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EXTRAMURAL CORONARY ARTERY DISEASE IN TYPE I DIABETES MELLITUS: A QUANTITATIVE AUTOPSY STUDY[1]

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ABSTRACT. Extramural coronary arteries of 17 type I diabetics and 22 control patients were examined at necropsy following a detailed methodology plan. There was a greater extent of luminal narrowing in the extramural coronary arteries in the diabetic patients than in the controls. While it is known that in patients with the advanced stage of type I diabetes mellitus significant coronary atherosclerosis is likely to be present, it is new information that they have a propensity for obstructive atherosclerosis, not just in the 3 major coronary arteries but also in the branches. Young type I diabetics with atherosclerosis of proximal portions of the coronary vasculature are likely to have equally severe atherosclerosis in the distal portions and branches as well. Atherosclerosis was less severe in the diabetic patients who did receive hemodialysis and/or a renal transplant than those who did not.

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INTRODUCTION

Patients with type I (juvenile-onset, insulin-dependent) diabetes mellitus have a propensity for coronary atherosclerosis (Paz-Guavera et al. 1975, Scott 1975, Skyler 1981). Moreover, many of them are young when they reach the stage of the disease process in which coronary artery disease becomes clinically significant (Weinrauch 1978, Bennett et al. 1978). Because of the possibility of therapeutic intervention (viz., bypass surgery), it is important to know the degree and extent of the coronary arterial luminal narrowing in distal portions of the 3 major coronary arteries as well as in the diagonal, posterior descending, obtuse and other marginal branches. Hence, our specific aim was to

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examine the extramural coronary arteries in type I diabetics with the above in mind.

METHODS AND MATERIALS

PATIENT SELECTION. The patients studied included 17 with type I diabetes mellitus (as defined by The National Diabetes Group 1979) and 22 patients without known diabetes mellitus. All subjects died of natural causes at the University of Cincinnati Hospital, Cincinnati, Ohio, from 1975 through 1981.

The diabetic patients had all been diagnosed and/or treated at the University of Cincinnati Medical Center. Average age at onset of diabetes was 13 ±1.5 years. Duration of the diabetic state was 23 ±2 years. Eight of the diabetic subjects were female, and 9 were male. Their mean age was 36 ±2 years. Mild hypertension (average systolic pressures of 140–160 mmHg; average diastolic pressures of 90–100 mmHg) was present in 14 of the 17 diabetics. Fifteen experienced renal failure; 11 underwent dialysis, and 5 of those had received a renal transplant. The causes of death occurring singly or in combination were: metabolic disturbance related to renal failure in 9 diabetics, infection in 8, and cardiovascular disease in 11. All diabetics had a morphologic diagnosis of diabetic nephropathy established either premortem or at necropsy.

Of the 22 patients without diabetes mellitus, 13 were female and 9 were male. Their mean age was 35 ±2 years. Seven patients had moderate or severe hypertension (diastolic pressures above 120 mmHg). Causes of death included sepsis in 12 (with renal failure in one), coagulopathy in one, respiratory failure in one, hepatic failure in one, renal failure in one, and intracerebral hemorrhage and bronchopneumonia in 6. Underlying disease processes were malignancy, liver disease, central nervous system disease, infection, asthma, and hypertension.

Optimal controls would have had uremia, dialysis, and transplantation without type I diabetes. Due to clinical success in managing young subjects with uremia, no such control group was available.

PATHOLOGIC EXAMINATION OF CORONARY ARTERIES. The entire extramural coronary arterial tree was dissected free from the epicardium as far as possible and fixed (10% buffered formalin), decalcified (if necessary), dehydrated, and blocked in paraffin according to standard methods. The schematic diagrams in figs. 1 and 2 are representative of the method by which the coronary arteries were examined in each case. The entire length of coronary artery was transsected at 5–mm intervals. A minimum of 3 histologic sections (each 6 μm thick) were made and usually obtained from the middle one-third of each 5–mm segment. Hematoxylin and eosin, Masson trichrome, and Movat stains were carried out on the histologic sections from each 5–mm segment. The latter stain was used to facilitate identification of structural components of the vessel wall, including the internal elastic lamina (Movat 1955).

