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LONGTERM NEUROENDOCRINE AND METABOLIC EFFECTS OF PHYSICAL TRAINING IN INTERMITTENT CLAUDICATION

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ABSTRACT. Twenty-five elderly patients with peripheral vascular disease and intermittent claudication were prospectively followed during a six-month session of physical training. Neuroendocrine and metabolic patterns as well as effects on walking performance were assessed during the training period. At the initial evaluation there was an inverse association between walking distance and serum cortisol and blood glucose levels. The walking distance increased during the training period. A positive effect on glucose homeostatis was seen with decreased basal fructosamine levels after training. During physical exercise a decrease in insulin and an increase in growth hormone was seen. Changes in growth hormone were, in contrast to insulin, more related to the pain level perceived than to the work load imposed. Apart from the marked effects on physical performance the results of the study suggest an improvement of hormonal and metabolic balance after physical training. This regularly applied exercise program improved the health status of rather old people.

Key words: intermittent claudication, arterial occlusive disease, exercise therapy, glucose, insulin, growth hormone, cortisol, stress, ageing.

The reported prevalence of intermittent claudication (IC) is 4–5% in men aged 50–59 years (16). Management of patients with peripheral vascular disease is expensive and requires a combination of social and medical resources. Considerable efforts are made for improvement of therapeutic and preventive measures.

The beneficial effect of physical training regarding walking capacity is well-documented in patients with IC (5, 12, 17, 24). Earlier studies have shown that the increase in walking distance is not due to an increase in leg blood flow capacity (21, 24). Peripheral blood pressures are also unaffected by physical training (17). It is known that patients with IC have an increased frequency of blood lipid and glucoregulatory disorders in comparison with healthy controls (6, 20). Metabolic and neuroendocrine factors are therefore most likely of importance for the arteriosclerotic process. There is a lack of reports, however, of metabolic and neuroendocrine longterm effects of a prospective controlled training program for older patients suffering from IC (5, 9).

The aim of the present study was to prospectively follow older patients suffering from IC and to assess anabolic and catabolic humoral responses. We selected a couple of primarily anabolic hormones, i.e. insulin and growth hormone and a major catabolic hormone, cortisol (1, 2, 3) and the metabolic concomitants in the form of rapidly changing blood glucose and in fructosamine, a slower changing indicator of average blood glucose for a preceding three-week period (4, 11). The selected glucoregulatory hormones are, in our view, of major importance to gauge possible metabolic changes induced by our regimen.

MATERIAL AND METHODS

We studied 25 patients, 15 men and 10 women, mean age 68 years (range 55–76). Exclusion criterias were diabetes mellitus, angina pectoris or ST-depression on the electrocardiogram (ECG) at treadmill test. The peripheral occlusive disease was ascertained by noninvasive methods. During the treadmill test all patients were limited by typical IC symptoms. Twenty-two of the patients smoked at the start of the program.

A six-month training program of two training sessions of 30 min each twice a week at the hospital, combined with daily training at home was lead by an experienced physio-therapist. Each session at the hospital included dynamic and static exercises of leg musculature, with both legs and also with each leg separately. The program consisted mainly of simple movements of feet and legs like heel-raisings and knee-bendings and walking exer-

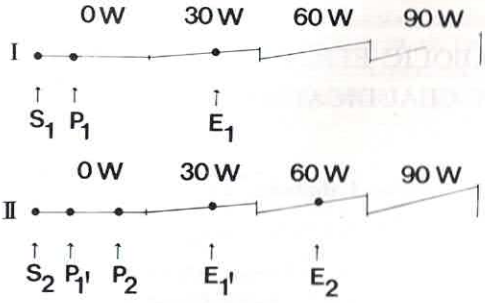

Fig. 1. Treadmill test before (I) and after a six-month physical training program (II). The load was increased by 30 W every sixth minute, determined by inclination related to body weight. Blood samples (↑) were taken before starting the treadmill (S_1, S_2), at onset of leg pain (P_1, P_2) and at the end of each test (E_1, E_2). A treadmill test after training blood samples were also taken at the same walking distance as sample P_1 (= $P_{1'}$) and E_1 (= $E_{1'}$).

cises beyond onset of leg pain. Each patient was provided with a similar program for daily training at home. They were also encouraged to take walks in addition to the home program. (A detailed description of the training program can be obtained from the authors on request.)

