inter le presentia de insultos vascular e le adequatia del "stabilisation," le dosage de insulina, o le duration del diabete.

Un correlation pare exister inter le occurrentia de morbo vascular e le presentia de substantias insulino-inhibitori in le sero.

Le signification de iste facto non es cognoscite. Studios concernite con iste problema es in progresso. Le spero es exprimite que iste studios va aperir nove avenues de attacco relative al problema de morbo vascular in diabete.

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When the ultraviolet absorption characteristics of pure methylarachidonate were compared with those of the isomerized C_{20} polyunsaturated fatty acid fractions from linoleate-fed and linolenate-fed animals, it was evident that there was an excess of from 3.5 to 6.0 per cent pentaene or hexaene acids in the fat from the linolenate-fed animals. These observations conform with the results of R. Reiser (*J. Nutrition 42*:325, 1950). Some presumptive evidence from columns in which incomplete separation of a portion of the C_{20} unsaturated fatty acids was obtained, indicated that most of the radioactivity in this fraction was present in the C_{20} pentaene acids. There was very little activity in the linoleate isolated directly from the main bromination mixture.

In summing up their observations, the authors state that if linolenate is converted to arachidonate it is not reduced to linoleate as the first step. Thus, if the Δ^{15} double bond is reduced, it evidently is not reduced until after the chain lengthening step has occurred. In view of the evidence from this study and that of others regarding the conversion of linolenate to more highly unsaturated fatty acids (Reiser, *loc cit.*; Houton et al., *J. Am. Chem. Soc. 76*:4970, 1954) it seems likely that linolenate "is converted to C_{20} and C_{22} pentaene and hexaene acids, possibly via a C_{20} tetraenoic acid isomeric with arachidonic acid." Thus the difference in the biological activity of linoleate and linolenate (Hume et al., *Biochem. J. 34*:879, 1940; Greenberg et al., *J. Nutrition 41*:473, 1950; Thomasson, International Conference on Biochemical Problems of Lipids, Brussels, p. 212, 1953) would appear to have a metabolic basis.

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