Diffuse Coronary Artery Disease in Diabetic Patients

Fact or Fiction?

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SUMMARY To compare angiographically-determined coronary artery disease in diabetic patients with controls, 1,653 patients coming to cardiac catheterization were reviewed retrospectively to find 37 diabetic and 79 control patients matched for sex, age (± 3 years), and risk factors (hypertension, hyperlipidemia, and smoking). The severity of coronary artery disease was assessed using an angiographic grading system. The following results were obtained: 16 of 37 diabetic patients (43%) had three-vessel disease compared to 20 of 79 controls (25%). Seventy-six of 111 (68%) diabetic vessels were diseased compared to 110 of 237 control vessels (46%) (P < 0.005). The total coronary score reflecting total extent of disease for diabetic patients was 371 (mean 10.0 ± 1.0 (SEM)) compared to 594 for controls (mean 7.5 ± 0.7, P < 0.01). Diabetic patients had a statistically similar number of diffusely diseased vessels as controls (28% vs 22%). There were only three of 76 diabetic vessels (4%) considered inoperable compared to seven of 110 (6%) control vessels. We conclude that diabetic patients with chest pain have more coronary artery disease than nondiabetics, but no more diffuse or inoperable disease.

MEDICAL OPINION PRESENTLY SUGGESTS that diabetic patients with coronary artery disease (CAD) are likely to have diffusely diseased inoperable vessels. However, a recent study claims that diabetic and non-diabetic patients coming to aortocoronary bypass surgery have similar angiographic findings in their coronary arteries and similar operative results. Since this was a surgical series, certain factors may have selectively eliminated those diabetic patients thought to be inoperable by angiographic criteria. No other detailed angiographic studies have been performed to determine whether or not diabetic patients with CAD do indeed have more diffuse disease of their coronary vessels than nondiabetic patients with CAD. The purpose of our case control study was to retrospectively analyze coronary angiograms of diabetic and carefully matched (age, sex, and risk factors) nondiabetic subjects undergoing cardiac catheterization to determine if there are differences in the severity and distribution of CAD found in both groups.

Methods

The plan of the study was to identify by chart analysis all diabetic patients undergoing cardiac catheterization at the Hershey Medical Center, for whatever reasons, over the period 1971–1976. Two controls for each subject were sought, based on the criteria detailed below, before any catheterization findings were reviewed. A total of 1,653 patients were reviewed to find 43 diabetic patients and 81 nondiabetic controls; for five diabetic subjects, only one control could be identified. Six diabetic patients and two control patients were excluded because they had not undergone coronary angiography. Thus, seven diabetic subjects still had one control after this process and thirty had two controls. Since analysis of the coronary angiograms was done without knowledge of the diabetic status of the subject, we did not initially eliminate the controls who were matched with the excluded diabetic subjects for fear that it would bias our results. We did, however, go back to the data to determine what changes, if any, the elimination of these subjects would make. In fact, no significant changes in the data were noted during this latter analysis.

All 37 diabetic patients were matched with at least one control for age (± three years), sex and high or low risk factor status. Criteria for selection of a subject as a diabetic patient was the established clinical diagnosis of diabetes plus treatment with insulin or oral hypoglycemic agents, or at least two random fasting blood glucose levels greater than 150 mg%. Control subjects did not fulfill these criteria. Of the 37 diabetics, 25 were on oral drugs, seven were insulin-dependent, and five were diet controlled. The age range of the diabetic group was 36 to 71 years (mean 56 years); for the control group the range was 37 to 69 years (mean 54 years). Controls were matched with diabetic subjects for high or low risk factor status. High risk was defined as the presence of two of the following risk factors: smoking, hyperlipidemia, and hypertension. Smoking was defined as more than ten cigarettes per day at the time of study; hyperlipidemia was defined as a fasting cholesterol level greater than 250 mg%, and/or a fasting triglyceride level greater than 180 mg%. Hypertension was defined as two random resting blood pressure recordings with systolic greater than 150 mm Hg and diastolic greater than 90 mm Hg.

