Exercise and Diabetic Microangiopathy

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Exercise has been advocated in the management of diabetes from time immemorial,[1] and its effects on diabetics have been studied with increasing intensity in recent years. Efforts have been made to examine both its metabolic and physiologic effects. Diabetics develop a disturbance of their microcirculation consisting of anatomic changes in the basement membranes of capillaries and the walls of arterioles and venules.[2] This microangiopathy can produce blindness, slowly developing neuropathic changes, and progressive renal insufficiency. The relationship between exercise and diabetic microangiopathy has not often been examined. In this report, we will review relevant effects of exercise on the diabetic, the effect of established microangiopathy on exercise response, exercise modification appropriate to diabetics with microangiopathy, and the use of exercise in testing for early microangiopathy.

THE EFFECT OF EXERCISE ON DIABETICS

Diabetics do not perform as well as nondiabetics of similar age, sex, and body size when tested for ability to exercise.[3,4] They have, on average, a lower maximum heart rate and fail to achieve as great a cardiac output at maximal exercise levels. They usually have a higher blood pressure during exercise. These changes reduce maximum oxygen consumption which, although improved by training, does not allow all diabetics to achieve a performance level comparable to individuals who do not have diabetes. The biochemical response of the diabetic to exercise suggests metabolic inefficiency. More fat is utilized for energy at moderate exercise levels,[5] but glucose utilization is strikingly impaired only when ketone bodies are elevated.[6,7] The ketotic diabetic's blood sugar actually rises during exercise. This impairment of glucose metabolism is attributable to marked insulin deficiency.

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Lactate and pyruvate levels rise strikingly during exercise in diabetes.[5,6] Increased lactate production occurs during vigorous exercise even when glucose utilization and oxygen consumption are not measurably impaired. This excess muscle lactate production provides less than 1% of the required mechanical energy.[5] A probable basis for increased lactate production by the exercising diabetic is impaired tissue oxygen delivery. Three changes in diabetes combine to produce the impairment. Erythrocytes pass through arterioles into capillaries arranged in parallel with muscle fibers. Diabetic erythrocytes deform less rapidly as they enter these capillaries because of changes in their viscous properties.[8] The proportion of time spent at the arteriolar end of the capillary is increased and the time at the venular end decreased. In the latter area the oxygen tension gradient is lowest and exchange most burdened. Adding to this inefficiency is an increase in the hemoglobin Alc (Hb Alc) content of diabetic erythrocytes, a direct effect of hyperglycemia.[9] The attachment of glucose to hemoglobin directly increases its affinity for oxygen and interferes with the reoxygenation-blocking effect of 2,3-diphosphoglycerate.[10] The increased Hb Alc content of diabetic erythrocytes therefore reduces their oxygen delivery ability adding to the erythrocyte deformability burden. Capillary basement membrane thickening in diabetes[2] further hinders the passage of oxygen across the vessel wall. This triple burden can produce a small localized oxygen deficit forcing a few muscle fibers to anaerobic metabolism.

Exercise has had a considerable recent advocacy in amelioration of ischemic heart disease.[11] At least two features of the response to exercise favor improved outcome in this condition. With exercise there is an increase in high density lipoprotein (HDL) cholesterol, important in the transport of sterols from the periphery to the liver,[12] and a rise in 2,3-diphosphoglycerate favoring improved oxygen delivery.[13] The elevations of HDL cholesterol and 2,3-diphosphoglycerate following exercise have not yet been demonstrated to occur in the diabetic.

Insulin administration has been found to cause a decline in plasma volume,[14] a change unfavorable to exercise per-

formance. In studies performed before it was demonstrated that activity itself mobilizes injected insulin,[15] exercise in the upright posture was demonstrated to favor an increased rate of loss of plasma volume in diabetes.[16] Insulin mobilized during activity might be responsible for some of the plasma volume decline. The osmotic effect of hyperglycemia and its reversal by a sudden drop in plasma glucose may also produce plasma volume changes.[17]

Two hormones that may favor the development of diabetic angiopathy become elevated during exercise in the diabetic and nondiabetic. These hormones are glucagon[6,18] and growth hormone.[19] The growth hormone rise occurs early in exercise and is especially marked in the poorly controlled diabetic. A clear understanding of the effects of exercise in diabetes should help us better define its use and limits.

