Physical Training and Glucose Tolerance in Middle-aged Men with Chemical Diabetes

B. SALTIN, F. LINDGÅRDE, M. HOUSTON, R. HÖRLIN, E. NYGAARD, AND P. GAD

Mature onset of diabetes is an increasing problem in Western populations.[1] A change in dietary habits and a lowered physical activity level may be contributing to this development. Both obesity and physical working capacity are related to glucose tolerance,[2,3] and a high frequency of pathological oral glucose intolerance is also found among men who are unfit and obese.[2,4] Middle-aged men who are normoglycemic but have a pathological oral glucose tolerance test (OGTT) have an increased risk for developing diabetes.[5] Moreover, cardiovascular diseases are also more common among these men.[6,7] In obese men the insulin level during OGTT was reduced by physical training.[4,8] The question then arises whether middle-aged men with pathological OGTT and similar body weights as age-matched controls also can benefit from physical training. We present a summary of several studies still in progress that deal with this question.

MATERIALS AND METHODS

Men 47–49 yr of age were screened and those who in two consecutive OGTTs had a blood glucose concentration above 6.9 mmol/L after 120 min were considered to have chemical diabetes. Some data characterizing these men and age-matched controls are given in Table 1. Over the past 2 yr approximately 100 men with chemical diabetes have been identified and engaged in therapeutic trials including dietary advice and/or physical training. Fifteen of these men were also subjected to studies of morphology and metabolic potential of their skeletal muscles.

The OGTT was performed in the morning after an overnight fast. 30 g glucose/m² body surface was ingested in 5 min as a 10% aqueous solution. Blood glucose was determined with the hexokinase method and plasma insulin with radioimmunoassay (RIA) at regular intervals before and for 120 min during the OGTT. Details as to measurements of physical characteristics, body composition, blood lipids, and physical work capacity, as well as the analysis of the muscle biopsies are given elsewhere.[2,8,9] The physical training consisted of two weekly 60-min sessions with various activities (calisthenics, walking–jogging, soccer, and badminton playing) under the guidance of a physiotherapist. More intense exercise was not performed for a longer duration except very late in the training period. The dietary advice was given initially (less plain sugar products, more fiber and unsaturated fat, and an overall reduction in energy intake) by a physician and a dietitian. For those who only received dietary advice, monthly meetings were arranged. In the following the effect of three regimens will be discussed: (a) physical training and initial advice about diet (n = 25; observations made at 0, 6, and 12 months); (b) dietary advice (n = 12; observations made at 0 and 6 months); and (c) physical training (n = 11; observations made at 0 and 3 months). The number of dropouts did not exceed two per group.

RESULTS

Physical characteristics and work capacity. Middle-aged men with chemical diabetes have similar body weights and skinfolds and blood lipids as a random sample of age-matched men with normal glucose tolerance (Table 1). However, the fitness level measured as the maximal oxygen uptake was 20% lower ($P < 0.001$). Maximal oxygen uptake increased with physical training ($P < 0.001$) and after 6 months was similar to the level of the controls (Table 1). Additional 6-months' training resulted in another 10% increase in maximal oxygen uptake ($P < 0.001$). The group that so far has only trained for 3 months improved maximal oxygen uptake from 2.19 to 2.69 L/min or close to 20% ($P < 0.001$). An increase in maximal oxygen uptake was also noticed for those who only received dietary advice, but this

From the August Krogh Institute, University of Copenhagen, Copenhagen, Denmark, and the Department of Preventive Medicine, Malmö General Hospital, Malmö, Sweden.
M. Houston's present address is Department of Kinesiology, University of Waterloo, Waterloo, Ontario, Canada.
Address reprint requests to Bengt Saltin, M.D., University of Copenhagen, August Krogh Institute, 13, Universitetsparken, DK 2100 Copenhagen, Denmark.

change was insignificant as several men in this group had a similar or only slightly increased maximal oxygen uptake. For the two groups who were given dietary advice, body weight was reduced by about 4.5 kg ($P < 0.05$; 6 months), whereas weight was essentially unchanged among the men who only trained.

