

CORONARY ARTERIOSCLEROSIS IN DIABETICS

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SERIOUS arteriosclerotic complications develop with unusual and discouraging frequency as the diabetic patient lives longer with his disease. Joslin and Root were among the earliest to stress the important influence of diabetes in the production of arteriosclerosis. It is generally conceded that myocardial infarction increases in frequency proportionately with the duration of diabetes, although there is considerable dispute as to the part played by the severity of diabetes. Root, Bland, and White (1) have shown that diabetics, and especially diabetic women between the ages of 51 and 80 (from postmortem evidence) have much higher incidence of severe myocardial infarcts than nondiabetics. As of the year 1940, it was found that (2a) angina pectoris usually occurred on an average of nine years after the onset of diabetes, and three times as often during the second decade of the disease as during the first decade (2b). Furthermore, 22% more diabetics than non-diabetics die primarily from myocardial infarction (3).

Root and Millard reported in 1948 (4) that in 110 diabetics autopsied at the New England Deaconess Hospital in the period 1940-1946 there was demonstrable coronary arteriosclerosis in 108. When one sees how universal coronary arteriosclerosis is in diabetes of long duration, it becomes apparent that most intensive study of the problem is needed if present efforts to control coronary arteriosclerosis are to be successful.

Bailey (5) feels that four factors favoring the development of arteriosclerotic heart disease are obesity, long duration of diabetes, severity of diabetes, and poor control of diabetes. Hypertension, heredity, abnormal lipid metabolism, sex, age, dietary habits, and possibly smoking are other variables which must be taken into account. It is with the effect of one factor, namely, the careful control of diabetes, on prevention and postponement of angina pectoris and myocardial infarction that this study is concerned.

METHODS

50 diabetic patients from the George F. Baker Clinic, all with diabetes of ten or more years' duration and all with convincing evidence of angina pectoris and/or myocardial infarction, were selected at random. All patients were living in 1949, at which time a detailed questionnaire was taken, and physical examination, electrocardiograms, and x-rays of the chest were done. Of the 50 patients, 35 were females and 15 were males. All of the patients were 50 to 82 years of age, except one 33 and one 46.

Inasmuch as our patients did not attain the ideal standards of diabetic control, we have established the following more practical criteria as to quality of control:

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CONTROL OF DIABETES

Good	Fair	Poor
Urine sugar tests:—done properly at least once daily—with urine being kept sugar-free or nearly so (clear green Benedict test).	done at varying and unknown intervals	done rarely with long periods of no testing at all
Blood sugar determinations: at least every 4 to 6 months	occasionally	rarely if ever
Diet: (a) good attempt (as ascertained from answers to careful questions) at carbohydrate restriction	poor or temporary attempts	rarely followed any diet for any length of time
(b) estimated dietary allowances frequently by use of household measures—cups, tpsps, etc.	household measures rarely used	never used
or (c) weighed diet at least during early period of instruction as to Rx	did not weigh	did not weigh
Insulin:—taken daily, with amount determined according to urine and/or blood sugar	taken daily in most instances—often without urine or blood sugar checks	not taken or taken sporadically
Regularity of examination by physician: 2 or 3 times a year	approximately once every year or two	only at intervals of many years
Coma:—never	never, or at most once (at time of discovery of diabetes)	0 to one or more times after diabetes diagnosed

A study of the incidence of coronary disease in a group of patients whose diabetes was ideally controlled is urgently needed. It would be very helpful if in the years to come a mass of data on diabetic medical students, nurses, and physicians were collected. It is notable that intelligence and/or the use and application of knowledge about diabetes and diabetic diets played a major part in putting certain of the patients into the *good* category.

According to the previously outlined criteria, 15 patients were classified as having been under good control for the greater part of the duration of their diabetes; 23 could be said to have had poor control. Of our other 12 patients we cannot be sure that their control was "fair" for long enough periods of time to justify any detailed conclusions.

Among the 23 patients who had controlled their diabetes poorly during most of the period since its onset, the following facts were impressive: (1) 8 patients had been in diabetic coma on at least one occasion each. (2) The regularity of a) urine sugar testing at home; b) blood sugar determinations; and c) examinations by a physician was very slight indeed. Each patient gave a history of a period of years (average 11.7, with range 3 to 20) during which time he had been lax and negligent in regard to one or more of the above three important methods of checking up on his

condition. (3) A poor attempt at following the prescribed diet was admitted by all 23 patients. Periods of improper diet habits varied from 5 to 21 years, with an average of 12 years.

