Peripheral Vascular Complications in Diabetes Mellitus

A Survey of 3,600 Cases

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The association of diabetes with pathologic changes in the arteries is indisputable.[1] Whereas many authors have implied or definitely stated that diabetes is in some way responsible, others[2] have challenged this relationship. The latter group has questioned whether it was necessary to maintain normal levels of blood sugar and aglycosuria if the patient's general condition was satisfactory. There also has been a tendency to attribute the development of complications either to the severity of the diabetes or to the duration of this disease. With these thoughts in mind, we are offering an analysis of a large group of diabetics. Three thousand and six hundred patients have been observed by the authors since 1921. The first series of 1,000 cases was gathered between 1921 and 1930; the second series of 1,000 cases, from 1931 to 1941; series III, 1,000 cases, from 1942 to 1951; and the present series IV, 600 cases, from 1952 to 1956 inclusive. They were consecutive cases seen in office and in the hospital. However, the vast majority were office cases. It may be added that the entire group has been observed since the advent of insulin; patients ranged from potential cases of diabetes to severe types and were of all ages.

In this survey, our interest was focused on the peripheral vascular system. Patients were questioned about symptoms of the circulation, and this was followed by examination of the extremities for evidence of impaired circulation.[3] Patients who showed possible involvement of the arteries were further examined by circulatory function tests, such as the oscillometer, capillary response to histamine, plantar ischemia and venous filling time. When necessary, skin surface temperature studies were performed, and, when indicated, soft tissue X rays of the vessels were made.

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The cases were placed in three categories: (a) impaired circulation, (b) threatened gangrene and (c) gangrene. Evidence of impaired circulation consisted of symptoms such as claudication, coldness and numbness, diminished or absent pedal pulses, and subnormal circulatory function tests. Threatened gangrene was based on the presence of cellulitis with discoloration of the toes or ulcerations. Almost invariably, these patients had evidence of impaired circulation. Gangrene was applied to that group showing focal or extensive necrosis.

An analysis of the 3,600 cases has been arranged in table 1. A glance at the number of patients with involvement of the peripheral vascular system showed a steady rise from 17.3 per cent in the first series to 21.6 per cent in the second series, 50.7 per cent in the third and 58.6 per cent in the current series. A breakdown of these figures according to the degree of involvement showed that those patients who were listed in Group A, namely those with impaired circulation, showed a progressive rise from 8.8 per cent in the first series to 47.3 per cent in the fourth series. The threatened gangrene group similarly showed a rise in the incidence, from 2.8 per cent to 7.6 per cent in the third, and then dropped to 4.5 per cent in the fourth series. The obvious gangrene cases have been more or less consistent, ranging from 5.7 per cent in the first group to 7.2 per cent in the second and to 6.8 per cent in the fourth series.

In an attempt to obtain more information about the factors in the relationship of diabetes to peripheral vascular disease, the 1,000 cases in series III and the 600 cases in series IV were further examined according to duration of the diabetes, severity, age and sex. The findings were arranged in tabular forms.

Duration of diabetes has been mentioned as a possible influence in the development of complications.[4] This is particularly true in juveniles who show a very high incidence of pathologic changes in the vessels, especially the smaller arteries, after fifteen to twenty years of the disease.[5] However, in adults the duration of the diabetes cannot be an important factor when considering the

TABLE 1

Showing the incidence of vascular complications in 3,600 cases of diabetes

Type of Case	Series I 1921-1930 (1,000 cases) Number	Per cent	Series II 1931-1941 (1,000 cases) Number	Per cent	Series III 1942-1951 (1,000 cases) Number	Per cent	Series IV 1952-1956 (600 cases) Number	Per cent
a. Impaired circulation	88	8.8	108	10.8	372	37.2	284	47.3
b. Threatened gangrene	28	2.8	36	3.6	76	7.6	27	4.5
c. Gangrene	57	5.7	72	7.2	59	5.9	41	6.8
Total	173	17.3	216	21.6	507	50.7	352	58.6

incidence of vascular complications. It is not unusual to see patients with thrombosis or gangrene in whom the diabetes has never been recognized until the patient comes under observation for vascular disease. One cannot help being impressed with the occurrence of 129 cases in which diabetes was discovered for the first time. In addition, there were 102 cases in which the vascular disturbance was recognized in diabetes existing for less than a year. The highest incidence of complications of the peripheral arterial system was in patients with diabetes of one to five years' duration, 314 cases. These, added to the first two categories, "Recently discovered" and "Less than one year," indicate that more than 60 per cent had developed changes of the arterial system within the first five years of the diabetes. The next highest, 165 cases, occurred in the six- to ten-year group.