Glucose tolerance. The OGTT improved for all three groups but was normalized only in the group with training and initial dietary advice (Figure 1). The insulin levels during the OGTT were reduced for the groups with dietary advice and physical training. For the group who only trained and had done so for 3 months, the reduction in plasma insulin concentration was insignificant.

Muscle fiber distribution. The relative occurrence of slow-twitch (ST) fibers in the gastrocnemius muscle was 67%, and of the fast-twitch (FT) fibers the *a* type (FTa) amounted to 13% and the *b* type (FTb) to 20%. No change in the percentage of the different fiber types was observed after training. The mean area of ST fibers was 4100 μm^2, the FTa 5100 μm,[2] and the FTb 5550 μm^2. Training resulted in less than a 10% increase in mean areas of the different fiber types. None of the observed variables were significantly different from a control group of healthy men, although both the relative number of FTb fibers and their size were quite large in the men with chemical diabetes.

Muscle capillaries. The gastrocnemius muscle of men with chemical diabetes was well supplied with capillaries. An average of 362 capillaries/mm² or 1.6 capillaries/fiber was found. In healthy men both these variables are closely related to physical working capacity. With the low maximal oxygen uptake in the men with chemical diabetes, greater values for the capillary supply in relation to fitness level were observed when comparisons were made with healthy men ($P < 0.001$). Other variables also used for expressing capillarization of muscle fiber indicate a larger than normal supply in the chemical diabetics. The number of capillaries per fiber type was from 4.1 to 4.5 for the three fiber types. Fiber type area supplied by one capillary ranged from 1000 μm^2 to 1100 μm^2.

TABLE 1
Some variables characterizing middle-aged men

	Controls	Chemical diabetes
Number	115	25
Age (yr)	48	48
Weight (kg)	77.4 ± 11.6	80.5 ± 10.9
Skinfold	196 ± 21.6	196 ± 10.0
TG (mmol/L)	1.82 ± 0.8	1.84 ± 0.7
Cholesterol (mM/L)	5.9 ± 0.9	5.9 ± 1.0
Maximum oxygen uptake (L/min)	2.7 ± 0.7	2.2 ± 0.5
Ml/kg/min	34.9 ± 8.7	27.6 ± 6.3

Mean value ± SD for some variables studied in random sample of 48-yr-old men living in a city and 25 normoglycemic men with a pathological OGTT. These 25 men all participated in group therapy consisting of physical training for 12 months and initial advice about diet.

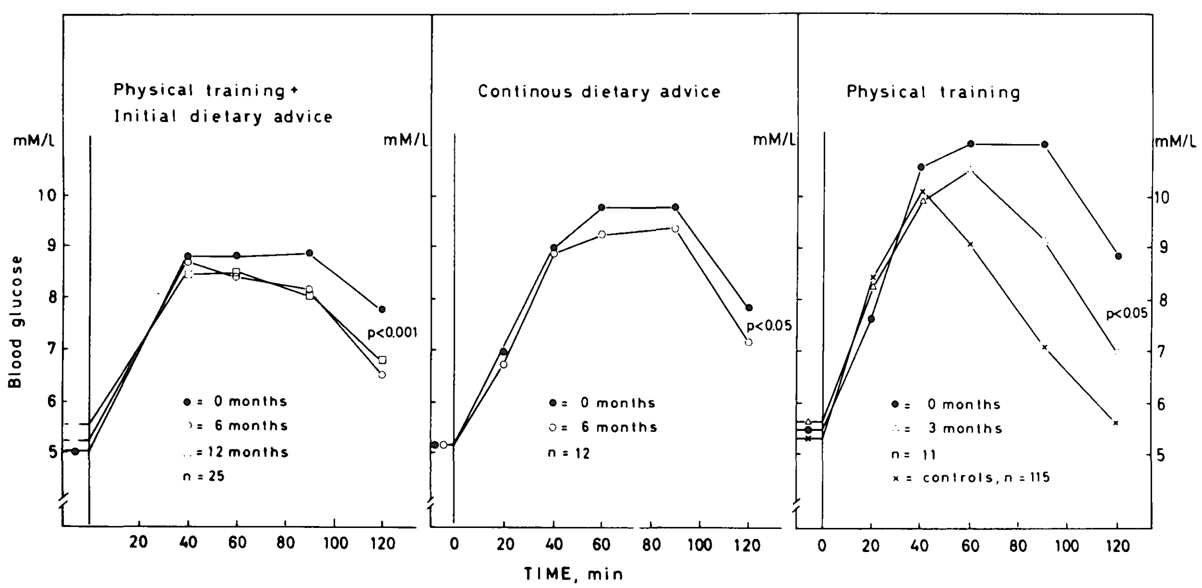
A small number of heavily stained capillaries were observed in most subjects before and after training. No attempt was made to analyze this finding in any depth, as PAS-positive material is no direct measure of the thickness of the basal membrane.