In contrast, the 15 patients with good control of their diabetes during the greater part of its duration made a good attempt (as nearly as we could ascertain) at following their diet, save for short periods up to a year in the aggregate. All had made honest efforts at restriction of carbohydrate, and in most cases they measured their food with household measures, for a part of the time—usually at the onset of their diabetes or after discharge from the hospital. Thereafter they judged their diets from what they had learned concerning the caloric values of foods. However, two patients weighed their food for nearly the entire duration of their diabetes. One, now 82 and a patient of Dr. Elliott P. Joslin since 1921, weighed her food every day for 27 years. She also kept a daily 24-hour urine collection and tested a representative specimen from this every day until she developed angina in 1949, at age 81.

Thus, the cooperation of some patients is rewarded. With strong visible and tangible incentives to control diabetes better, more patients can be persuaded to discipline themselves effectively.

Constant instruction and also encouragement of the patient are important, for not only knowledge, but also the ability and determination to apply it, are required for success. Confidence on the part of the physician is necessary. In general, in our series, the patients with "good" control seemed to have a fair degree of understanding concerning diabetes, especially as compared with that found to be possessed by the 23 poorly-controlled diabetics.

Duration of Diabetes: The average duration of diabetes in the entire group of 50 patients was 18.1 years as of December 1949. (One patient died in December, 1949 and two early in 1950) 46 out of the 50 (92%) had a history of obesity at some time in

their life. 42 (84%) had had hypertension (either systolic above 140 or diastolic above 90). 10 (67%) of the 15 males and 32 (91.4%) of the 35 females were hypertensive. 5 had been hypertensive before the onset of diabetes. In 26, diabetes definitely preceded hypertension; and in 11 the time of onset of hypertension was not known. Altogether, 45 (90%) developed angina pectoris and 17 (34%) suffered myocardial infarctions.

Among the patients with good control of diabetes, the average age at time of onset of coronary artery disease was 65.6 years. In the 23 with poor control during the greater part of their diabetic life, the average age at the time of onset of coronary artery disease was 56.1 years. This is interesting in view of the fact that the average age, among our whole group of 50 patients, at onset of coronary artery disease was 60.2 years.

Findings: The following table presents data as to duration of diabetes (in the three groups of patients) before the onset of angina pectoris and of myocardial infarction.

From the table it can be seen that the ages of patients in the three groups are comparable, small though the groups admittedly are. Furthermore, it seems that the better-controlled patients live longer with their diabetes before developing cardiac complications secondary to coronary arteriosclerosis than do the poorly controlled patients.

In ten patients with duration of diabetes from 10 through 15 years, poorly controlled, the average age at onset of manifest coronary artery disease was 60.2. In 13 poorly controlled diabetics with diabetes of 16 to 38 years' duration, the average age at onset of manifest coronary artery disease was 53. On the other hand, in 13 patients with "good" control of their diabetes which had been of 16 to 38 years' duration the average age at onset of manifest coronary artery disease was 67.

TABLE I
QUALITY OF CONTROL AND POSTPONEMENT OF CARDIAC COMPLICATIONS IN DIABETES

Category of Control	Total No. Patients	Sex		Average age at onset of Diabetes Mellitus			Av. No. yrs. Duration of Diab. until onset of coronary artery disease	Average number of yrs. duration of Diabetes Mellitus at onset of				Number of patients with					
		M	F	Total Group Years	M Years	F Years		By Whole Groups		Angina Pectoris		Myocardial Infarction		Angina Pectoris		Myocardial Infarction	
								M	F	M	F	M	F	Total	M	F	Total
Good	15	5	10	47.9	45.0	49.3	17.7	19.0	18.6	13.3	25	12	3	9	5	3	2
Fair	12	2	10	49.0	48.0	49.2	12.3	12.5	12.3	—	12	12	2	10	3	0	3
Poor	23	8	15	44.2	39.6	46.6	12.0	12.33	11.67	10.5	16.2	21	6	15	9	4	5
Total	50	15	35									45	11	34	17	7	10

The following table gives the age distribution (by decades) of our 50 patients' onset of diabetes and clinical coronary artery disease.

