Changes in Basement Membrane Thickening and Pulse Volume Concomitant with Improved Glucose Control and Exercise in Patients with Insulin-dependent Diabetes Mellitus

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Ten patients with type I diabetes mellitus were enrolled in a program of exercise and carbohydrate "control" using self-monitored glucose determinations and self-adjusted insulin. Glucose control was improved for the group, although normoglycemia was not uniformly achieved. Pulse volume measurements performed at the onset and after 8–10 mo documented a drop in systolic arm blood pressure with increases in the ankle-arm index ($P < 0.001$). Quadriceps biopsy was successfully performed at the beginning and after 8–10 mo for analysis of basement membrane thickening (BMT) in seven patients. Six patients showed a decrease in basement thickening on rebiopsy ($P = 0.02$). One patient showed increased BMT. This was the only patient to maintain a mean hemoglobin A_{1c} of greater than 10% for the duration of the study. These observations indicate that abnormalities of BMT and pulse volume recordings may be more labile measurements than previously thought and may be amenable to therapeutic intervention. The relationship of these variables to the severe micro- and macrovascular sequelae of diabetes mellitus remains to be established. DIABETES CARE 3: 586–589, SEPTEMBER–OCTOBER 1980.

Recent studies in patients with diabetes mellitus have documented that certain phenomena associated with hyperglycemia are reversible if the hyperglycemia is corrected, determined by serial measurements of blood glucose and minor hemoglobin levels.[1–5] Reversible sequelae documented to date include abnormalities in cholesterol and triglyceride levels, red cell survival, white cell adherence, platelet hyperaggregation and hormonal profiles including growth hormone in type I diabetic individuals, and the hormonal profile of pregnancy in pregnant diabetic women. Reduced fibrinogen survival suggestive of a fibrinocoagulopathy has also been shown to return to normal when diabetic patients are made normoglycemic.

Pathologic involvement of the clotting system involving the platelet and fibrinogen kinetics as well as lipid abnormalities have been implicated as risk factors in the development of vascular disease.[6–8] The observation that abnormalities involving lipids, platelets, and fibrinogen turnover reverse when hyperglycemia is corrected in individuals with diabetes mellitus would imply that vascular abnormalities also might be prevented or reversed. However, these phenomena are at best risk factors for vascular disease. On the other hand, a protocol to evaluate microvascular disease (e.g., retinopathy) or macrovascular disease (e.g., cerebro- and cardiovascular events) as a function of carbohydrate control is difficult to assess over a short time span in a small number of patients.

Muscle capillary basement membrane thickening (BMT) has been identified as a microvascular change associated with diabetes mellitus, although the relationship of this change to retinal or kidney disease remains controversial.[9,10] Pulse volume recordings have been shown to be a reliable means of documenting large vessel disease in the peripheral arteries,[11] but the technology has not been applied prospectively to patients with type I diabetes.

To more accurately assess the utility of these measurements and the role of treatment programs in influencing the progression of vascular disease in diabetic patients, measurements of muscle capillary BMT and pulse volume recordings were performed serially in a group of type I diabetic patients. They participated in a program of home monitoring and exercise to improve diabetic control.

PATIENTS AND METHODS

Patients were referred by their local physicians, generally for problems in management. The mean age of the group at the onset of the study was 25 yr, with a mean duration of diabetes of 10 yr. The patient population and the method of im-

proving glucose levels in this group has been described elsewhere.[4] The program involved patient-monitored glucose determinations with split-dose insulin and insulin adjustment by the patients based on their glucose readings. In addition, the patients underwent an exercise regimen, which consisted of training three times per week with a trainer and included a general format of at least a 35-min exercise session. The exercise session was divided into a 5-min period of warm-up and stretching, a 15-min period on an odometer bicycle or similar equipment, and a 15-min period using equipment designed to exercise specific muscle groups with a graded resistence. Bike intervals were graded by gradually increasing workload and increasing the work-to-rest ratio to maintain the heart rate at 70% of a patient's maximum.

