Thin Muscle Capillary Basement Membranes in Myotonic Dystrophy

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SUMMARY

Muscle capillary basement membrane width (MCBMW) was measured in 18 myotonic dystrophy patients and compared with that in age- and sex-matched normal and diabetic subjects. The MCBMW in myotonic dystrophy patients (773 ± 258 Å) was significantly thinner than in normal subjects (925 ± 181 Å, $P < 0.05$) or in diabetics (1224 ± 614 Å, $P < 0.01$). An increase in MCBMW with advancing age was present in all groups but was greatest in the myotonic dystrophy groups ($r = +0.59$, $P < 0.01$). There was no relation between MCBMW and either the degree of glucose intolerance or insulin hypersecretion in the myotonic dystrophy group, though none had fasting hyperglycemia. This is the first report of a condition associated with thinner-than-normal capillary basement membrane. DIABETES 28:686–689, July 1979.

Capillary basement membrane thickening (CBMT) in subjects with diabetes mellitus was first described by Friedenwald in 1950.[1] Subsequently, a markedly increased prevalence of muscle CBMT was reported in patients with primary diabetes who had fasting hyperglycemia.[2–4] In patients with milder glucose intolerance, a smaller but statistically significant increase in prevalence of CBMT also was observed.[5,6] In secondary types of diabetes, such as those that occur in acromegaly[5] and as a result of pancreatitis,[2,7] CBMT in muscle also is seen, though perhaps to a milder degree. Thus, CBMT is not an abnormality that is found uniquely in persons with primary or idiopathic diabetes. Data, accumulated in the laboratory of two of the authors (J.R.W. and C.K.), suggest that muscle CBMT is the result of chronic hyperglycemia and/or the other metabolic derangements that occur in the presence of an absolute or relative insulin deficiency.[8]

An association of muscle CBMT with presence of retinopathy in diabetes has been reported.[9] An increased prevalence of CBMT probably is associated also with the presence of diabetic nephropathy.[10] However, this does not necessarily imply a causative role of CBMT in the pathogenesis of diabetic microangiopathy. The relationship of CBMT to the diabetic neuropathic syndromes has not been studied.

We were interested in studying muscle capillary basement membrane width (MCBMW) in patients with myotonic dystrophy, because these patients frequently have mild carbohydrate intolerance but considerably increased circulating insulin concentrations, particularly after a glucose load.[11] In addition, diabetes-associated macrovascular or microvascular disease appears to be rare in these patients. However, anterior segment fluorescein angiography has revealed a consistent microvascular tortuosity and fluorescein leakage in the iris of the eye that was not present in patients with other neuromuscular diseases or in normal subjects.[12]

MATERIALS AND METHODS

18 myotonic dystrophy patients, ranging in age from 22 to 62 yr, were studied: 15 were male and three were female. For comparison, 18 age- and sex-matched normal subjects and 18 age- and sex-matched noninsulin-dependent diabetic subjects were used. In addition, 17 normal subjects matched for age and degree of obesity (weight/height^2) with 17 myotonic subjects were used for comparing the plasma glucose and insulin responses to a standard glucose load. There was no family history of diabetes in the normal subjects, and glucose tolerance was within normal limits. The glucose tolerance test was standardized as

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TABLE 1
Clinical features and MCBMW values for myotonic dystrophy, age- and sex-matched controls, and diabetic subjects

