CARDIOVASCULAR COMPLICATIONS OF DIABETES MELLITUS

BASED ON A STUDY OF 349 CASES

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Ever since the advent of insulin, cardiovascular complications have commanded increasing attention as a cause of morbidity and mortality among diabetic patients. It is believed that certain peculiarities in the type of diabetes found in the tropics affect the incidence of these complications. Hugh-Jones (1955), after excluding the age factor, showed that hypertension was much less common in type "J," which has so far been described only in the tropics. Cosnett (1959) pointed out the exceptionally common occurrence of nephropathy among Indian diabetics in Natal. Therefore, in view of these observations and the fact that cardiovascular complications are often considered to be associated with the severity or lack of control of the diabetic state (Rabinowitch, 1935; *J. Amer. Med. Ass.*, 1947; Lawrence *et al.*, 1951; Wilson *et al.*, 1951; Bradley and Bryfogle, 1956), it was thought that factors such as lack of treatment in a high percentage of cases and the stressed mildness of diabetes in tropical countries (de Zoysa, 1951; *British Medical Journal*, 1959) may affect the frequency and pattern of these complications.

Material

This study is based on an analysis of 349 confirmed diabetics seen in the two medical units and the cardiology clinic of Victoria Jubilee Hospital, Amritsar, during a period of five and a half years (January, 1953, to June, 1958). Blood-glucose levels above 120 mg./100 ml. (fasting) or above 180 mg./100 ml. (after glucose) were considered to be diagnostic of the disease. The series represents a fair cross-section of all classes of patients, both rural and urban. Table I shows the age and sex distribution, Table II the incidence of complications studied, and Table III their frequency in various age-groups.

Coronary Heart Disease

Clinical and/or electrocardiographic evidence of coronary disease was present in 76 (21.7%) cases (Table II). This, however, may be somewhat lower than the real incidence, as electrocardiograms were not taken in some of the younger diabetics who were considered to be free from cardiovascular disease on clinical grounds.

Age and Sex Incidence.—Although 39 (51.3%) of the 76 diabetics with coronary disease fell in the age-group 50–59, the peak incidence (52.9%) was observed in the eighth decade (Table III). Only one patient—an obese man aged 38—who had been diabetic for eight years was under 40. A comparison of the age distribution of coronary disease in diabetics with that in an

unselected series of cases (Malhotra and Pathania, 1958) is given in Table IV. These figures do not support the view that coronary disease develops at a relatively earlier age among diabetics (Friedberg, 1956). In the present series coronary disease was 1.7 times commoner in males than in females (Table II), compared with a figure of 6.7 times in Malhotra and Pathania's (1958) series.

The duration of diabetes in patients with various complications is shown in Table V. The duration of diabetes was known in 58 out of 76 coronary diabetics and was over five years in 41 (71%).

The average, maximum, and minimum fasting blood-sugar values are given in Table VI.

TABLE I.—Age and Sex Distribution.

Sex	Age-group in Years								Total
	10–	20–	30–	40–	50–	60–	70–	80+	
Male	10	22	22	42	85	50	13	2	246 (70.5%)
Female	4	13	4	24	36	17	4	1	103 (29.5%)
Total	14	35	26	66	121	67	17	3	349

TABLE II.—Incidence of Complications.

Complication	Total		Above 40 Group		Male		Female		Sex Incidence Ratio
	No.	%	No.	%	No.	%	No.	%	
Coronary disease	76	21.7	75	27.4	61	24.8	15	14.6	1.7 : 1
Hypertension	97	27.8	94	34.3	72	29.3	25	24.3	1.2 : 1
Cerebral vascular lesions	20	5.7	20	7.3	15	6.1	5	4.8	1.3 : 1
Diabetic nephropathy	20	5.7	20	7.3	15	6.1	5	4.8	1.3 : 1

TABLE III.—Incidence of Complications in Various Age-groups.

Age-group	No. of Diabetics	Coronary Disease		Hypertension		Cerebral Vascular Lesion		Diabetic Nephropathy	
		No.	%	No.	%	No.	%	No.	%
20–29	35	0		2	5.7	0		0	
30–39	26	1	3.8	1	3.8	0		0	
40–49	66	6	9.1	12	18.2	0		4	6.1
50–59	121	39	32.2	46	38.0	9	7.4	9	7.4
60–69	67	21	31.3	30	44.8	8	11.9	7	10.4
70–79	17	9	52.9	5	29.4	3	17.6	0	
80+	3	7*		1	33.3	0		0	
Total	335	76		97		20		20	

* Uncertain, inasmuch as one died in diabetic coma without an electrocardiogram having been taken.