Hemoglobin A_{1c} (HbA_{1c}) concentrations were measured by radioimmunoassay.[12] Biopsy specimens of the anterior quadriceps were obtained from the right quadriceps 8 cm below the anterior superior iliac crest in the mid-thigh. Specimens were processed according to the method of Kilo and Williamson as modified by Esterly et al.[10,13,14]

Pulse volume recordings were obtained using a Life Science instrument as described by Darling et al.[15] Position and pressures were standardized for each patient and exercise was produced using an electric treadmill at a 10% grade with the patient walking 2¼-miles per hour. This exercise was continued until symptoms occurred or for 5 min. Immediately after exercise, pulse volume recordings and pressures were measured at the ankle level and were compared with resting values. A preprogrammed module for paired samples and bivariate analysis of variance (Texas Instruments Model 58/59) were used for statistical evaluation.

RESULTS

As can be seen from Figure 1, glucose "control" was improved in the group as reflected by HbA_{1c} values and mean blood glucose values, although normoglycemia was not achieved. All patients participated in the exercise program except for patient #6, who participated for about 1 mo, and patient #10, who was in the exercise program for 4 mo. All other patients maintained an exercise program at least 3 days per week as described.

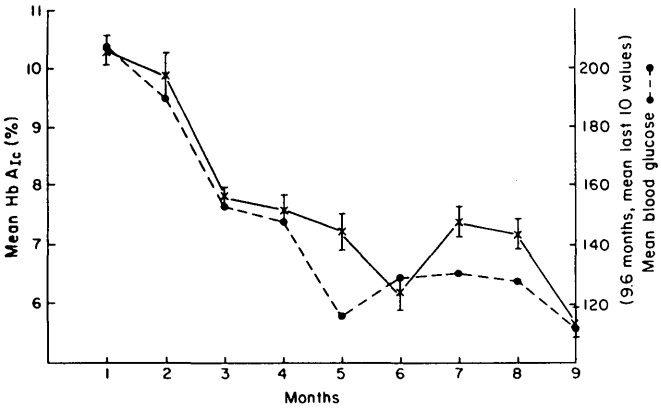

FIG. 1. Mean HbA_{1c} measurements ± SEM (normal < 6%) and blood glucose values in the group during the period of study.

The pulse volume recordings obtained in the patients are shown in Table 1. As reported previously, systolic arm blood pressure decreased somewhat for the patients participating in the study.[4] A more striking change was the difference in the ankle-arm index ($P < 0.001$). This measurement represents the ratio of the pressure in the lower extremity measured at the ankle to that measured at the arm. In each case, there was an increase in this ratio, which implies relative increased blood flow to the lower extremities. It is of note that patient #6, who did not participate in the exercise program, showed the least improvement in this particular variable and was the only patient who smoked cigarettes. Increase in the ankle-arm index was accompanied by an increase in ankle pressure. It is noteworthy that this change in the ankle-arm index occurred with an actual decrease in the ankle pressure curve. In view of the pressure changes, it would appear unlikely that this decrease in the pressure curve reflects lack of flow, but might rather reflect increased vascular compliance. Metatarsal pressures improved slightly, but the difference was not significant, nor were the changes in metatarsal pressure curves or in the postexercise ankle pressure curves.

The changes in muscle biopsy capillary BMT in those patients who underwent satisfactory biopsy at the beginning and after 8–10 mo of the study are shown in Table 2. BMT decreased in all patients studied except patient #10. BMT increased in this patient, the only one to have the same HbA_{1c} determination at the beginning and end of the study and the only patient who maintained a mean HbA_{1c} of above 10%. If patient #10 is eliminated from the analysis, the difference in BMT at the beginning and the end of the study is statistically significant ($P = 0.02$).

DISCUSSION

The present study documents that a program of improved glucose control and exercise may influence the vascular status of patients with diabetes mellitus as reflected by BMT of quadriceps capillaries and by pulse volume recordings. The relative contribution of decreased glucose levels and exercise cannot be distinguished.

A decrease in BMT occurred even in the presence of elevated glucose and HbA_{1c} levels. However, improvement did not occur when there was no change in HbA_{1c} levels, as noted in patient #10, who also did not participate in the exercise program for 5 mo before rebiopsy. The data would indicate, moreover, that BMT may be a more labile measurement than was previously thought. The implications of these changes regarding other microvascular disease in diabetes remain to be established. For example, whether BMT of muscle capillaries reflects pathology in the kidney or eye remains controversial.