	Myotonic dystrophy subjects				Controls		Diabetics		
Case no.	Age (yr) and sex	Glucose intolerance	Family history, diabetes	MCBMW SD (Å)	Age (yr) and sex	MCBMW SD (Å)	Age (yr) and sex	Duration (yr)	MCBMW SD (Å)
1	22 M	—	+	530 ± 128	22 M	862 ± 207	22 M	new	1167 ± 260
2	24 M	—	+	619 ± 239	23 M	852 ± 162	24 M	new	691 ± 161
3	26 F	—	—	588 ± 262	24 F	914 ± 348	24 F	new	1268 ± 552
4	27 F	—	—	532 ± 134	25 F	845 ± 274	28 F	15	954 ± 305
5	27 M	—	—	699 ± 210	25 M	558 ± 103	27 M	new	1093 ± 598
6	31 M	—	+	653 ± 244	31 M	779 ± 263	29 M	5	929 ± 173
7	36 M	—	—	565 ± 159	35 M	1018 ± 277	33 M	1.5	922 ± 261
8	38 M	—	—	506 ± 121	36 M	632 ± 122	38 M	new	1048 ± 349
9	39 M	—	—	847 ± 219	39 M	1085 ± 85	39 M	13	754 ± 150
10	43 M	+	—	807 ± 273	43 M	891 ± 152	40 M	new	888 ± 471
11	49 M	—	—	1326 ± 338	48 M	1132 ± 250	49 M	new	908 ± 393
12	50 M	+	—	683 ± 407	49 M	1242 ± 461	50 M	new	2638 ± 1452
13	52 M	+	—	1113 ± 749	50 M	1178 ± 392	52 M	1.5	928 ± 278
14	53 M	—	+	1269 ± 491	52 M	930 ± 280	53 M	new	1040 ± 406
15	55 M	—	—	512 ± 143	54 M	1078 ± 252	55 M	?	1228 ± 535
16	56 M	+	—	873 ± 350	56 M	820 ± 278	56 M	5	819 ± 147
17	61 F	—	—	769 ± 399	61 F	1024 ± 388	61 F	8	2845 ± 2335
18	62 M	+	—	1023 ± 378	62 M	805 ± 202	60 M	5	1914 ± 1291
Mean	42	—	—	773	41	925	42	—	1224
SD	12.7	—	—	258	13.0	181	12.9	—	614

recommended by the American Diabetes Association.[13] Written, informed consent was obtained from all participants.

An integrated glucose response also was determined for each subject by cutting out and weighing the area above the fasting level circumscribed by the three-hour glucose curve. This value is expressed in arbitrary units. An integrated insulin response was determined over the same time period using the same technique. Plasma glucose was determined by a neocupramine method[14] adapted to the Technicon AutoAnalyzer. Plasma insulin was determined by immunoassay[15] using antibodies supplied by Pharmacia Laboratories, Piscataway, New Jersey. The mean MCBMW was determined as reported previously.[4,16] Specimens were obtained by needle biopsy from the midlateral thigh.

Because of the asymmetric distribution of MCBMW values in the general population[4] as well as in the present subjects, statistical evaluation was done using Student's *t* test and regression analysis on log-transformed data. All mean values are geometric means with respective standard deviations. Graphed regression data are displayed conventionally. Data for integrated glucose and insulin responses were analyzed assuming a normal distribution.

RESULTS

Five myotonic dystrophy patients had mild glucose intolerance by the criteria of Fajans and Conn.[17] By the UGDP criteria,[13] only one had glucose intolerance. Four additional patients had a family history of diabetes but their glucose tolerance was normal (Table 1).

The mean integrated plasma glucose response after glucose administration was 531 ± 298 in the myotonic dystrophy patients and 470 ± 188 in the age- and obesity-matched controls. These values suggest a slight, but not significant, glucose intolerance in the myotonic group ($P > 0.4$). The integrated insulin response was 1068 ± 1135 and 528 ± 370 in the myotonic and control groups, respectively. Although the mean insulin area in the myotonic dystrophy group was twice as great as in the control group, this did not reach statistical significance because of the wide differences in response among the myotonic patients ($P < 0.1$).

The mean MCBMW in the myotonic dystrophy group was 773 ± 258 Å (Table 1). For the control group, the mean was 925 ± 181 Å. This difference was statistically significant ($P < 0.05$). The mean in the diabetic group was 1224 ± 614 Å. This also was significantly different from the mean in the myotonic group ($P < 0.01$).