Treadmill tests were performed during standardized conditions, the speed used was 1 m×sec^{-1}. The patients started for six min on a flat level and continued for six min with an external load of 30 W, determined by inclination related to body weight. The load was then increased by 30 W every sixth minute. Continuous ECGs were recorded. Blood samples were taken before *starting* the treadmill (S), at onset of leg-*pain* (P) and at the *end* of each test (E). At treadmill test following six months of training blood samples were also taken (Fig. 1). Blood was analysed for fructosamine, insulin, growth hormone and cortisol. Blood glucose was analysed before and after each treadmill test. Hormone levels were determined in duplicates by radioimmunoassay with commercially available kits. Intraassay and interassay coefficients were below 10% and 20%, respectively.

Data are expressed as mean ± SEM, differences of means were tested for statistical significance by two-sided *t*-test for paired observations within groups and unpaired *t*-test for inter group differences. Linear regression was used for analysing variables associated with the initial walking distance. Statistical significance was set at $p<0.05$.

RESULTS

Basal values before training. All patients had reduced ankle systolic blood pressure (Table I). When the initial walking distance was related to hormone and glucose levels at the start of the study an inverse association was found between walking distance and cortisol ($p<0.05$) and blood glucose ($p<0.05$). We found no such relation between ankle blood pressures and the analysed blood parameters.

Table I. *Ankle systolic blood pressure and arm-ankle systolic pressure gradient in the patient's worst leg, mean ± SEM*

Ankle systolic blood pressure (mmHG)	Arm-ankle pressure gradient (mmHG)
81±5.7	69±6.5

Basal values after training. The walking distance increased markedly from 575±69 m to 924±92 m after six months of training ($p<0.001$). The painfree walking distance was also significantly increased, 111±21 m and 270±68 m respectively ($p<0.01$). No change in body weight was observed.

Blood glucose levels at the start of each treadmill test were unchanged. Fructosamine levels were significantly lower after six months compared to values at the start of the program ($p<0.02$), (Fig. 2). When analysing the specific hormones no difference was found in basal values before and after training. Insulin levels decreased significantly ($p<0.05$), however, if the comparison was restricted only to patients with a marked increase in walking distance (>415 m). Furthermore, in patients with only a minimal increase in walking distance (<220 m) there was a tendency of increased insulin levels ($p<0.10$).

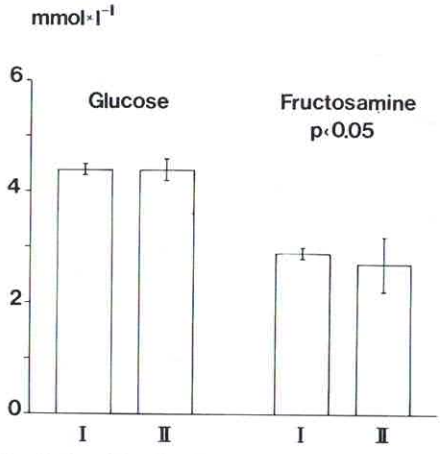

Fig. 2. Basal levels of glucose and fructosamine, mean ± SEM, blood samples taken before each treadmill test. I = before training, II = after training.

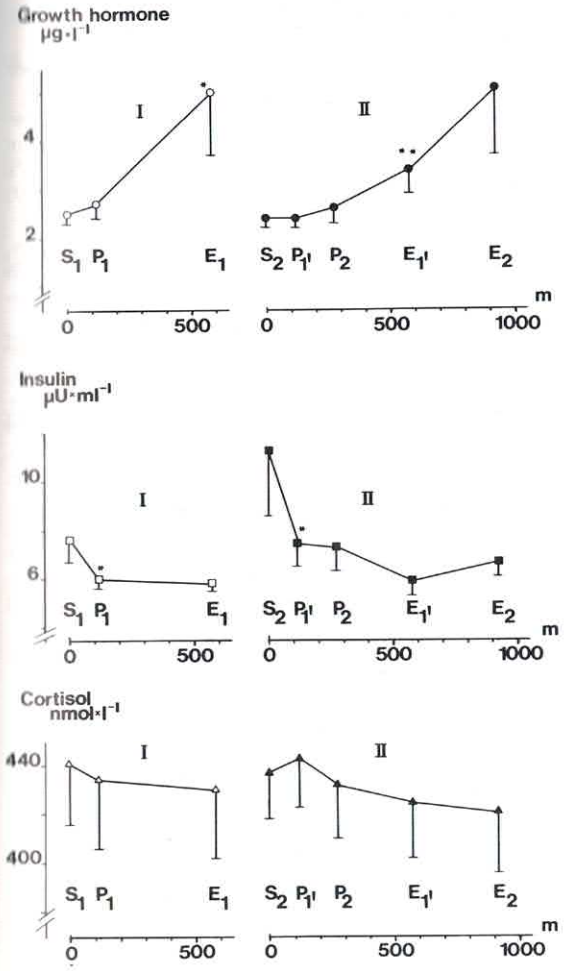

Fig. 3. Exercise-induced changes in hormone levels, mean ± SEM. Blood samples taken at treadmill test before (I) and after (II) a six-month physical training session. S_1, S_2 = values before each test. P_1, P_2 = values at onset of leg pain at each test. E_1, E_2 = values at the end of each test. $E_{1'}$, $P_{1'}$ = values at treadmill test after training taken at the same walking distance as E_1 and P_1 during treadmill test before training. $^*p<0.05$, $^{**}p<0.01$.