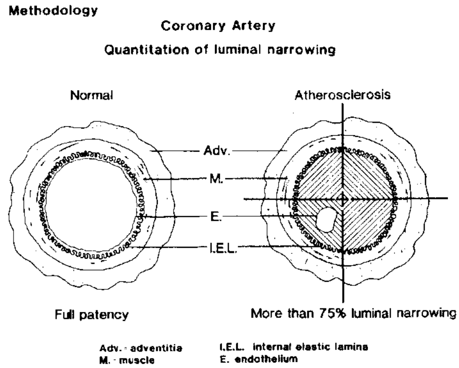

FIGURE 1. The evaluation of degree of luminal narrowing by atherosclerosis can be facilitated by imaginary division of the circular area outlined by the internal elastic lamina (I.E.L.) into 4 equal parts. The right side of the diagram depicts an atherosclerotic artery with more than 75% luminal narrowing.

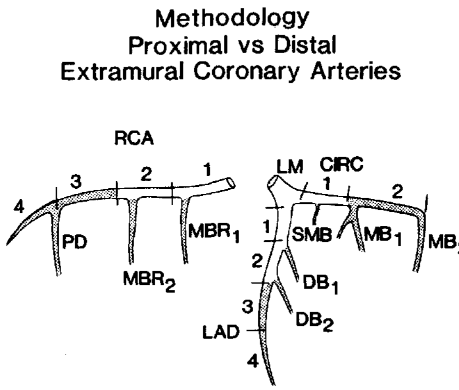

FIGURE 2. The unshaded portion of coronary artery, which is designated as "proximal" in the text, consists of: left main coronary artery, the proximal one-half of the anterior descending and circumflex artery, and the proximal two-thirds of the right coronary artery from its origin until the takeoff of the posterior descending branch. The shaded portion, which is designated as "distal" in the text, consists of all segments beyond the "proximal" portion and all branches originating from the 3 major coronary arteries. CIRC = circumflex artery; MBR = marginal branch of RCA; DB = diagonal branch; PD = posterior descending branch; LAD = anterior descending branch; RCA = right coronary artery; LM = left main coronary artery; SMB = small marginal branch; MB = marginal branch.

The cross sectional area of luminal narrowing (of each histologic section) of each 5–mm arterial segment was quantitated according to a well-established methodology (Crall and Roberts 1978, Roberts and Virmani 1979) explained in fig. 1. Two persons, who had no prior knowledge as to which group of patients the sections belonged, each performed the measurements with light microscopy. A segment was considered to be more than 50% narrowed or more than 75% narrowed if both observers concurred that the mean of the measurements from the 3 histological sections of that segment was more than 50% or 75%, respectively. As shown in fig. 2, length of proximal narrowing was determined by summing the involved segments of the left main coronary artery and the proximal parts of the 3 major coronary arteries. Likewise, length of distal narrowing was determined by summing the involved segments of the distal parts and branches of the 3 major coronary arteries. Although this is a modification from the one used by Crall and Roberts (1978), this methodology was designed taking into consideration that these distal vessels frequently serve as anastomotic sites when bypass procedures are performed to circumvent severe luminal narrowing in the left main and/or proximal portions of the 3 major coronary arteries.

Statistical examination of the data was by analysis of variance and covariance except where noted otherwise.