EXERCISE ABILITY AND DIABETIC MICROANGIOPATHY

Diabetic microangiopathy is a progressive disorder in which functional disturbances precede anatomic change.[20] The latter consists of a thickening of the walls of capillaries, particularly notable in skeletal muscle; increase in connective tissue elements in the intima and media of smaller arterioles; and changes in the media of muscular arteries.[21] When diabetics with microvascular changes in the eyes and kidneys are exercised, they have a greater blood pressure rise than either early diabetics or nondiabetics.[3] They also have a lower maximal exercise ability.[3,4] Both changes are linked to the development and progression of microangiopathy.

Proteinuria develops regularly during prolonged vigorous exercise. The phenomenon occurs at a lower level of activity in diabetics than in nondiabetics.[22] Testing for proteinuria during moderate exercise has been suggested to detect latent diabetic nephropathy. The basis for the early proteinuria appears to be an exercise-mediated reduction in kidney blood flow in the presence of arteriolosclerotic and glomerulosclerotic change.

Studies of capillary diffusion capacity (CDC) and capillary filtration coefficient (CFC) have been carried out in diabetics. CDC is usually measured during postexercise reactive hyperemia. The leg's CDC, a measure of the exchange of low-molecular-weight substances, is regularly increased in diabetes.[23] It is even more strikingly increased in diabetics with microangiopathy. This occurs despite absence of an increased resting leg CFC. CFC is usually considered to be a measure of vascular surface area. Other studies have shown that forearm CFC is actually somewhat lower in early diabetics than in nondiabetics.[24,25] As duration of diabetes increases, forearm CFC rises to become significantly elevated after 20 yr of diabetes.[24] Diabetics of long duration also develop maximum reactive hyperemia in the leg unusually rapidly following ischemic exercise.[26] The rate of escape of albumin from the plasma volume is abnormally elevated in long-term diabetics.[27] This albumin escape increase is correlated with diastolic blood pressure and parallels observations in hypertension.[28] Mild ketoacidosis is also accompanied by a rise in forearm CFC and an increase in the rate of escape of albumin from the circulation.[27]

We may conclude that the development of diabetic microangiopathy is adverse to exercise performance. It reduces the ability of the peripheral vasculature to dilate and favors increased loss of protein and water from the plasma.

EXERCISE LEVEL IN DIABETICS WITH MICROANGIOPATHY

Improved blood glucose and insulin levels have been demonstrated in obese individuals and mild diabetics following exercise.[29] Glucose metabolism in the insulin-requiring diabetic is also improved by an exercise program.[30] Long-term diabetes, particularly that associated with recognizable evidence of microangiopathy—neuropathy, nephropathy, or retinopathy—is associated with impaired ability to carry out heavy physical work. Changes occur that suggest that excessive cardiovascular stress may be detrimental, but, since improved blood glucose control is desirable, total limitation of activity should not be advised.

The distribution of blood changes during exercise in diabetes with angiopathy because of the reduction in cardiac output. At the same work level a higher proportion of the heart's output will therefore pass through exercising tissues. The viscera will get less than their usual blood flow,[31] including the kidney. The diabetic with advanced nephropathy may develop cortical ischemia. It is even possible that prolonged vigorous exercise might produce acute renal insufficiency like that following contrast radiographic studies.[32] The rise in systolic and diastolic blood pressure during exercise is of concern to the diabetic with retinopathy. The increased pressure may stress the vessels of the eyes, provoking hemorrhage. The diabetic usually undertakes only levels of activity within appropriate bounds, but emphasis on exercise to control heart disease may generate greater activity levels.

The pattern of declining maximal heart rate and increasing blood pressure rise associated with longer duration of diabetes and evidence of more small vessel changes does not apply equally to all diabetics. The response to mild exercise of both heart rate and blood pressure may be tested either formally in a treadmill test or informally by a rapid walk of modest duration. Activity limited to that producing a heart rate 80–85% of that considered maximal for age[33] and a blood pressure rise to less than 200/105 would seem wise. A simple limitation of activity to moderately rapid walking will usually suffice in diabetics with advanced angiopathy. The virtue or hazard of physical activity over very extended periods has not been established, but a limitation to 1 or 2 h of activity in the untrained also appears sound.