The MCBMW increased with advancing age in all three groups. However, only in the myotonic dystrophy patients (Figure 1) was this increase statistically significant ($P < 0.01$). The MCBMW in the patients with myotonic dystrophy did not correlate with either the glucose response ($r = +0.27$) or the insulin response ($r = +0.25$).

DISCUSSION

We have no satisfactory explanation for thinner-than-normal MCBMW in myotonic dystrophy. The correlation between postglucose, integrated glucose and insulin values and the MCBMW is poor. MCBMW has been shown previously to be positively correlated with advancing age in both normal and diabetic subjects.[4] Because of the small number of subjects included in the present study, this relationship does not reach statistical significance for either group, and their mean MCBMW values do not differ significantly. In the myotonic dystrophy group, however, the age relationship is clearly significant. The seven younger patients, who were normally active, had proportionately thinner MCBMW than

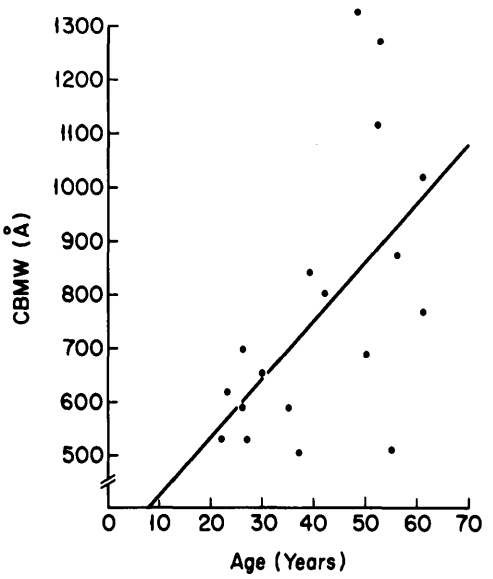

FIGURE 1. Relation of muscle capillary basement membrane width (MCBMW) to age in myotonic dystrophy patients.

had their age-matched controls (598 Å:833 Å); the difference was greater than in the older and more disabled patients (884 Å:983 Å).

Accelerated catabolism of endogenous and exogenous immunoglobulin (IgG) is known to occur in myotonic dystrophy[18,19] and may have some unrecognized parallel in the catabolism of basement membrane proteins that results in membrane attrition and thinning. However, we know of no data to support this hypothesis.

In both diabetics and nondiabetics, capillary basement membrane thickening appears to be modulated by hormonal factors.[8] There may be some hormonal restraint on progression of thickening in nondiabetic women during the childbearing years, evidenced by the plateau of muscle CBMT that occurs during this period. In childhood, the muscle CBMT in both sexes is the same; at menopause, the membrane in women thickens rapidly to catch up with that of men.[4] The possibility that gonadotropins act in a permissive way is consistent with the rarity of microangiopathy or excessive MCBMT in prepubertal diabetic children, regardless of duration of diabetes, as opposed to that in postpubertal diabetics.[20] Gonadotropin deficiency is not, however, a feature of myotonic dystrophy. Male patients with this disease frequently have seminiferous tubule degeneration and nearly always have elevated levels of follicle-stimulating hormone. Also, testosterone levels are frequently low and luteinizing hormone levels are high.[21] Growth hormone also appears to play at least a permissive role in diabetic retinopathy. However, this hormone is not deficient in the majority of patients with myotonic dystrophy.[22–24] Indeed, male patients and postmenopausal patients may in some respects be hypersensitive to the anabolic effects of growth hormone.[23]

There is evidence to suggest that thinner MCBMW may also be present in at least some other muscular dystrophies and perhaps neuromyopathies as well.[25] However, appropriately age-matched control subjects for each of the various groups were lacking.

The present study thus suggests that myotonic dystrophy is associated with thinner-than-normal muscle capillary basement membranes, a phenomenon that has not been reported previously and remains unexplained. Whether or not elucidation of the factors producing this phenomenon will further the understanding of the mechanisms by which CBMT occurs in diabetes mellitus also remains to be determined, but further investigations in this area are indicated.

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