RESULTS

Diabetic subjects showed a greater extent of luminal narrowing than did non-diabetic subjects. Using the criterion of >50% narrowing, the percentages of vessel lengths narrowed proximally and distally in the diabetics vs. non-diabetics, respectively, were: proximal 40.2 ±7.3 vs. 9.6 ±3.5 ($p < .002$) and distal 41.9 ±7.1 vs. 3.8 ±1.8 ($p < .001$). See also fig. 3. For >75% occlusion (fig. 4), more of the diabetic vasculature was similarly involved: proximal 23.6 ±5.9 vs. .9 ±.6 ($p < .002$) and distal 26.2 ±5.9 vs. 1.1 ±.6 ($p < .001$). There was an apparent increase in extent of narrowing in proximal segments from the hypertensive subpopulation of non-diabetics, but the difference was insignificant at the .05 probability level. Due to physiologic aging, not atherosclerosis, the normal intima may thicken, but this accounts for less than 20% narrowing of the original lumen.

By 2-sample rank testing for unpaired measurements, a greater percentage of distal narrowing was present in those 6 diabetic subjects who had received neither dialysis nor renal transplantation ($p < .01$) than the 11 diabetics undergoing dialysis/ transplantation.

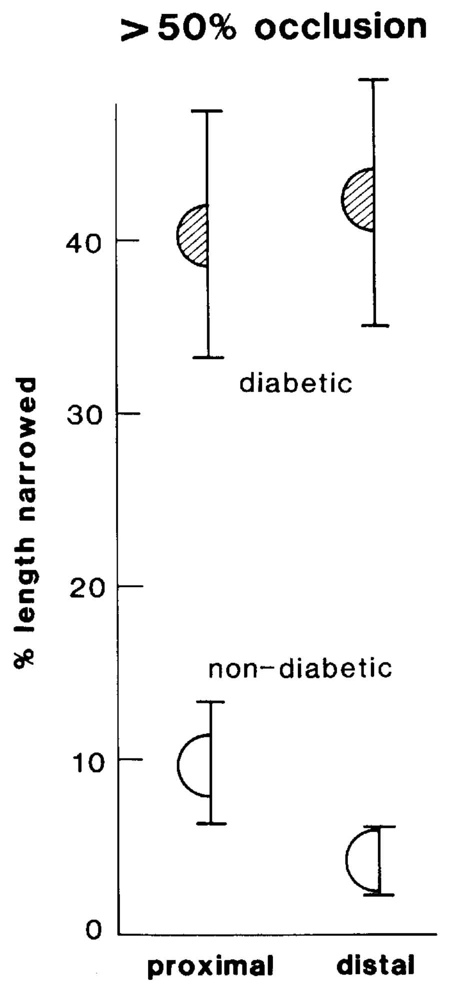

FIGURE 3. Mean ±SD (bar) percentages of vessel lengths narrowed >50% (half circle) proximally and distally in diabetics vs. non-diabetics, $p < .002$ for comparison of proximal vessel narrowing, $p < .001$ for comparison with distal vessel narrowing, diabetics vs. non-diabetics.

Narrowing of proximal segments of the coronary arteries was significantly associated with narrowing of their branches and distal segments of the 3 major ones in the diabetic subjects; the correlation coefficient for >50% occlusion was .79, significantly greater than 0 ($p < .001$). Correlation of proximal percentage length with distal (including the branches) percentage length for the >75% occlusion criterion was .81 ($p < .001$). The correla-