TABLE II
AGE AT ONSET OF DIABETES AND OF CORONARY DISEASE

Age at Onset	No. cases Coronary Artery Disease		No. cases Diabetes Mellitus		No. cases Angina Pectoris	No. cases Myocardial Infarction (with or without angina)
11-20	0	0%	1	2%	0	0
21-30	1	2%	3	6%	0	1
31-40	1	2%	7	14%	1	1
41-50	4	3%	19	38%	12	2
51-60	17	34%	18	36%	15	5
61-70	20	40%	2	4%	19	6
71-80	6	12%	0	0%	7	2
81-90	1	2%	0	0%	1	0
	50		50		45	17
	88% with onset at 51 or older				44/45 or 97.8% at 41 or older	15/17 or 88.2% at 41 or older

The average age, for the whole group of 50, at onset of clinical coronary artery disease was 60.2 years.

Among the 15 males the average was 56.4 years; and among the 35 females, 61.8 years.

The average age of the above 45 patients with recognized angina at the time of its onset was 60.7 years. The average age of the above 17 patients at the time of first myocardial infarct was 57.1 years.

For comparison with the above age-at-onset distribution table, the following one prepared by White and Jones (1928) (6) is included.

AGE AT ONSET OF CLINICAL CORONARY HEART DISEASE

0 through 39 years	0.2%
40 through 49 years	6.1%
50 through 59 years	22.7%
60 through 69 years	44.1%
70 years and over	26.9%

Thus, 93.7% of the patients (in a series of 864) had the onset of their disease apparently at the age of 50 or over. (These were not diabetics). Our figures are seen to be in general agreement with this larger series.

Further comparison is offered with other charts of White, Bland and Miskall (1943) (7) and of Bland and White (1936) (8).

Series of 497 patients—1943

Age at onset of Angina Pectoris

0 through 30 years	4	0.8%
31 through 40 years	16	3.2%
41 through 50 years	106	21.4%
51 through 60 years	206	41.4%
61 through 70 years	131	26.4%
71 through 80 years	34	6.8%
Over 80	0	0.0%
		96%

Series of 461 patients—1936

Age at onset of clinical coronary thrombosis with myocardial infarction

0 through 29 years	3	0.7%
30 through 39 years	16	3.5%
40 through 49 years	80	17.4%
50 through 59 years	169	36.6%
60 through 69 years	142	30.8%
70 through 79 years	47	10.2%
Over 80	4	0.9%
		95.9%

White (9) states that in this series the average age at onset of angina pectoris was 56.5 years, with an age range of 20 to 80; and that the average age at onset of myocardial infarction was 56.2 years, with a range from 22 to 81. The percentages in our small series are in good general agreement with the above. However, it must be noted that in the above 1936 series of patients with infarctions, 85% were males; whereas only 7/17 or 41.2% of our diabetic patients were males. Likewise, in the above 1928 series of patients with coronary heart disease, 60% were males, whereas only 30% of our diabetic series of 50 are males. This seems to bear out the strong impression that diabetes completely does away with the female's relative "immunity" to severe coronary arteriosclerotic disease. Stearns, Schlesinger and Rudy (11) find that diabetic women over 40 have as high an incidence of coronary arteriosclerosis, angina pectoris and mortality from myocardial infarcts as have diabetic men over 40. E. T. Bell (12) has found, in 1214 diabetic autopsies, that coronary artery disease *caused death* twice as often in male diabetics as in male non-diabetics, and three times as often among diabetic as among non-diabetic females.

SEVERITY OF DIABETES AND INCIDENCE OF CORONARY ARTERY DISEASE

The average total dose of insulin administered at the beginning of its use near the time of onset of diabetes in the 15 patients with good control was 21 units. The average total initial dose among the poorly-controlled patients was 24 units. In 1950, the better-controlled patients were taking an average dose of 39 units daily; and the poorly-controlled patients, 49 units. Among 12 of the poorly-controlled patients who first took 20 units of insulin or less daily, the average age at onset of coronary artery disease was 57.7 years. Among 11 others, also poorly controlled, taking more than 20 units daily at first, the average age at onset of coronary artery disease was 54.4 years. In this connection, it is interesting to note that Stearns, Schlesinger and Rudy (11) in a post mortem study of 643 hearts with coronary arteriosclerosis (54 of which were diabetics') found that the severity of coronary arteriosclerosis was proportional to the duration—but not to the severity of diabetes. This lends further emphasis to the importance of diagnosing diabetes early and then instituting careful control of it.