TABLE IV.—Age Distribution of Coronary Heart Disease Among Diabetics and Unselected Population.

	Age in Years							Total
	20–29	30–39	40–49	50–59	60–69	70–79	80+	
Diabetics (present study)	0 (0%)	1 (1.3%)	6 (7.9%)	39 (51.3%)	21 (27.6%)	9 (11.8%)	0 (0%)	76
Unselected series (Malhotra and Pathania, 1958)	3 (0.35%)	36 (4.2%)	143 (16.5%)	341 (39.3%)	223 (25.7%)	109 (12.6%)	12 (1.4%)	867

TABLE V.—Duration* of Diabetes in Various Complications.

Complication	Duration of Diabetes in Years					Uncertain
	< 5	5–10	11–20	21–30	> 30	
Coronary disease	17	17	14	9	1	18
Hypertension	23	16	27	15	—	16
Cerebral vascular lesions	2	4	2	3	—	9
Diabetic nephropathy	4	2	10	2	—	2

* As judged by the patient's knowledge of the onset of diabetes or the presence of symptoms suggestive of diabetes, whichever occurred earlier.

Electrocardiographic Findings.—The incidence of various electrocardiographic abnormalities in the coronary and hypertensive diabetics is shown in Table VII. Evidence of recent or old myocardial infarction was shown in 25 (32.9%) cases in the coronary group—20 (8.1%) were males and 5 (4.9%) females—a male-to-female incidence ratio of 1.7:1, which is the same as for the whole group of 76 cases. These findings are in agreement with those of Warren (1952), but at variance with those of Liebow *et al.* (1955), who found myocardial infarction to be 3.2 times commoner among male diabetics.

Banerjea and Roy (1959) noted a special predilection for infarction in the antero-septal region, but this was not observed in our series.

Associated Features.—Hypertension occurred in 31 (40.8%) of the 76 patients, of whom 18 (23.7%) were obese. The incidence of associated hypertension and

The duration of diabetes was known in 81 of the 97 hypertensive diabetics, and was over five years in 58 (71.6%).

Gradation of Hypertension.—Friedberg's (1956) criteria were used. Most patients (59.8%) were in

TABLE VIII.—*Gradation of Hypertension.*

Age-group	No. of Hypertensives	Grade I S150–200 D90–110		Grade II S200–230 D110–120		Grade III S230–280 D120–140		Grade IV Papilloedema	
		No.	%	No.	%	No.	%	No.	%
20–29	2	2	100	0		0		0	
30–39	1	1	100	0		0		0	
40–49	12	5	41.7	1	8.3	4	33.3	2	16.7
50–59	46	27	58.7	10	21.7	8	17.4	1	2.2
60–69	30	21	70.0	7	23.3	2	6.6	0	
70–79	5	1	20.0	2	40.0	2	40.0	0	
80	1	1	100	0		0		0	
Total	97	58	59.8	20	20.6	16	16.5	3	3.1

TABLE VI.—*Blood-sugar Values in Various Complications.*

Complication	Fasting Blood Sugar (mg. 100 ml.)		
	Maximum	Minimum	Average
Coronary disease	330	91	181.5
Hypertension	444	80	184.6
Cerebral vascular lesions	364	134	240.2
Diabetic nephropathy	444	95	196.6

TABLE VII.—*Electrocardiographic Abnormalities.*

E.C.G. Abnormality	Coronary Group	Hypertensive Group
Myocardial infarction	25*	9
Coronary insufficiency	30	18
Left ventricular hypertrophy and/or strain	7	32
Heart-blocks	10	4
Other arrhythmias	9	2
Normal electrocardiogram (resting)	7	21

* Anterior, 9; posterior, 8; antero-septal, 7; anterolateral, 1.

obesity was almost the same as in the unselected coronary series of Malhotra and Pathania (1958)—which was 38.2% and 29% respectively. Thus in the present study there is no evidence that hypertension and obesity are more commonly associated with coronary disease in diabetics than in the cardiac cases generally.

Hypertension

Basal figures above 150 mm. Hg systolic and 90 mm. Hg diastolic were arbitrarily chosen as signifying hypertension. Hypertension, thus defined, was detected in 97 (27.8%) of the diabetics.