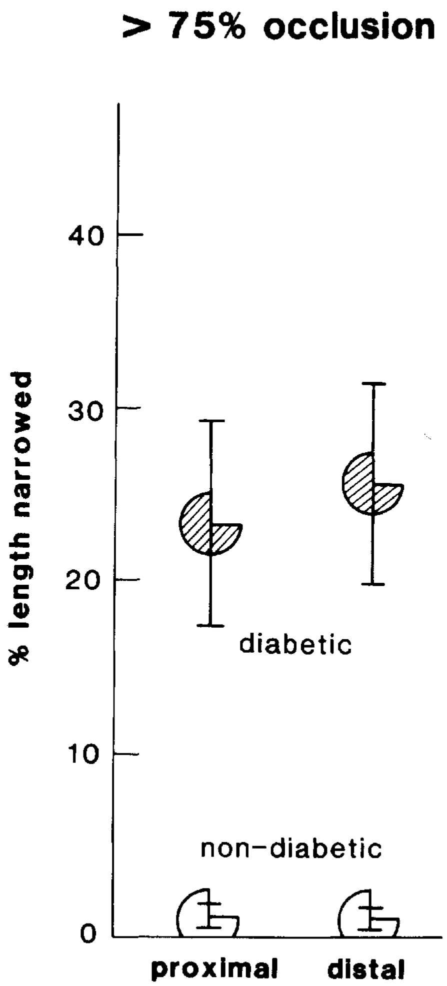

FIGURE 4. Mean ±SD (bar) percentages of vessel lengths narrowed >75% proximally and distally in diabetics vs. non-diabetics, $p < .002$ for comparison of proximal vessel narrowing, $p < .001$ for comparison of distal vessel narrowing, diabetics vs. non-diabetics.

tion coefficient of proximal at >50% with distal at >75% was .80 ($p < .001$).

The correlation of duration of diabetes with distal occlusion at >75% was .71 ($p < 0.01$).

Figs. 5, 6 and 7 are examples of coronary artery morphology found in the different groups of patients studied. Following our methodology, the characteristics of the atherosclerotic process did not appear different in diabetics compared to those of the other patients. In other words, by viewing an unknown histologic section of coronary artery, we could not determine from the morphology of atherosclerosis whether the section was that of a diabetic or not. While our specific aim was directed mainly towards extramural coronary artery disease, the morphology of the intramural vessels was similar to that described by Ledet (1976).

DISCUSSION

Methodologies used to examine coronary arteries of diabetics at necropsy differ significantly among authors (Crall et al. 1978, Ledet 1976, Factor et al. 1980, Waller et al. 1980, Vigorita et al. 1980). However, none of these included the quantitation of all the branches (e.g. diagonal and marginal) which are in continuity with the 3 major ones. Our results are therefore of special significance, as they emphasize and reinforce the propensity for distal vessel disease in type I diabetes.

Dortimer et al. (1978) concluded from their angiographic studies that diabetic patients had statistically a similar number of diffusely diseased vessels as controls (28% vs. 22%). Chychota et al. (1973) studied myocardial revascularization in diabetic and non-diabetic patients. However, 90% of their patients had adult onset diabetes. While the mean luminal diameter of grafted coronary arteries was similar in their 2 groups of patients, there was a statistically significant difference in mean blood flow through the grafted arteries. This suggested to them some difference, either qualitatively or quantitatively, in the distal vascular tree or microvascular bed. They thought that it was due to arteriosclerosis being more diffuse in diabetic subjects. This was supported by their findings in a double-blind study of coronary angiographic lesions in subjects with diabetes and age- and sex-matched control subjects, which showed that diabetic individuals have both a greater number and more severe atheromatous lesions in medium- to smaller-sized coronary vessels.

FIGURE 5. Proximal (A) and distal (B) anterior descending coronary artery of non-diabetic patient with a clinically normal heart. Movat stain (magnification ×12.04).

Weinrauch et al. (1978) and Bennett et al. (1978) performed coronary angiograms in patients with type I diabetes (mean age 32) with end-stage renal disease before renal transplantation was to be performed. They found significant coronary arteriopathy which was asymptomatic. Moreover, these patients had a poor postoperative survival. According to these investigators, it was not apparent whether these patients had significant "distal" disease and, if so, whether such could have been adequately visualized at all by coronary angiogram. According to the results of our necropsy study, however, patients with a considerable extent of >75% narrowing proximally most likely also had a correspondingly great percentage of length with more than 75% narrowing in the distal portions of the 3 major coronary arteries, as well as in the branches.