TABLE 2

Duration of the diabetes when the vascular condition was recognized (1,600 cases*)

Type of Case	Recently discovered	Less than 1 year	1 to 5 years	6 to 10 years	11 to 15 years	16 to 20 years	21 years plus	Not recorded
Impaired circulation	112	75	248	128	44	37	12	
Threatened gangrene	7	15	34	20	12	7	7	1
Gangrene	10	12	32	17	14	9	6	
Total	129	102	314	165	70	53	25	1

*Series III and IV.

The question may be raised as to whether or not the diabetic condition may have existed for some time before being recognized clinically, a question which cannot be taken up here.

Severity of the diabetes: It is difficult to find a method of grading diabetes according to severity. However, the following types seem to be commonly accepted: *mild* cases, those who can be controlled by diet alone or in whom the daily insulin requirement is 20 units or less. If the dose of insulin was as much as 40 units, patients were classed as *moderate* and when the daily requirement was more than 40 units, the classification was *severe.*

In table 3, it will be noted that of the 1,600 cases, 859 patients showed various degrees of vascular involvement. The highest incidence of vascular disturbances was noted in 539 patients with mild diabetes, with 216 cases occurring in the moderate diabetics and 99 cases in those who were classed as severe. It may be mentioned that gangrene was more frequent in severe diabetes (26.1 per cent) as compared to 8.3 per cent in the mild form.

TABLE 3

Various grades of vascular disorders according to the severity of the diabetes (1,600 cases*)

Type of case	Mild	Moderate	Severe	Not recorded
Impaired circulation	444	146	65	2
Threatened gangrene	50	33	17	2
Gangrene	45	37	17	1
Total	539	216	99	5

*Series III and IV.

In view of these figures, one would expect a high incidence of vascular disorders in the severe diabetic. However, the incidence of vascular disturbances among mild cases would indicate that there may be some other influences which are responsible for these findings.

Age: In table 4, analysis of the age groups was made in relation to the various degrees of peripheral vascular disorders. It was noted that the highest number of 348 cases of vascular disorders occurred in the seventh decade. The next highest was 296 in the sixth decade group. The occurrence of peripheral vascular disorders in the younger age groups is quite low. Six cases were found among juvenile diabetics in the second and third decades. This concurs with White's observation of the infrequency of these complications in juvenile diabetics, less than ten years' duration.

Sex: A survey of the 1,600 cases showed that the male-

TABLE 4

Age at time vascular disorder was detected (1,600 cases*)

Type of Case	Number of Patients at Age (Years)							
	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80 plus
Impaired circulation	2	3	16	90	221	267	52	5
Threatened gangrene	—	1	2	11	41	38	10	—
Gangrene	—	—	—	10	34	43	12	1
Total	2	4	18	111	296	348	74	6

*Series III and IV.

female ratio in the entire group was 1:1.32. A further analysis of the various degrees of vascular disorders in relation to sex is recorded in table 5. It will be noted that there were 475 cases with vascular disorders among the females and 384 among the males. This preponderance, although slight, is evidenced in all three of the grades, namely impaired circulation, threatened gangrene and gangrene. The ratio of the degree of involvement in reference to male and female was 1:1.24. It may be pertinent to mention that most of these cases were in the older age groups, when the diabetic female has reached the menopausal stage and no longer benefits from the protective influence of the estrogens.

TABLE 5

Relative incidence of vascular disorders in reference to sex (1,600 cases*)

Type of Case	Males	Females	Ratio
Impaired circulation	294	363	1:1.23
Threatened gangrene	46	56	1:1.22
Gangrene	44	56	1:1.27
Total	384	475	1:1.24

*Series III and IV.