Age and Sex Incidence.—The largest number (46, 38%) of hypertensive diabetics were aged 50–59 (Table III), a finding which is similar to that of Wig *et al.* (1953) in a study of unselected hypertensives. The highest percentage (44.8%) was observed in the seventh decade. The incidence fell in the eighth and ninth decades (Table III). It is significant that 5.7% of diabetics under 30 years were hypertensives. The youngest was a man, aged 24, with a five-year history of diabetes and a blood-pressure of 160/100 mm. Hg. There was no clinical or laboratory evidence of renal involvement in this case. Hypertension was found to be 1.2 times more frequent among male diabetics (Table II). Observations on the relative sex incidence of hypertension among the general population of India are not in entire agreement, but, in contrast to the Western reports (White, 1951; Friedberg, 1956) hypertension is generally stated to be 1.6 to 10.4 times commoner among men than among women (Gour, 1959; Padmavati, 1959).

grade I (Table VIII). None of the diabetics beyond the age of 59 had grade IV hypertension, but the highest incidence of grade III was noted in the eighth decade.

Associated Features.—Coronary disease was present in 31 (32%) of these 97 hypertensive diabetics. This incidence is about twice that of coronary disease among non-hypertensive diabetics (17.9%). This observation agrees with those of Root *et al.* (1939) and Liebow *et al.* (1955), who found that hypertension increases the incidence of coronary disease in diabetics. Sixteen (16.2%) cases had cerebral vascular lesions, 17 (17.5%) had diabetic nephropathy, and as many as 42 (43.3%) were obese.

Cerebral Vascular Lesions

Cerebral vascular lesions, recent or old, occurred in 20 (5.7%) cases (cerebral thrombosis 16, cerebral haemorrhage 3, hypertensive encephalopathy 1). Of these 20, 16 were hypertensive. As with coronary disease, the highest incidence was observed in the eighth decade. The duration of diabetes was known in 11 hypertensive subjects and was over five years in nine of them.

Diabetic Nephropathy

Employing the diagnostic criteria laid down by Clark and Skillern (1955)—namely, oedema, albuminuria, hypertension, renal failure, retinopathy, and hypoalbuminaemia—we found this complication in 20 (5.7%) of the diabetics. Total and differential protein levels were, however, not available in all cases.

Age and Sex Incidence.—These are shown in Tables III and II respectively. All patients were aged between 40 and 70 years, the highest incidence being in the seventh decade.

The duration of diabetes was over five years in 14 (77.8%) of the 20 cases (Table V), the average being 13.9 years.

TABLE IX.—*Clinical Features and Laboratory Findings in Diabetic Nephropathy.*

Clinical Features	Present Study (20 Cases)	Clark and Skillern (100 Cases)	Laboratory Findings	Present Study (20 Cases)	Clark and Skillern (100 Cases)
Oedema	18	63	Albuminuria	20	98
Ascites (clinical)	2	0	Raised blood urea (above 50)	10	66
Hypertension	17	88	Raised E.S.R.	15	?
Retinopathy	10*	98	Glycosuria	10	?
Anaemia	20	77			

* In the remainder, observation could not be made or be relied upon because of lens or corneal opacities or other reasons.

The important clinical and laboratory features are summarized in Table IX. The raised blood-urea levels ranged from 75 to 248 mg./100 ml., with an average of 104.7 mg./100 ml. The albuminuria was in traces in two cases, one plus in 12, two plus in five, and three plus in only one case.

The maximum, minimum, and average fasting blood-sugar values are shown in Table VI. It may be significant that the fasting blood-sugar values were within the normal range in as many as seven cases. In all, 14 cases had fasting blood-sugar values below 200 mg./100 ml. On the other hand, two advanced cases had values above 400 mg./100 ml.

Discussion

The incidence of cardiovascular complications among diabetics in the present series is appreciably less than in most of the reported studies (Table X). This is particularly true of hypertension, more so in view of the lower blood-pressures chosen for this study to signify hypertension.

