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THE ETIOLOGICAL ROLE OF DIABETES MELLITUS IN CARDIOVASCULAR DISEASE

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A survey of a significant and representative sample of the population of Malta, carried out in 1964, revealed that the incidence of diabetes mellitus was 19.9% (1). The disease was predominantly of the late-onset type, starting after the age of 30 years in 97.1% of the cases. The peak age-of-onset was 50 to 54 years in both sexes. Sixty percent of the diabetics (as against 44% of nondiabetics) were obese.

The clinical association of diabetes and atherosclerosis is well known and accounts for the fundamental importance of diabetes in cardiology. However, in view of the intimately associated, potentially pathogenetic factors (aging etc.), differential objective evidence is essential in order to prove the role of diabetes in the etiology of atherosclerosis. The purpose of this work was to provide this evidence from relevant facts collected during the abovementioned survey. This study was limited to "large vessel" disease.

MATERIAL AND METHODS

As part of a survey for diabetes in the rural and urban population of Malta, 5,757 subjects of all ages had their urine specimens examined. Glycosuria was found in 513 (8.9%) (Table 1).

A questionnaire was filled out and physical examination and glucose tolerance tests were carried out in 324 of these subjects and in a matched sample of 392 control individuals who had no glycosuria: 227 (70%) of the former and 59 (15%) of the latter proved to have diabetes mellitus (as defined by a 2-hr capillary blood glucose level of over 100 mg% in association with a peak level of over 150 mg% after 50 g oral glucose load). The incidence of diabetes in the whole sample was therefore 19.9%.

The criteria for establishing the presence of coronary artery disease (CAD), cerebrovascular disease (CVD), peripheral vascular disease (PVD) or of established diastolic hypertension (DH) were the following:

History of angina on effort, acute coronary insufficiency or myocardial infarction (for CAD); strokes or definite recent memory disturbances, not ascribable to other cerebral pathology (for

TABLE 1. *Results of Malta diabetes survey (1965)*[a]

No glycosuria 5,244 (91.1%) Glucose-tolerance test 392				*Glycosuria 513 (8.9%) Glucose-tolerance test 324*			
Diabetes	*Lag storage curve*	*Renal glycosuria*	*Normal*	*Diabetes*	*Lag storage curve*	*Renal glycosuria*	*Normal*
59 (15.0%)	61 (15.7%)	6 (1.5%)	266 (67.8%)	227 (70.1%)	24 (7.4%)	24 (7.4%)	49 (15.1%)

[a] Population (rural and urban), 6,579; provided urine specimens, 5,757 (87.5%).

TABLE 2. *Prevalence of arterial complications in diabetics and nondiabetics aged 30 years and over*

Arterial disease	*Diabetics (274)*			*Nondiabetics (277)*		
	No. of affected patients	*No. with complications*	*Prevalence of complications %*	*No. of affected patients*	*No. with complications*	*Prevalence of complications %*
PVD	62 (14)[a]	76	27.7	32 (8)[a]	40	14.4
CVD	21 (6)[a]	27	9.8	8 (1)[a]	9	3.2
CAD	27 (2)[a]	29	10.6	21 (3)[a]	24	8.6
DH	36 (18)[a]	54	19.7	44 (5)[a]	49	17.7
Total no. of affected patients	146	—	53.2	105	—	37.9

[a] Affected patient(s), already included under another, more prominent, cardiovascular complication.

CVD); intermittent claudication, or gangrene (for PVD).

Physical signs of neurological sequelae of strokes; absence of one or both arterial pulses in the feet; evidence of present or healed gangrene; a diastolic blood pressure of 105 mm Hg or more.

Other instrumental examination findings (ophthalmoscopic, oscillometric, X-ray, cardiographic etc.) were not taken into consideration in arriving at the prevalence of cardiovascular disease, as not all cases were submitted to these tests.

RESULTS

One hundred and forty-seven (51.9%) of the 283 diabetics (three cases were excluded because of inadequate records) showed evidence of arterial disease. On the other hand, only 110 (26.1%) of 421 nondiabetic individuals were similarly affected. The incidence of vascular disease among diabetics was therefore nearly twice that in the controls.

However, as the incidence of diabetes in subjects under the age of 30 was found to be only 2.9%, it was believed that restriction of the comparison with nondiabetics to subjects older than 30 years would give a more accurate estimate of the relative incidence of arterial disease. One hundred and forty-six out of 274 diabetics aged 30 years and over (53.2%) and only 105 out of 277 nondiabetics (37.9%) had arterial complications (Table 2). These figures constitute the basis for the present study, unless otherwise indicated.

More than one of the four conditions studied (PVD, CVD, CAD and DH) was present in 40 of the affected diabetics and in 17 of the control subjects.