Coronary arteriograms were performed by the Sones or Judkins techniques using a six-inch cesium iodide image intensifier; injections were filmed in multiple views and recorded on 35 or 70 mm film. A scoring system to determine the severity of coronary artery disease was devised (fig. 1). Severity of lesions were graded 0 — no disease; 1 — intimal disease to less than 50% stenosis; 2 — 50 to 69% stenosis; 3 — 70 to 95% stenosis; 4 — 96–99% or subtotal occlusion; and 5 — totally occluded. The maximum score for any vessel was the sum of the score of all diseased segments. For example, a totally occluded RCA (four segments) would warrant a score of 20 (see below). CAD
was considered to involve a vessel diffusely if three of five segments of the left anterior descending artery were considered to have a significant stenosis (70% or greater, grades 3–5); if three of five segments of the left dominant circumflex coronary artery were graded 3 to 5; if two of four segments of the left nondominant circumflex artery were graded 3 to 5; or if two of four segments of the right dominant right coronary artery were graded 3 to 5.

An additional analysis was performed to evaluate the extent of coronary disease in these subjects. We could not match diabetic with control subjects for the number of vessels diseased in order to determine if the extent of disease in a single vessel was greater or less in one group or the other. In fact such a matching would have been inappropriate since we were trying to determine if diabetics did indeed have more vessels diseased than nondiabetic controls. We did, however, analyze for the number of segments per vessel that were significantly stenotic (grade 3 to 5) and the results for each group are reported below. In a vessel considered significantly stenotic (grade 3 to 5), a crude clinical assessment was made as to whether it was considered suitable or unsuitable for coronary artery bypass grafting, i.e., whether there was an adequate distal vessel in terms of size and distal runoff and whether it was free of other significant disease. The angiograms of diabetic patients and their controls were interpreted in a blinded fashion by three separate trained observers. Statistical analysis of data was performed using the Chi square test without Yates correction.

**Results**

**Extent of Coronary Artery Disease**

No significant differences were noted in the presence of normal vessels or of one, two or three-vessel CAD between normal and diabetic patients (fig. 2). Although the number of diabetic patients with three-vessel coronary artery disease (16/37, 43%) was larger than control patients with comparable disease (20/79, 25%), the difference was not significant (fig. 2D). Of 111 total vessels in the diabetic groups, 76 (68%) were diseased compared to 110 of 237 vessels (46%) in the control group ($P < 0.005$) (fig. 3A). Thus, the mean coronary score per patient was $10 \pm 1.0$ (SEM) per diabetic patient and $7.5 \pm 0.7$ per control patient ($P < 0.01$) (fig. 3B). In the diabetic subjects there were 82 segments with
grade three or greater stenosis or 2.2 segments/subject, whereas in the control group there were 128 segments or 1.6 segments/subject ($P < 0.02$).

**Extent of Diffuse Coronary Artery Disease**

Of the 37 diabetic patients, none had three-vessel diffuse coronary artery disease, while five had two vessels diffusely diseased, and seven had one vessel diffusely diseased. Of the 79 control patients, none had three-vessel diffuse disease, while four had two vessels diffusely diseased and 23 had one vessel diffusely diseased. Of 76 diseased vessels in the diabetic group, 17 (22%) were diffusely diseased, according to our criteria. Of 110 diseased vessels in the control group, 31 (28%) were diffusely diseased (fig. 4). Of 76 diseased vessels in the diabetic group, three (4%) were considered inoperable by our clinical criteria, including state of distal vessel, luminal diameter, and extent of distal involvement. Of 110 diseased vessels in the control group, seven (6%) were considered inoperable. Finally, of the 33 diabetic patients with CAD, 19 (58%) had at least one system of collaterals supplying occluded vessels. Of the 58 control patients with CAD, 24 (41%) had collaterals. These differences were not significant.

**Discussion**

The estimated prevalence of overt diabetes mellitus in the United States is nearly five million. Numerous autopsy and clinical studies have attested to the frequency of coronary artery disease in patients with diabetes mellitus. Coronary artery disease accounts for more than half of the 300,000 deaths in diabetic subjects in whom the onset of the disease occurs after age 20. Numerous diabetic patients are referred for coronary angiography to determine if they are candidates for aortic coronary bypass grafting for the treatment of refractory angina pectoris. If such diabetic patients have more diffusely diseased vessels, one might consider them to be poorer surgical candidates since their distal runoff would be poor. Therefore, one might be reluctant to consider them for heart catheterization.