HEREDITY

35 of the 50 patients knew that there was diabetes in their family. 19 knew of familial coronary artery disease, and 28 (including the 19 above) knew of familial cardiovascular disease of whatsoever form. 21 knew of familial diabetes, but thought there was no familial cardiovascular disease. Among these 21, the average age at onset of coronary

artery disease was 63.7 years. 5 knew of no familial diabetes, but only cardiovascular disease. Among those 5, the average age at onset of coronary artery disease was 54.4 years. 14 patients knew that both conditions were present among members of their families. The average age at onset of coronary artery disease among these 14 patients was 54.6 years. It happened that among the 15 patients with good control of their diabetes, only 4 knew of any incidence of coronary disease in their family, whereas 15 of the 23 poorly controlled patients knew of familial coronary artery disease. 9 of the 50 patients knew of neither any diabetes nor coronary artery disease in their families. These 9 had an average age of 64.3 years at the onset of coronary artery disease. Among the 28 with a known history of familial cardiovascular disease the average age at onset of coronary artery disease was 55.3 years.

The known incidence of familial diabetes both with and without cardiovascular disease, and of familial cardiovascular disease by itself, is significantly higher in our small series than it was in that of Root and Graybiel (10). This fact may be related to our observation of an average age at onset of diabetes somewhat younger than the mean noted by Root and Graybiel.

DISCUSSION

It is noteworthy that the average age at onset of coronary artery disease among our 50 patients is the same as it was in Root and Millard's larger 1946 series (4) of diabetics. At that time there had been an average of 9 years of diabetes before the onset of angina. Even our poorly controlled patients had had diabetes on the average longer than 9 years before developing manifestations of coronary disease. Most of our 12-to-14-year diabetics have had an opportunity to have used protamine insulin most of those years, whereas the long duration patients of 1946 went back to the pre-protamine days of less-prolonged 24-hour control.

The use of low-cholesterol diets has not been a confusing factor in this study. Probably our patients might have had less atherosclerosis and fewer myocardial infarcts if they had been on low cholesterol diets, but they were not. It will remain for future investigators to compare the results obtained with good control of blood and urine sugar alone against the results obtained with such control plus the control of dietary cholesterol. In any event, it seems quite likely that a large part of the body and blood cholesterol is formed within the body more or less independent of food intake. Cholesterol determinations, however, do not seem to be the most accurate means of assaying whether or not the process of atherosclerosis is going forward actively at any time. The work of Gofman and his associates (13) seems to indicate that diabetics and patients with marked atherosclerosis, whether or not they show hypercholesterolemia, tend to show consistently a significant serum level of certain low-density, cholesterol bearing lipid and lipoprotein components. These components, the so-called Sf 12-20 group,—which can be detected and quantitated at present by differential ultracentrifugation—are found in much lower concentrations in normal patients without diabetes or atherosclerosis—and in especially low concentrations in young women. Their concentration apparently can be lowered in a high percentage of patients by dietary cholesterol and fat restriction.

In discussing the value of good diabetic control, and the vital importance of following a proper diet consistently, it is well to reemphasize that the diet must be made practical for the patient. It must keep him from being hungry; it must take into consideration his financial means, his place of work, and the amount and type of work he does. His food should not be conspicuously different from that eaten by his friends and associates. His likes and dislikes must be an important factor in the planning of his diet, as must be his and his family's eating habits. One must remember whether or not certain foods that one would like to have the patient eat will be available, and how good the patient's teeth are. If the patient appreciates the physician's efforts to consider all such aspects, he is more likely to cooperate—and thus help himself.

It is difficult to ascertain the true significance of the results presented above because of the influence of various other factors contributing to the development of coronary artery disease. Some of these are 1) heredity (not only for coronary artery disease but also for cardiovascular disease in general and for diabetes); 2) abnormal lipid metabolism; 3) obesity; and 4) hypertension. However, we are convinced that careful control of diabetes helps to keep the diabetic in optimal health for a maximal period of time.