Exercise-induced changes. A marked and significant increase in serum growth hormone levels was found at both treadmill tests. The rise started at both occasions after the induction of leg pain and the maximum level was found at the end of the test when the perceived pain was so intense as to force the patient to stop the treadmill exercise ($p<0.05$). As a result of training, however, the increase in growth hormone was less marked at the second test when compared at the same work loads.

Serum insulin levels decreased during each of the exercise sessions ($p<0.05$). The decrease was significant already at the initial induction of pain at the first treadmill test and at the corresponding walking distance at the test following six months of training, at which time samples were taken before pain-induction ($P_{1'}$). Blood glucose levels were unchanged before and after exercise during both tests.

Serum cortisol did not show any significant changes in response to pain and physical exercise.

Exercise induced hormonal changes are summarized in Fig. 3.

DISCUSSION

We found an inverse relationship between initial walking distance and blood glucose levels in older patients with IC. These results are in line with earlier observations of a positive relation between level of physical fitness and glucose tolerance found both in middle-aged healthy men and in males with non-insulin-dependent diabetes (14). It has also been reported that patients with peripheral arterial disease have abnormal glucose tolerance tests in comparison with healthy controls (6). Physical training improves glucose homeostasis in patients with manifest diabetes and in normoglucemic men with pathological oral glucose tolerance test (15, 18). In patiens with IC a tendency towards a decrease in the cumulative concentrations of insulin and glucose during glucose tolerance test after training has been described (5). Our results with decreased fructosamine levels following training further underline the hypothesis that training in patients with IC leads to an improved hormonal balance and a lowering of overall glucose burden.

Basal serum insulin decreases in sedentary healthy men following physical training (23). In our group of older subjects we found a varying response to physical training. In the subgroup where the walking distance markedly increased the basal insulin levels decreased, indicating a relation to the total amount of exercise performed.

We observed a marked decrease in insulin levels already during light exercise in contrast to earlier studies in healthy men where a similar decrease was measured at much higher work loads (13, 19, 22). The most likely explanation for this reaction proposed so far is a catecholamine mediated effect on pancreatic beta cells (19, 22). Thus, the marked insulin decrease seen at the beginning of walking would then imply a catecholamine release at onset

of the exercise. No further fall of insulin was seen at higher work loads and the insulin response was —unlike growth hormone—not modulated by leg pain perceived by the patient.

Serum cortisol did not show any clear-cut changes during the study period. During the initial evaluation there was an inverse association between cortisol levels and walking distance. This might reflect a higher physiologic stress level in the most disabled patients.

Growth hormone is characterized by rapidly changing blood levels sensitive to changes in circulating blood glucose and physiologic stress (1, 2, 7). Moreover, growth hormone is known to respond to psychologic factors more than to physical work load (7, 10). Growth hormone was found to increase during exercise as earlier has been reported in young healthy men (8, 13, 19). The increase came in the present study, however, at lower work loads and occurred at the time when the perceived leg pain was of such an intensity as to force the patient to stop walking. In fact, growth hormone level increased in a similar way as ischemic leg pain. After six months of training the increase of growth hormone at the treadmill test was elicited at higher work load but of the same magnitude as before. This suggests that physiologic mediators stimulate growth hormone secretion and might possibly also signal local hypoglycemia in the muscles leading to gluconeogenetic signals (7).

Our study demonstrates that, despite high age of our participants, exercise training has measurable beneficial effects on the walking distance and on neuroendocrine and metabolic parameters.