We analyzed our population of diabetic patients coming to heart catheterization to determine if they have more diffuse disease of their vessels on coronary angiography than a carefully matched control group. The selection of an adequate control group with which to compare our diabetic subjects was most important since there are a number of risk factors associated with a high prevalence of coronary atherosclerosis. Perhaps the single most important factor is age. Because of the youth of certain members of our diabetic population, the finding of two age-matched controls (± 3 years) for each subject proved to be the most difficult aspect of the matching process, especially when it was necessary to identify a young woman control. Besides age and sex, our control subjects were also matched for high or low risk on the basis of the three most common alterable risk factors, cigarette smoking, hyperlipidemia, and hypertension. The presence of two of these constituted high risk. Every diabetic patient had one control identified; most had two. It is interesting to note that in our angina patients we found a significant increase of coronary artery disease in diabetic subjects compared with control subjects. Only 11% of the diabetic patients had normal vessels, whereas 27% of the control group were free of coronary atherosclerosis (fig. 2A). Sixty-eight percent of the diabetic vessels had a hemodynamically significant stenosis (greater than 70%) as compared to 46% of the vessels in the control population (fig. 3A) and the coronary score was 25% higher in the diabetic group (fig. 3B).

Certain diabetic vascular lesions are well known. Diabetic patients have been shown to have specific microangiopathy morphologically, characterized by thickening of the basement membrane with periodic-acid Shiff positive material in capillaries of skeletal muscle, glomerulus, and retina. It may be that diabetic microangiopathy gives rise to sludging and sequestration of formed elements of blood. Microplethysmographic studies have shown decreased digital vascular circulation in young diabetic subjects. Recently, fibrinolytic activity also has been shown to be decreased and platelet adhesiveness abnormally enhanced in a diabetic subject compared to a nondiabetic subject. Such findings might predispose the diabetic patient to atherosclerosis independent of other major risk factors.

This suggestion concurs with our results and with the study of Pell et al. which concluded that hyperglycemia per se was an independent risk factor in a risk factor-controlled comparative study of mortality in diabetic patients. Similarly, Epstein concluded that hyperglycemia was an independent risk factor in the development of arterial dis-
ease in diabetic subjects. However, a recent abstract has suggested that subjects with an abnormal glucose tolerance test but not overt diabetes mellitus have no more coronary artery disease than control subjects.\textsuperscript{14} This does not dispute our results, since all of our patients were overt diabetics and most were being treated with either insulin or oral agents.

The number of segments/vessel with significant disease was greater in the diabetic group (2.2) than in the control group (1.6). Although this result is statistically significant ($P < 0.02$) it is not clinically significant in terms of surgical management. Thus, we developed more stringent criteria for diffuse coronary disease (3 of 5 LAD segments, 2 of 4 RCA or LCF segments). There were no more diffuse disease or inoperable vessels in diabetic subjects (28\%) than in non-diabetic subjects (22\%) (fig. 4). Therefore, according to the most widely used criteria to determine operability of a vessel (i.e., the presence of an adequate distal vessel), our diabetic subjects would be considered just as operable as our control group. We recognize the limitations of coronary angiographic techniques in evaluating the small coronary vessels. Certainly, if diabetic patients had small vessel disease, this might limit runoff and lead to lower coronary graft flows, even though the distal coronary circulation looked adequate on angiography. In fact, a comparative study of diabetic vein graft flows by Chychota et al.\textsuperscript{15} revealed a statistically significant reduction of graft flow in diabetic patients compared with control subjects. Verska et al.,\textsuperscript{3} however, found no difference between flows in diabetic grafts compared to control grafts, a finding which would support our own findings of a similar prevalence of diffuse disease in both groups.

Of course, other factors might also preclude a successful bypass procedure in diabetic subjects. Their problems with wound healing, infections, and cerebral and peripheral vascular disease would need to be evaluated when considering the diabetic patient with angina for coronary angiography as a prelude to coronary artery bypass surgery.

We do not consider that the diabetic patient has any more diffuse coronary disease than the nondiabetic patients. The diabetic patient does have a greater likelihood of having more coronary vessels involved in the atherosclerotic process and may need more extensive grafting. Thus, we have no hesitation at the present time in recommending that diabetic patients who have symptomatic coronary artery disease should be considered for angiographic evaluation and aortocoronary bypass in the same manner as nondiabetic patients.

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