TABLE 1
Pulse volume recordings

Patient no.	Age (yr)	Resting ankle press curve (mm) Right Pre*	Right Post	Left Pre	Left Post	Ankle arm index Right Pre	Right Post	Left Pre	Left Post	Postexercise† ankle pressure (mm Hg) Right Pre	Right Post	Left Pre	Left Post	Resting ankle pressure (mm Hg) Right Pre	Right Post	Left Pre	Left Post
1 (M)	23	13	8	18	5	1.08	1.14	1.17	1.21	152	178	152	180	140	150	152	160
2 (F)	32	12	9	28	10	1.16	1.20	1.11	1.16	158	154	152	154	142	154	136	148
3 (M)	16	21	14	32	14	0.90	1.20	0.97	1.14	162	178	158	170	130	168	140	160
4 (F)	21	15	13	19	12	1.08	1.29	1.08	1.27	140	168	130	164	130	160	130	158
5 (F)	26	28	20	29	13	1.08	1.30	1.08	1.36	130	134	140	134	130	130	130	136
6 (F)	34	7	8	9	7	1.16	1.30	1.29	1.30	136	158	140	152	130	144	130	130
7 (F)	19	8	10	9	12	1.02	1.25	1.00	1.18	110	138	120	132	122	138	120	130
8 (F)	37	25	14	27	14	1.20	1.27	1.12	1.27	154	140	154	144	142	142	132	142
9 (M)	24	19	11	21	13	1.15	1.36	1.15	1.36	150	144	146	140	138	150	138	150
Mean		16.4	11.9	21.3	11.1	1.09	1.26	1.11	1.25	144	155	144	152	134	148	134	146
SD		7.3	3.9	8.4	3.2	0.09	0.07	0.09	0.08	16	17	12	17	7	12	9	12
P		0.001		0.002		0.0004		0.0009		NS		NS		0.006		0.002	

* Pre = at beginning of program; post = after 8–10 mo.
† After exercise as defined in METHODS.

Pulse volume recordings correlate with large vessel disease in the peripheral vasculature. Again, a change was obtained in this particular group of patients. Whether changes in the peripheral vasculature reflect the more important pathology that accompanies diabetes mellitus in the heart and cerebral vessels also remains to be determined. The present study has documented that improvements in pulse volume recordings can be demonstrated in patients with insulin-dependent diabetes mellitus. Moreover, these changes have been shown to occur concomitantly with improvement in carbohydrate "control" and participation in an exercise program. Further work is required to define the relative contributions of exercise and levels of glucose "control" and whether the cerebrovascular and cardiovascular lesions that accompany diabetes will improve with control of hyperglycemia and exercise. Nevertheless, serial measurements of BMT of muscle capil-

TABLE 2
Muscle biopsy results

Patient no.	Age (yr)	Duration diabetes (yr)	Basement membrane thickening (Å)	SD	Coefficient of variation	HbA_{1c}(%)	Patient mean HbA_{1c}(%)	SD HbA_{1c}
1 (M), initial	23	11	1618.3	±587	36	11.9	9.14	±3.06
10 mo			884.5	±192	21	7.4		
3 (M), initial	16	02	1331.0	±228	24	8.6	6.75	±1.98
8 mo			767.9	±132	17	4.4		
4 (F), initial	21	08	1094.2	±615	56	10.6	7.94	±2.28
10 mo			942.0	±200	21	6.4		
5 (F), initial	26	01	756.0	±114	15	9.9	7.63	±2.49
10 mo			731.0	±233	31	6.5		
7 (F), initial	19	05	868.0	±193	22	9.8	8.45	±2.38
10 mo			746.8	±256	24	4.4		
8 (F), initial	37	18	1648.9	±1088	66	8.1	5.79	±2.18
10 mo			803.5	±100	12	2.3		
10 (F), initial	19	02	1071.0	±221	26	11.3	10.90	±2.25
9 mo			1584.5	±604	38	10.2		
Normal (N = 95)			824	±125		3–6%		

laries and pulse volume recordings may be useful variables to longitudinally study vascular disease in patients with insulin-dependent diabetes.

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