Individual vascular complications in diabetics and in controls aged 30 years and over. It may be seen from Table 2 that PVD and CVD were significantly more frequent in diabetics, while CAD and DH were found almost equally in both groups.

In both diabetics and nondiabetics there was a rise in the overall incidence of vascular disease with age (Table 3). This was much higher in diabetics after the age of 50 years: The behavior of the individual arterial complications with advancing age was as follows.

PVD (Table 4). There was a progressive in-

TABLE 3. *Variations in overall incidence of occlusive arterial disease with age in diabetics and nondiabetics aged 30 years and over*

Age-group years	*Diabetics (274) %*	*Nondiabetics (277) %*
30 to 39	28	11.3
40 to 49	25.9	40.5
50 to 59	56.6	41.1
60 to 69	63.6	50.0
70 to 79	82.6	66.6
80 and over	75.0	—
Total incidence	53.2	37.9

TABLE 4. *Variations in incidence of PVD with age in diabetics and nondiabetics aged 30 years and over*

Age-group years	*Diabetics %*	*Nondiabetics %*
30 to 39	16.0	6.5
40 to 49	13.0	14.9
50 to 59	30.1	15.5
60 to 69	27.3	17.4
70 to 79	56.5	25.0
80 and over	75.0	—

crease of prevalence with age in diabetics and, to a lesser extent, in the control subjects. The rate of increase was higher in diabetics. In the 50 to 59 years age-group the incidence of PVD was nearly double in diabetics (30.1 and 15.5% respectively). The prevalence of PVD in diabetics aged 30 to 39 years was similar to the prevalence in control subjects aged 50 to 59, indicating the earlier occurrence of atherosclerosis in diabetes.

CVD. The prevalence of this complication increased with age in diabetics more than in the control subjects. Thus, in the 50 to 59 years age-group, it was 13.2% in diabetics and only 4.4% in nondiabetics. However, the frequency of CVD was much smaller than that of PVD.

CAD. Analysis of the findings showed a higher overall prevalence in diabetics as compared to controls. However, the difference in the various age-groups was less marked and, under the age of 70, of doubtful significance. Diabetics over the age of 70 were affected significantly more frequently.

DH. The overall prevalence in diabetics (19.7%) and in age-matched controls (17.7%) was not significantly different. The differences in the various age-groups were all less marked and often of dubious significance, except in the 50 to 59 years age-group where the prevalence was 25.3 and 17.7% in diabetics and nondiabetics respectively. Thus, while the effect of age on the difference in prevalence of PVD in diabetics and nondiabetics was very marked, and that of CVD definite but less pronounced, the effect on the difference in prevalence of CAD and DH between the two groups was generally slight and insignificant.

Sex distribution of occlusive arterial disease in diabetics and in controls aged 30 years and over. Sixty-five (44.5%) of 146 diabetics with occlusive arterial disease were males and 81 (55.5%) females. Before the age of 50 the prevalence was higher in males, but after this age it was higher in females (Table 5).

Of the 105 nondiabetics with arterial disease, 54.3% were males and 45.7% females. The prevalence in females was higher throughout all age-groups. PVD was more frequent in male diabetics throughout all age-groups (Table 6). The overall prevalence of PVD in nondiabetics was smaller in all age-groups;

TABLE 5. *Prevalence (by sex) of occlusive arterial disease in diabetics and nondiabetics aged 30 years and over*

Age-group years	*Diabetics (146), %*			*Nondiabetics (105), %*		
	M	*F*	*Total*	*M*	*F*	*Total*
30 to 39	35.7	18.2	28.0	8.8	14.3	11.3
40 to 49	37.3	14.8	25.9	38.1	43.7	40.5
50 to 59	51.4	60.4	56.6	33.3	51.3	41.1
60 to 69	52.5	73.9	63.6	44.8	58.8	50.0
70 to 79	80.0	84.6	82.6	66.6	—	66.6
80 and over	66.6	100.0	75.0	—	—	—

TABLE 6. *Prevalence by sex of PVD in diabetics and nondiabetics aged 30 years and over*

Age-group years	Diabetics, %		Nondiabetics, %	
	M	F	M	F
30 to 39	21.4	9.1	5.8	7.1
40 to 49	18.5	7.4	16.6	12.5
50 to 59	37.1	25.0	15.7	15.4
60 to 69	30.9	24.0	20.7	11.7
70 to 79	80.0	38.5	16.6	—
80 and over	—	—	—	—
Total prevalence	31.2	21.9	14.9	12.1

TABLE 7. *Variations in prevalence of occlusive arterial disease in diabetics (all ages) with changes in 2-hr blood glucose after a glucose load*