The lower incidence of these complications in the present series assumes greater significance in view of the alleged relationship of cardiovascular complications with the control of the diabetic state. The vast majority of our diabetics had had no appreciable treatment, yet complications were not more frequent in these patients than in others who were regularly treated in diabetic clinics (Balme and Cole, 1951; Lundbæk, 1954; Liebow *et al.*, 1955; Bradley and Bryfogle, 1956). This makes us doubt the claim advanced by several workers that poor control of diabetes increases the incidence of cardiovascular complications. Mirsky (1945), too, believed that, so far as vascular disease is concerned, "it makes little difference how the diabetic is treated." Dolger (1947) and Friedberg (1956) came to similar conclusions.

Only 1 out of 76 diabetics with coronary disease was under 40 years of age. This, taken with the data shown in Table V, makes us doubt whether diabetes really predisposes the subject to develop coronary disease, as is generally believed (Friedberg, 1956). This belief stems almost exclusively from necropsy studies (Root *et al.*, 1939; Clawson and Bell, 1949; Feldman and Feldman, 1954). The study of the available scanty data on living diabetics, however, substantiates the infrequency with which coronary disease develops in diabetics under 40. Liebow *et al.* (1955) and Banerjea and Roy (1959), in a study of 383 and 175 diabetics respectively, did not find clinical coronary disease in any diabetic under 40 years, while Lundbæk (1954) also found coronary disease exclusively in the elderly diabetics. In Bradley and Bryfogle's (1956) series of 394 diabetics, only one with clinical coronary disease was under 40.

TABLE X.—Incidence of Cardiovascular Complications as Reported by Various Authors.

Author	No. of Diabetics Studied	Coronary Heart Disease	Hypertension	Cerebral Vascular Lesions	Diabetic Nephropathy
Chakravarti (1949)	100	—	41%	—	—
Balme and Cole (1951)	209	—	60%	—	—
Lundbæk (1954)	234	66%*	68%	—	25%
Liebow <i>et al.</i> (1955)	383	42%	42.8%	—	—
Bradley and Bryfogle (1956)	394	40%	—	—	—
Cosnett (1959)	207	1.4%†	30.4%	5.8%	11%
Banerjea and Roy (1959)	175	14%	43.4%	4.0%	3%
Present series	349	21.7%	27.8%	5.7%	5.7%

* In patients over 60 years of age. † Myocardial infarction only.

The well-known disparity between "pathological" coronary atherosclerosis and "coronary disease" (Friedberg, 1956) renders evident the need for caution in applying necropsy data to living diabetics. As it is, with the clinical studies contradicting the post-mortem evidence, the belief that diabetes accelerates the onset of coronary disease rests on unsure ground.

Whereas the highest incidence of coronary disease and cerebral vascular lesions was noted among diabetics in the eighth decade, the incidence of hypertension showed a distinct fall after the seventh decade. This is at variance with the result obtained by Friedman (1935), Edeiken (1945), Balme and Cole (1951), and Banerjea and Roy (1959), who observed a rising incidence of hypertension with age. A close study of Balme and Cole's (1951) series, however, shows that the rise was not uniformly progressive, the incidence being 46% in the fourth decade and 31% in the fifth.

The increase in the incidence of diabetic nephropathy from 40 years until the seventh decade is in agreement with the observations of Hall (1952).

The nearly equal sex incidence of these complications in the present series is in contrast to the observation of Banerjea and Roy (1959), who noticed no such "change of affairs" in the sex incidence. However, the number of female diabetics (25) in their series was perhaps too small to refute the conclusion arrived at by several workers (Lundbæk, 1954; Liebow *et al.*, 1955; Bradley and Bryfogle, 1956) that diabetes knocks out the relative feminine immunity against arteriosclerotic disease. The predisposing effect of diabetes as evidenced by the nearly equal sex incidence of these complications in the present series must be quite strong, more so in view of the sheltered and unhurried life of women in India.

The observation that 16 of the 20 diabetics with cerebral vascular lesions were hypertensive emphasizes that it is associated hypertension rather than diabetes mellitus *per se* which is an important cause of such lesions in diabetics.

The present clinical and laboratory observations in diabetic nephropathy are in general agreement with those of Clark and Skillern (1955). The higher incidence of this complication among males differs from the observations of other workers, who find that females are affected nearly twice as often as males (Kimmelstiel and Porter, 1948; Wilson, 1957).

It is believed by many authorities that diabetic nephropathy occurs usually in the mild and easily controlled diabetics (Wilson, 1957). It is therefore of interest that the fasting blood-sugar values were within normal range in 7 out of 20 diabetics with this syndrome. However, fasting blood-sugar levels above 400 mg./100 ml. in two established cases in this series serve to remind one of Gilliland's (1951) and Clark and Skillern's (1955) observations that the syndrome may well supervene on, and exist with, severe diabetes.