Of the 17 type I diabetic subjects, 15 had uremia, with 11 undergoing dialysis and 5 of these 11 had renal transplants, the ultimate atherosclerotic lesions might represent not only those related to type I diabetes, but also those related to uremia (Bagdade et al. 1968, Freidman et al. 1974), uremia and dialysis (Burke et al. 1978, Lowrie et al. 1974, Lindner et al. 1974, Ibels et al. 1977), and to transplantation (Ibels et al. 1977). Indeed, it would be impossible to dissect out the relative contributions of all of the atherogenic precursors in these type I diabetics. It has been shown that diabetics who have undergone dialysis and/or renal transplantation have a greater propensity for coronary atherosclerosis than do non-diabetics who have undergone the same treatment (Najarian et al. 1977). In this collection of patients, however, diabetics who under-

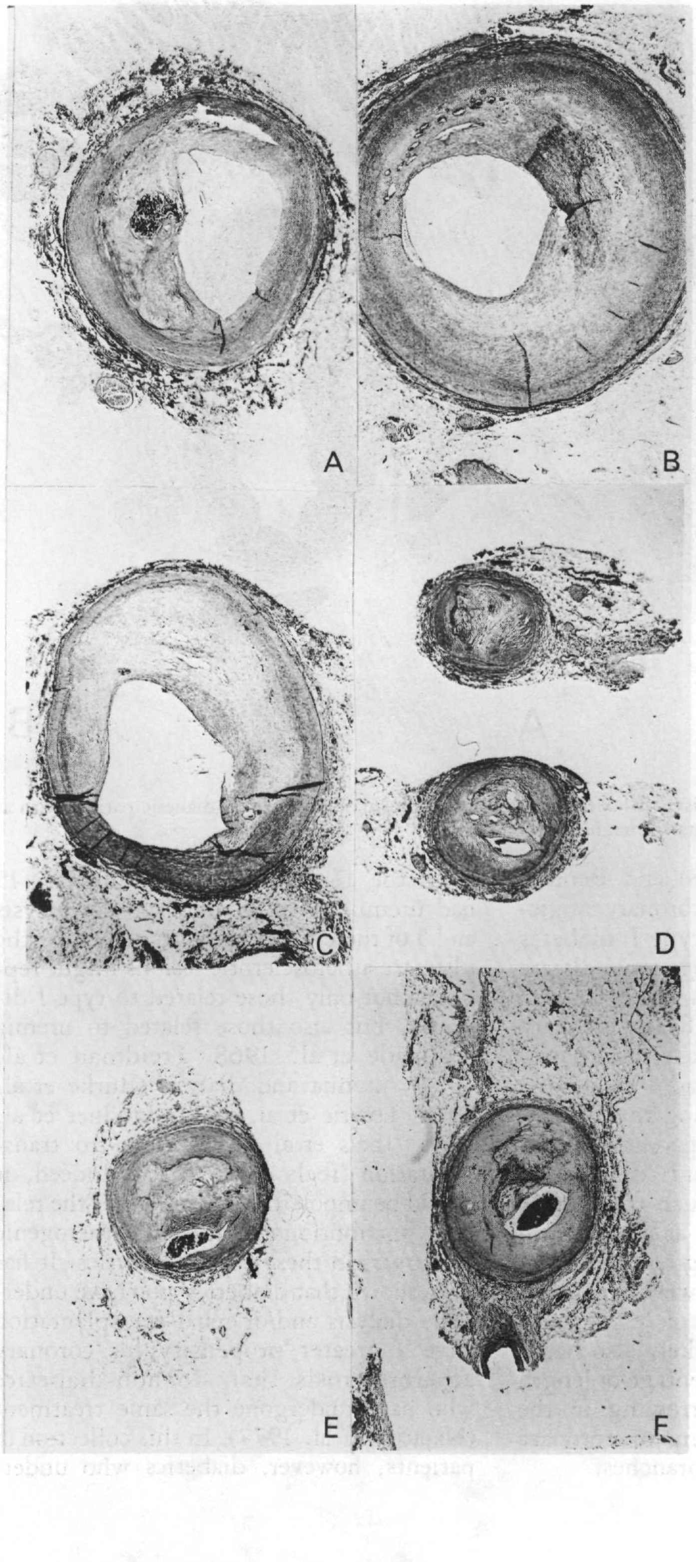

FIGURE 6. Proximal (A, B, C) and distal (D, E, F) coronary arteries of a patient with type I diabetes mellitus showing severe proximal as well as distal luminal narrowing by atherosclerosis. Movat stain (magnification ×7.7). A = RCA_1; B = LAD_1; C = $CIRC_1$; D = $CIRC_3$; E = RCA_4; F = LAD_{-4} (see fig. 1 for identification of localization).