2-hr blood glucose mg%	Arterial disease No. cases	No arterial disease No. cases	Total prevalence	
			No. cases	%
100 to 139	34	43	77	44.2
140 to 179	26	29	55	47.3
180 to 219	23	20	43	53.5
220 to 259	25	15	40	62.5
260 to 299	16	14	30	53.3
300 and over	23	15	38	60.5

TABLE 8. *Variations in prevalence of occlusive arterial disease in diabetics (all ages) with activity*

Degree of activity	Arterial disease No. cases	No arterial disease No. cases	Total prevalence	
			No. cases	%
Sedentary	57	35	92	61.6
Moderate	80	91	171	46.8
Intense	10	10	20	50.0
TOTAL	147	136	283	51.9

TABLE 9. *Variations in prevalence of occlusive arterial disease with duration of diabetes (known, all ages)*

Duration of diabetes years	Arterial disease No. cases	No arterial disease No. cases	Total prevalence	
			No. cases	%
< 1	1	1	2	50.0
1 to 5	33	26	59	55.9
6 to 10	21	16	37	56.8
11 to 20	18	11	29	62.1
> 20	7	4	11	63.6
TOTAL	80	58	138	58.0

the preponderance in males was still present, but to a lesser extent.

Other arterial affections, e.g. CVD, CAD and DH, after the age of 50 years were definitely more prevalent in females; before that age, CAD and DH prevailed in males and CVD in female diabetics. Their overall prevalence rose with advancing age in both sexes. The prevalence in control subjects was smaller and it rose less steeply and less regularly with advancing age; the higher prevalence in females after the menopause was less constant or absent.

The salient biochemical feature of diabetes is hyperglycemia. Nevertheless, opinions in the literature differ on the etiopathogenetic importance of the high blood glucose level in atherosclerosis (2–4). It was, therefore, desirable to correlate the 2-hr blood glucose level following glucose load with the incidence of arterial disease in diabetes. Table 7 shows that a slow, progressive rise in prevalence of arterial complications was present with rising 2-hr blood glucose levels to 259 mg%; no significant further rise was apparent with higher glucose levels. Analysis of the prevalence of arterial disease at various 2-hr blood glucose levels showed no definite preponderance of either sex.

The effect of physical activity entailed by the occupation of diabetic subjects detected in the survey on the prevalence of occlusive arterial disease is shown in Table 8. Sedentary workers were found to have the highest prevalence (61.6%).

The duration of diabetes is accepted as an important factor in the pathogenesis of microangiopathy. Its etiological importance in "large vessel" disease was studied in patients in whom the duration of the disease was

known (Table 9). The frequency of arterial disease increased slowly, but definitely, with the duration of the diabetes.

CONCLUSIONS

This study suggests that diabetes is associated with: a) a higher overall incidence of arterial disease; b) an earlier age-of-onset of atherosclerotic complications; c) a more rapid rise in prevalence of vascular complications with advancing age.

These phenomena are very well exemplified with respect to peripheral vascular disease. CVD, CAD and DH showed essentially similar, but (notably CAD and DH) quantitatively less marked differences from nondiabetics.

Among 146 diabetics affected by vascular complications, there was a definitely higher prevalence of arterial disease in males below the age of 50 and in females over this age. The prevalence of PVD was higher in males and of CVD higher in females throughout all age groups. CAD and DH conformed to the stated overall sex-distribution pattern. All (except PVD) were strikingly more frequent in postmenopausal female diabetics.

The prevalence of occlusive arterial disease in diabetics was higher in individuals with a sedentary occupation (61.6%) and rose definitely and progressively with an increasing (post-oral-glucose load) 2-hr blood glucose level and with increasing duration of the disease.

Having thus established that cardiovacular disease is not equally distributed between diabetics and nondiabetics, as would have been expected had the aging process or heredity alone been responsible for its pathogenesis, each of these factors is excluded as solely accountable for the increased prevalence of cardiovascular complications in diabetes. The distribution of obesity as survey-established in diabetics and nondiabetics of all ages in Malta is, alone, numerically insufficient to explain the difference in incidence of cardiovascular disease in the two categories. Similarly, hypertension was found to be associated with other cardiovascular complications in only an exiguous fraction (12.3%) of the total of affected diabetics and hence is also ruled out as the sole pathogenetic factor. Thus, while each of the factors mentioned may contribute to cardiovascular disease complicating diabetes, none alone could numerically account for the different prevalence of arterial disease between diabetics and nondiabetics. On the basis of this study it is concluded that the increased prevalence and other peculiarities of arterial disease in diabetes mellitus could only be the result of the diabetic state itself.

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