Foot care, a major need of the older diabetic, when perception and pain thresholds are elevated in the lower extremity, should also be emphasized. Neuropathy will produce a foot that can be damaged by the recurrent compression that occurs during prolonged walking, running, or jogging. With anesthesia, damage will occur without recognition. The use of shoe liners to distribute weight and the interdiction of prolonged, vigorous foot-utilizing activities appear wise.

Sensible modification of excercise to moderate levels and periods of time combined with attention to foot protection should be basic advice to the diabetic with evident microangiopathy.

EXERCISE TESTING TO DETECT DIABETIC MICROANGIOPATHY

A frustrating feature in evaluating the diabetic is the difficulty in establishing his or her rate of development of small blood vessel disease. After one or two decades of adult diabetes, there is a large difference among individual diabetics in the seriousness of microvascular sequelae. Development of new microaneurysms, the hallmark of retinopathy, occurs periodically and is slow in healing.[34] Vibration sense measurement is useful in detection of asymptomatic neuropathy, but the threshold normally rises with age. Proteinuria develops quite late and its presence is not unequivocal evidence of nephropathy. Serious problems such as retinal hemorrhage or kidney failure often give little advance warning. More suitable means to detect development of microangiopathy are needed, and exercise that stresses the cardiovascular system may be useful in its detection.

Provocation of proteinuria in the diabetic who normally has no urinary protein has already been mentioned.[22] It may be more noticeable in untrained (sedentary) diabetics, since training improves the distribution of blood at the same activity level.[35] Diabetics with exercise proteinuria need to be followed for development for diabetic nephropathy to establish the value of this mode of testing.

Overall blood flow is very little impaired even in advanced microangiopathy. No difference in maximum blood flow in the lower extremity can be demonstrated until quite advanced diabetic changes are present.[26] In diabetics, the rapid onset of maximum blood flow in reactive hyperemia has been attributed either to increased arteriolar pressure or to greater flow resistance in the capillary bed.

The pressor effect of exercise is enhanced in diabetes. The rise in arterial pressure is due to increased sympathetic tone. It is known to be modified by training to the extent that a greater physical activity level is required to produce the same increase. Short-term exercise at near-maximum oxygen consumption appears to be a reasonable means of measuring this effect, but the relationship of blood pressure rise to diabetic microangiopathy does not appear to be close.[3]

It may be that exercise blood pressure rise may be combined with some other means of microvascular testing to improve its value. One such possibility is arterial pulse-tracing analysis. The arterial pulse tracing is usually used to detect arterial wall stiffness. The technique measures the effects of arterial wall thickening and reduction in the elastic properties of the wall. Pulse propagation is abnormally rapid in diabetes, evidence of vessel stiffness. It is usually accompanied by loss of the dicrotic notch produced at closure of the aortic valve.[36] The level of peripheral (arteriolar) resistance has an effect on the secondary characteristics of the arterial pulse. Examination of these characteristics in diabetes has not yet been reported.

Studies of forearm CFC, blood flow, and venous compliance have been used in an attempt to detect the presence of diabetic microangiopathy.[24,25] They have not met with complete success. Most difficult to explain is the tendency for CFC to be low in the early diabetic and high in long-standing diabetes. CFC is also affected by exercise. Tonic forearm exercise increases filtration, while intermittent forearm exercise lowers it.[25] The classic picture of filtration as a passive process linearly dependent on pressure gradient does not explain these observations. Perhaps as we understand better the physiologic basis of the filtration and recovery of tissue water, we will be able to improve the sensitivity of this simple, noninvasive technique.

The decline of plasma volume that occurs during upright exercise is a documented feature of diabetes.[14,16] It raises hematocrit and blood viscosity to reduce cardiac return. It is enhanced by the administration of insulin[14] and may play a role in producing the orthostatic symptoms seen in diabetic neuropathy. Plasma volume decline can be estimated by determining hematocrit rise. Development of a standardized process for measuring its decline during exercise in diabetics appears to have some potential, since it estimates the degree of activity impairment that can be expected.

Several exercise-mediated tests of the microvascular systems in diabetics have promise in early detection of developing microangiopathy. They may be even more useful when combined.

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