Metabolic potential. The activity of hexokinase (HK) was 0.42 mmol/kg/min, wet weight. The phosphorylase activity was 12.2 and the LDH activity 210 mmol/kg/min, wet weight. As a marker for mitochondrial enzymes, the activity of succinate dehydrogenase (SDH) was determined and found to average 4.9 mmol/kg/min, wet weight. This level as well as the one for HK were lower than found in muscles of healthy controls (Figure 2), whereas the glycolytic enzymes were similar to what was found for a control group. Training for 6 months resulted in an increase of 35 and 75% for HK and SDH, respectively ($P < 0.001$). Phosphorylase was essentially unchanged and LDH slightly increased.

DISCUSSION

The present data clearly demonstrate that middle-aged men with a pathological OGTT are unfit. They have a low physical

FIGURE 1. Blood glucose concentration during an oral glucose tolerance test for middle-aged men who in a screening had >6.9 mmol/L at 120 min (men with chemical diabetes). In the panel to the right are the results for the control group.



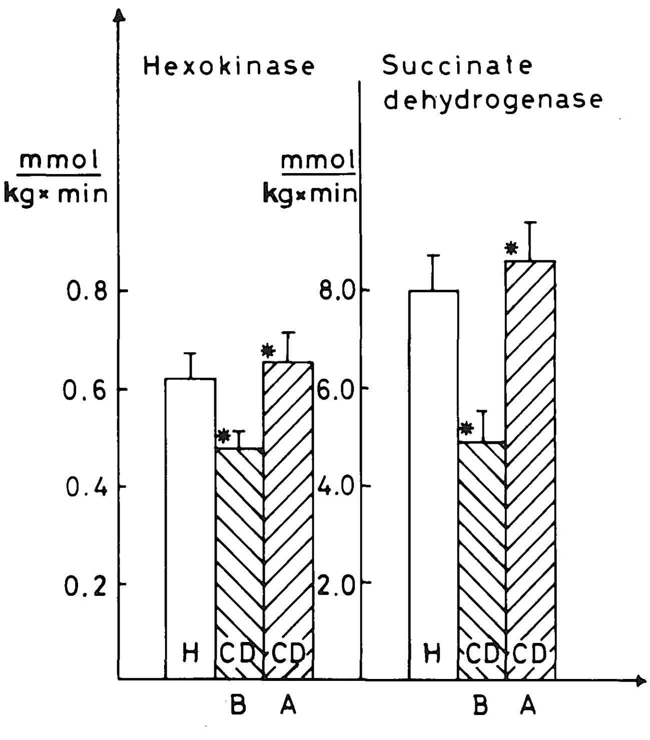


FIGURE 2. The activity for hexokinase and succinate dehydrogenase is given for the middle-aged men with chemical diabetes (CD) before (B) and after (A) training. For comparison, data on healthy (H) men of the same age are also given. The asterisks denote significant differences between H and CD before training and CD before and after training.

work capacity and low levels of oxidative enzymes in their skeletal muscles. However, they are not more overweight than age-matched controls and they have a rich capillarization of their skeletal muscles in relation to their low work capacity.