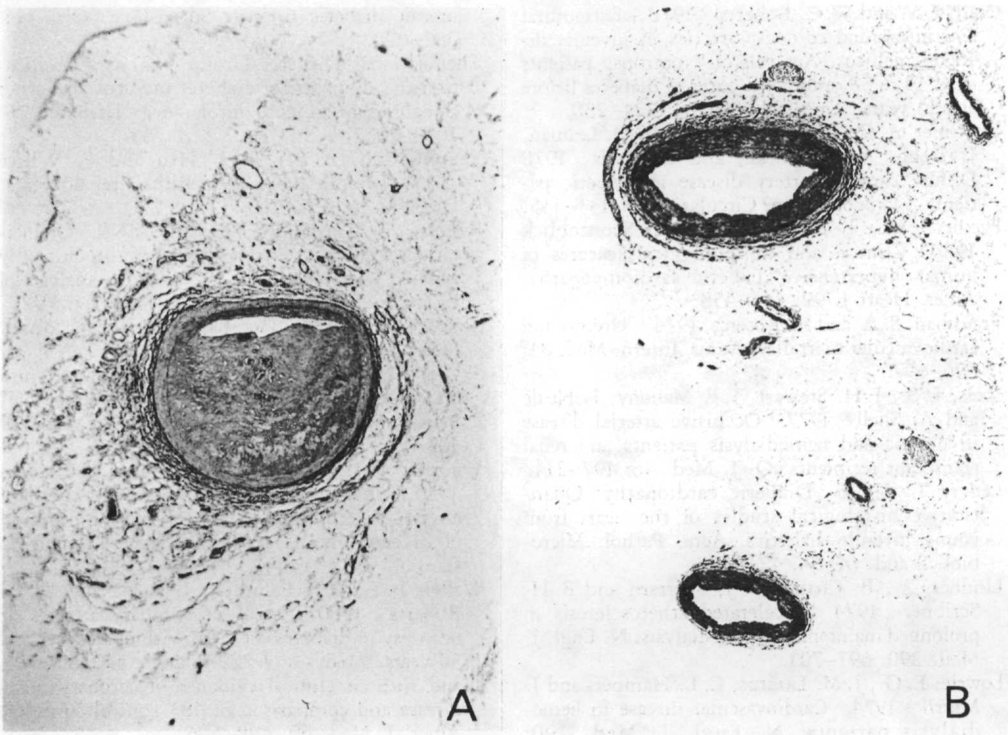

FIGURE 7. Diagonal branch of a patient with type I diabetes mellitus (A) compared to that of a hypertensive patient (B). Movat stain (magnification ×11.76).

went dialysis and/or renal transplantation had a lesser propensity for distal coronary atherosclerosis than did diabetics who had not received such treatment. Thus, severe distal coronary artery disease occurring in this group of diabetics cannot be accounted for by the presence of dialysis and transplantation which, by themselves, are considered to be associated with accelerated atherogenesis. Within this frame of reference, our study allows an examination of the pathologic anatomy of type I diabetics' coronary arteries, with the commonly superimposed clinical complications of renal failure and its sequellae, including dialysis and transplant. As such, it should have considerable clinical pertinence for dealing with such patients.

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