Summary

An analysis of cardiovascular complications in 349 diabetics is presented.

An incidence of 21.7% for coronary disease, 27.8% for hypertension, 5.7% for cerebral vascular lesions, and 5.7% for diabetic nephropathy was found. The male-to-female sex ratio was 1.7:1, 1.2:1, 1.3:1, and 1.3:1 respectively.

The lower incidence of these complications as compared with most of the published reports is pointed out. Its significance in view of lack of treatment in the vast majority of diabetics in the present series is discussed.

Differences in relation to sex incidence are compared with observations made by previous workers.

It is difficult to support the widely held view that coronary heart disease occurs at an earlier age in diabetics.

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According to the Soviet Information Service there are 21,708 people in the Soviet Union able to produce documentary confirmation that they were born over a century ago. This figure is one of a number on longevity which has recently been issued by the U.S.S.R.'s Central Statistical Board. These figures confirm that 592 were at least over 120. The champions are the people of Nagorno-Karabakhskaya, an autonomous republic of Azerbaijan in the Caucasus: 144 citizens there are over 100 years old. Azerbaijan as a whole has 84 centenarians per 100,000; Georgia has 51; Yakutia, in the Arctic region, has 32; 4,436 of the centenarians live in urban areas, 17,272 in the country; 5,432 are men and 16,276 are women. The majority are just over 100; 13,350 under 105; 4,183 are between 105 and 110. The rest are over 110. This gives an average number of centenarians of 10 per 100,000 of the population.

IMPORTANCE OF POTASSIUM SUPPLEMENTS DURING THE USE OF SPIRONOLACTONE AND THIAZIDE DIURETICS

BY

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A leading article entitled "The Spirolactones" in the *British Medical Journal* (1960) states: "There is thus a general agreement that spironolactone can be of value in preventing wastage of potassium during orthodox diuretic therapy. Farrelly and his colleagues (1960) have concluded provisionally that this action is of more clinical value than any diuresis of sodium the drug may produce. They point out that, though loss of potassium can usually be combated by giving potassium chloride by mouth, this form of potassium therapy is not acceptable to all patients, and spironolactone may be preferable to some."

Considerations of cost alone should be sufficient to make it impracticable to use spironolactone ("aldactone") at the present time as an alternative to potassium supplements. Experience has also shown that potassium wastage can occur in some cases during combined therapy with thiazide diuretic and spironolactone which could lead to hypokalaemia. In addition, sodium diuresis and loss of weight are augmented in some cases if potassium supplements are given. The relevant data are presented below.

Potassium Loss During Combined Therapy with Spironolactone and Hydrochlorothiazide

Case 1.—This patient, a woman aged 42 with idiopathic oedema, was without cardiac, renal, or hepatic disease and had a normal plasma-protein concentration. She had oedema of face, hands, legs, and ankles. She was observed for 14 days, during which she received a constant low-salt diet (Na intake, 18 mEq/day). After three control days she was given spironolactone, 100 mg. six-hourly, for seven days. On the third day of spironolactone therapy hydrochlorothiazide, 50 mg. b.d., was added. The urinary excretion of sodium and potassium during this period is shown in Fig. 1. Doubt exists about the completeness of the urine collection on day 9. The administration of spironolactone alone did not increase sodium-excretion, but there was a reduced potassium loss during this period. The addition of hydrochlorothiazide to this regime resulted in a clinically worth-while sodium diuresis with loss of weight. It also increased potassium diuresis.

Case 2.—A woman aged 65 who suffered from cirrhosis had tense ascites and generalized oedema. Her plasma albumin concentration was 1.8 g./100 ml. She was on a low-salt diet (Na intake, 18 mEq/day) on which her sodium excretion was only 1.2 mEq/day. Potassium supplements were not given. She was placed on spironolactone 400 mg./day. This had virtually no effect on sodium excretion. The addition of hydroflumethiazide increased sodium excretion from 2 to 20–25 mEq/day. The injection of mersalyl, 2 ml., in addition to the other two substances greatly increased sodium excretion (Fig. 2). Potassium excretion was increased threefold by the addition of hydroflumethiazide, compared with the period when spironolactone alone was given. The injection of mersalyl resulted in a further increase of potassium excretion on two of the three occasions on which it was given.