Peripheral insulin resistance in middle-aged men is frequently associated with obesity.[3,4] In this respect the present middle-aged men with pathological OGTT are clearly different. Although body weight was reduced during the activity period, the loss amounted to only a few kilograms. Furthermore, in the men who did not lower their body weight the effect of training on OGTT was also significant. It is also of note that in contrast to studies of the beneficial effects of physical training on the peripheral insulin resistance in obese individuals, the present group of men also attained a normal OGTT with the activity period.

Any definite role of physical training, as opposed to a change in diet, in causing the observed beneficial effects cannot at present be established. The group with only physical training obtained a distinct improvement in OGTT with only 3 months of training in spite of no change in body weight. It is of interest that the group with "combined" treatment initially received only dietary advice, and it is likely that only minor changes in dietary habits may have occurred for some of the men in this group. Thirdly, in the dietary group some of the men also increased their activity levels as indicated by improvements in maximal oxygen uptake of a magnitude that is only observed with physical training. Thus it is felt that the training may be more important than the dietary modification in accounting for the observed improvements in glucose tolerance.

The coupling of increased physical activity and increased work capacity on one hand and the improved capacity to handle glucose on the other is not easily apparent. In the study by Maehlum and coworkers[10] the importance of the distribution of the oral intake of glucose is emphasized. Under normal conditions the liver may take up 80–85% of the ingested glucose and leaving only 15–20% for the rest of the organism. The small quantity of muscle glycogen remaining after intense prolonged exercise will increase the proportion of glucose passing the liver and permit more glucose to be taken up by peripheral tissues. This could have been anticipated to play a role in explaining the improved OGTT after training in the present study. However, such an explanation is not likely, as no physical training was performed during the last 3 days before an OGTT. The slope of the blood glucose concentration during the OGTT showed no major change in the initial phase (rate of rise in blood glucose, peak height, and time to the peak). However, the observation that, during the latter phase of the OGTT, blood glucose concentration returned to control levels significantly faster after training may speak in favor of a faster peripheral glucose utilization. Whether such a change can be linked to the improved metabolic potential of the skeletal muscles with the training awaits further studies.

ACKNOWLEDGMENT
The studies summarized in the present article have been made possible by grants from Danish and Swedish Associations for Diabetes, and from NOVO.

REFERENCES

[1] Report of Nat. Comm. on Diabetes to the Congress of U.S., Vol. 3, U.S. Dept. Publ. Health, Education and Welfare, Washington, 1975.

[2] Lindgärde, F., Hörlin, R. and Saltin, B.: Glucose tolerance and physical work capacity in a random sample of middle-aged men. Acta Med. Scand. Submitted for publication, 1978.

[3] Holm, G.: Studies on the metabolic effects of physical exercise. Thesis, Göteborg University, Sweden, 1977.

[4] Björntorp, P., Holm, G., Jacobson, B., Schiller-de-Joinge, K., Lindberg, P. A., Sjöström, L., Smith, U., and Sullivan, L.: Physical training in human hyperplastic obesity. IV. Effects on the hormonal status. Metabolism *26*:319–28, 1977.

[5] Jarret, R. J., and Keen, H.: Hyperglycemia and diabetes mellitus. Lancet *2*:1009–12, 1976.

[6] Keen, H., Rose, G. A., Pyke, D. A., Boyns, D. R., Chlouverakis, C., and Mistry, S.: Blood-sugar and arterial disease. Lancet *2*:505, 1965.

[7] Jarrett, R. J., and Keen, H.: Diabetes and Artherosclerotis. *In* Complications of Diabetes, p. 179–303, London, Edward Arnold, 1975.

[8] Hörlin, R., Lindgärde, F., and Saltin, B.: Physical training and dietary advice in middle-aged men with chemical diabetes. Acta Med. Scand. Submitted for publication, 1978.

[9] Saltin, B., Houston, M., Nygaard, G., Graham, T., and Wahren, J.: Muscle fiber characteristics in healthy men and patients with juvenile diabetes. Diabetes *28* (Suppl. 1):93–110, 1979.

[10] Maehlum, S., Felig, P., and Wahren, J.: Splanchnic glucose and muscle glycogen metabolism after glucose feeding during post-exercise recovery. Am. J. Physiol. *234*: In press, 1978.