DISCUSSION

The problem of the relationship of diabetes mellitus and the high incidence of peripheral vascular complications is not new. Hitherto, two factors that have been considered important in the development of these complications have been the duration and/or the severity of the diabetes. The result of this survey showed that there was a progressive increase in the incidence of vascular changes, ranging from 17.3 per cent in the first series of 1,000 cases to 58.6 per cent in the current series. When taking these figures into consideration the fact that diabetes is being detected more often in early stages and that constant efforts are being made to control possible hypercholesterolemia by low-fat diet and other therapeutic means must be remembered. The apparent increase of the incidence of vascular pathology is striking and poses the question as to whether we are justified in assuming that the diabetes per se is responsible for these changes. The tables show that the high incidence of peripheral vascular complications occurred in diabetics in whom the condition was recognized within the first five years of the disease. Similarly, the high incidence of peripheral vascular disturbances was more significant in the milder forms of diabetes. The findings of the survey suggest that the basic cause for atherosclerosis might best be sought for in other fields. Further investigations in the field of metabolic disorders, besides cholesterol and carbohydrates, may give added information. Observation of uric acid levels in a series of patients with vascular diseases has indicated that it is not unusual to find hyperuricemia.[6] This need not necessarily imply that uric acid itself is responsible for these changes, but a disturbance of the uric acid metabolism may be a contributory influence. In delving into the possible explanation for atherogenesis, a greater knowledge of tissue metabolism of the individual cells may be helpful.[7] With a better understanding of the functioning of the intimal cells and what influences may disturb normal cell metabolism, the answers to these problems would be more easily achieved.[8]

Thus far, we have been successful in developing ways and means of detecting an impaired circulation even in the early stages. By recognizing these cases and treating them accordingly, it has been possible to contain the incidence of gangrene. Since it has been demonstrated that some form of atherosclerosis may be reversible, efforts should be made to investigate the various causes that induce atherosclerosis.

SUMMARY AND CONCLUSIONS

1. A survey of 3,600 cases of diabetes has indicated that the incidence or diagnosis of vascular complications is increasing.

2. The duration of diabetes alone is not a significant factor. The highest incidence seems to be in the first five years. This applies to the adult groups of diabetics.

3. Similarly, the severity of the diabetes is not a definite factor, because the vast majority of complications have occurred in patients with milder forms of the disease.

4. Age and sex have, likewise, been analyzed and discussed, and do not offer any significant explanation for the rise of the incidence of vascular complications.

5. Although our findings lead us to assume that diabetes per se is not responsible for the increasing incidence of complications, we still believe that it is advisable to continue with our rigid control of the diabetes and also with low-fat diets.

SUMMARIO IN INTERLINGUA

Complicationes Periphero-Vascular In Diabete Mellite: Un Revista De 3.600 Casos

1. Un revista de 3.600 casos de diabete ha indicate que le incidentia del diagnose de complicationes vascular se trova crescente.

2. Le duration del diabete non es—per se—un factor significative. Le plus alte incidentia pare concentrar se in le prime cinque annos del diabete. Isto vale pro le patientes de etate adulte.

3. Similemente, le grado de severitate del diabete non es definitemente un factor, proque le vaste majoritate del complicationes esseva constatate in patientes con plus leve formas del maladia.

4. Etate e sexo ha etiam essite analysate e discutite e etiam non offere un explication significative pro le augmentate incidentia del complicationes vascular.

5. Ben que nostre constatationes fortia nos a concluder que diabete per se non es responsabile pro le crescente incidentia de complicationes, nos adhere—non-obstante—al conviction que il remane recommendabile continuar le rigide control de diabete e etiam le dieta a basse contento de grassia.

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The real frontier areas of biochemistry now reach to the borderlines of physiology, genetics, cytology, medicine and theoretical chemistry. The biochemical description of muscular contraction, nerve conduction, glomerular filtration, and secretion and membrane phenomena is still relatively virgin territory. The structural analysis and interpretation of the way in which mitochondria, nuclei, membranes, myelin sheaths and other complex cellular structures are constructed in a chemical sense have yet to reach even the blueprint stage. A fabulous area of exploitation awaits the investigators who can hurdle the conceptual barriers in the way of the biochemical study of hormone action at the molecular level. If current progress on the reconstruction of in vitro systems or synthesis of protein is to serve as a guide, then we must surely anticipate the polygamous marriage in the not too distant future, of biochemistry with genetics, immunology, hematology and virology. The older problems of biochemistry are clearly moribund but the newer problems have the fascination and challenge of youth.

DeWitt Stetten, Jr., p. 9, in *Currents in Biochemical Research,* edited by David E. Green. Copyright Interscience Publishers, Inc., New York, 1956.