The following tables (14), published by the Metropolitan Life Insurance Company from the experience of the George F. Baker Clinic, demonstrate the value of good control of diabetes (14). A study of 139 patients with onset of diabetes between 15 and 30 years of age indicated that careful management and good cooperation between the diabetic and the physician pay dividends in lowered frequency of retinitis and calcified arteries.

Criteria of Control	Fair control	Poor control
Insulin	Early and continued	Delayed
Diet	Good nutrition	Unregulated
Medical Supervision	Regular	Infrequent
Blood and Urine Tests	Frequent	Rare
Coma	None	One or more attacks
Retinitis		
Diabetes of Duration 10-19 years		Diabetes of Duration 20-29 years
Fair control	32% of patients	19% of patients
Poor control	63%	88%
Calcified Arteries		
Fair control	62% of patients	76% of patients
Poor control	74%	96%

CONCLUSIONS

How can physicians help to prolong the lives of diabetic patients especially before, but also after the development of coronary artery disease? We recommend the following measures:

1. Good control of diabetes, as judged by our standards. (This involves persistent sincere efforts on the part of both physician and patient).

2. Weight reduction if patient is obese: weight to be kept at normal level or slightly below during entire adult life.

3. Attempts to restrict the ingestion of exogenous cholesterol unless, or until such time as the patient's serum can be shown to contain no abnormal concentration of low-density cholesterol-bearing lipid or lipoprotein components such as are described by Gofman.

4. Early and continuous education of the diabetic.

5. Treatment of the diabetic patient as a whole—the psyche as well as the soma. (This is particularly important because of the deprivations which diabetics must endure.)

6. Efforts to reduce the cost of good diabetic care.

7. Best possible treatment for hypertension whenever its onset.

6. Close cooperation and understanding between the patient and physician is of vital importance if the patient is to achieve and maintain optimal control of his diabetes. In this series, the patients with the best-controlled diabetes seemed to be those with the most understanding of the disease.

7. Optimal control includes making efforts to (a) consider the diabetic patient as a whole, (b) make his care as economical as is feasible, (c) keep his weight, blood pressure and activities normal; and (d) maintain the patient's proper motivation.

8. It is urged that data relative to the frequency, age, and time of incidence of coronary artery disease in a large group of optimally-controlled diabetics (which should include physicians and nurses and their families) are sorely needed.

SUMMARY

1. The fact that coronary artery disease strikes long-duration diabetics, and especially diabetic women, much oftener and harder than non-diabetics is re-emphasized.

2. Criteria for calling diabetic control good, fair or poor have been listed.

3. A group of 50 diabetics has been studied in an effort to determine the effect of relatively good diabetic control on prevention or postponement of coronary artery disease.

4. 15 patients whose diabetic control seemed to have been reasonably good had diabetes an average of 17.7 years before the onset of manifest coronary artery disease, and developed coronary artery disease at an average age of 65.6 years. On the other hand, 23 with poor control had their onsets of manifest coronary artery disease after an average of 12.0 years of diabetes, and at an average of 56.2 years.

5. Mildness of diabetes seemed to play less of a part in postponement of coronary artery disease than did good control. It is emphasized that good and prolonged control depends on early detection of diabetes.

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OBESITY, ITS ASSOCIATED DISEASES AND TREATMENT

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INTRODUCTION

IT IS INTERESTING to note that the normal nutritional state commonly called obesity—so well known to all of us, is more or less difficult to define for the purpose of nosography. Bauer (1) aimed at a definition, in which he stated "Obesity is a compulsory tendency toward marked overweight due to abnormal accumulation of fat, by persons who are left alone to their automatic regulations, and are not supervised as far as the intake of food and expenditure of energy is concerned." This definition, it seems to me, offers little that is descriptive of the obese state or its causes. The importance of increased food consumption and pro-

portionally low expenditure of energy are generally admitted by all. The degree to which the endocrine system is involved; by which we mean the thyroid, pituitary adrenals, the gonads and the pancreas, is emphasized by some and minimized by others. The central nervous system has been implicated, inasmuch as it has been noted that injury to the hypothalamus in the experimental animal, incites an inordinate desire for food which is followed by a striking increase in body weight. Recently the relatively older concept of Newburgh (2) and others has been revived. Newburgh emphasized the emotional and unstable personality of certain obese patients who seek relief in the comfort of food when in a state of stress, which may be more or less continuous in such individuals.

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