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REFERENCES

1. Arnetz, B. B., Theorell, T., Levi, L., Kallner, A. & Eneroth, P.: An experimental study of social isolation of elderly people: psychoendocrine and metabolic effects. Psychosom Med *45:* 395, 1983.
2. Arnetz, B. B., Fjellner, B., Eneroth, P. & Kallner, A.: Neuroendocrine response selectively to standardized psychological stressors. Int J Psychosomatics *33:* 19, 1986.
3. Axelrod, J. & Reisine, T. D.: Stress hormones: Their interaction and regulation. Science *224:* 452, 1984.
4. Baker, J. R., O'Connor, J. P., Metcalf, P. A., Lawson, M. R. & Jonsson, R. N.: Clinical usefulness of estimation of serum fructosamine concentration as a screening test for diabetes mellitus. Br Med J *287:* 863, 1983.
5. Dahllöf, A.-G., Björntorp, P., Holm, J. & Scherstén, T.: Metabolic activity of skeletal muscle in patients with peripheral arterial insufficiency. Effect of physical training. Eur J Clin Invest *4:* 9, 1975.
6. Fellin, R., Manzalo, E., Rorai, E., Baggio, G., Baiocchi, M. R., Dalla Costa, F. & La Scala, G.: Insulin, glucose tolerance, lipid, and lipoprotein interrelationships in patients with peripheral artery disease. *In* International Conference on Atherosclerosis (ed. L. A. Carlson, R. Paoletti, C. S. Sirtori & G. Weber), pp. 397–402. Raven Press, New York, 1978.
7. Greene, W. A., Conron, G., Schalch, D. S. & Schreiner, B. F.: Psychologic correlates of growth hormone and adrenal secretory responses of patients undergoing cardiac catheterization. Psychosom Med *32:* 599, 1970.
8. Hartley, L. H.: Growth hormone and catecholamine response to exercise in relation to physical training. Med Sci Sports *7:* 34, 1975.
9. Holm, J., Dahllöf, A.-G., Björntorp, P. & Scherstén, T.: Glucose tolerance, plasma insulin, and lipids in intermittent claudication with reference to muscle metabolism. Metabolism *22:* 1395, 1973.
10. Hyyppä, M. T., Aunola, S. & Kuusela, V.: Psychoendocrine responses to bicycle exercise in healthy men in good physical condition. Int J Sports Med *7:* 89, 1986.
11. Johnson, R. J., Metcalf, P. A. & Baker, J. R.: Fructosamine: a new approach to the estimation of serum glycosylprotein. An index of diabetic control. Clin Chim Acta *127:* 87, 1982.
12. Jonason, T., Jonzon, B., Ringqvist, I. & Öman-Rydberg, A.: Effects of physical training on different categories of patients with intermittent claudication. Acta Med Scand *206:* 253, 1979.
13. Kindermann, W., Schnabel, A., Schmitt, W. M., Biro, G., Cassens, J. & Weber, F.: Catecholamines, growth hormone, cortisol, insulin, and sex hormones in anaerobic and aerobic exercise. Eur J Appl Phys *49:* 389, 1982.
14. Lindgärde, F., Malmquist, J. & Balke, B.: Physical fitness, insulin secretion and glucose tolerance in healthy males and mild type-2 diabetes. Acta Diabetol Lat *20:* 33, 1983.
15. Reitman, J. S., Vasquez, B., Klimes, I. & Nagulesparan, M.: Improvement of glucose homeostasis after exercise training in non-insulin-dependent diabetes. Diabetes Care *7:* 434, 1984.
16. Reunanen, A., Takkunen, H. & Arooma, A.: Prevalence of intermittent claudication and its effect on mortality. Acta Med Scand *211:* 249, 1982.
17. Rosetzsky, A., Struckmann, J. & Mathiesen, F. R.: Minimal walking distance following exercise treat-

ment in patients with arterial occlusive disease. Ann Chir Gynaecol *74:* 261, 1985.
18. Saltin, B., Lindgärde, F., Houston, M., Hörlin, R., Nyygard, E. & Gad, P.: Physical training and glucose tolerance in middle-aged men with chemical diabetes. Diabetes *28:* 30 1979.
19. Sawhney, R. C., Malhotra, A. S. & Gupta, R. B.: Plasma insulin, growth hormone and blood sugar during exercise in man. Ind J Physiol Pharmacol *26:* 119, 1982.
20. Skrede, S. & Kvarstein, B.: Hyperlipidemia in peripheral atherosclerotic arterial disease. Acta Chir Scand *141:* 333, 1975.
21. Sørlie, D. & Myhre, K.: Effects of physical training in intermittent claudication. Scand J Clin Lab Invest *38:* 217, 1978.
22. Wirth, A., Diehm, C., Mayer, H., Mörl, H., Vogel, I., Björntorp, P. & Schlierf, G.: Plasma C-peptide and insulin in trained and untrained subjects. J Appl Physiol Respirat Environ Exercise Physiol *50:* 71, 1981.
23. Woodhouse, S. P., Sutherland, W. H. F., Nye, E. R., Sargent, J., Waite, G., Merthens, C., Cruickshank, F. M. & Balcher, M. R.: Physical training and fasting serum insulin levels in sedentary men. Clin Physiol *4:* 475, 1984.
24. Zetterqvist, S.: The effect of active training on the nutritive blood flow in exercising ischemic legs. Scand J Clin Lab Invest *25:* 101, 1970.

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