The effects of physical training on insulin secretion and effectiveness and on glucose metabolism in obesity and Type 2 (non-insulin-dependent) diabetes mellitus

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Summary. Obese subjects with normal glucose tolerance ($n = 55$), and, in another study, a group of patients with Type 2 (non-insulin-dependent) diabetes ($n = 33$), and controls ($n = 13$) matched for body weight and age but with normal glucose tolerance, participated in an individualized physical training program for 3 months. Under controlled dietary conditions, metabolic studies were performed before and in steady state after the last exercise session after training in the subjects showing signs of physical training in VO_2 max and heart rate measurements. No changes occurred in body weight, body cell mass, body fat or adipose tissue cellularity. Oral glucose tolerance was improved in the patients with diabetes mellitus only. In both diabetic and control subjects initially elevated C-peptide concentrations decreased, while low C-peptide values increased and which was particularly pronounced in diabetic subjects with subnormal values. Peripheral insulin values did not change. Glucose disposal rate measured with the glucose clamp technique was similar in diabetic patients and control subjects. An improvement was seen at both submaximal and maximal insulin levels in both groups, correlating with improvement in glucose tolerance in the diabetic subjects.

No changes were found in adipocytes in insulin binding or the antilipolytic effect of insulin at submaximal insulin levels, but there was a normalization of a decreased glucose incorporation into triglycerides.

These results indicate that both insulin secretion and effectiveness are altered by physical training in different ways in different clinical entities. They suggest that in insulin resistant conditions with high insulin secretion (as indicated by high C-peptide concentrations) the increased peripheral insulin sensitivity is followed by a decreased insulin secretion. This is not associated with an improvement of glucose tolerance. In Type 2 diabetes with low insulin secretion, an increased insulin secretion results from physical training, perhaps due to accompanying sensitization of the autonomic nervous system. Peripheral insulin concentrations are not altered, suggesting that the extra insulin produced is captured by the liver. This mechanism, as well as the improved peripheral insulin responsiveness seen in the whole body and also seen at the cellular level, probably both contribute to an improvement in glucose tolerance.

Key words: Type 2 diabetes, obesity, physical training, glucose tolerance, insulin, C-peptide, glucose clamp, insulin binding, adipocytes.

By tradition exercise is one of the basic principles in the therapy of diabetes mellitus to stabilize glucose homeostasis and to improve diabetic control. The documentation of such effects is, however, surprisingly incomplete. Only recently have well-controlled studies been performed with the purpose of trying to better define the place of regular exercise and physical training in the therapy of diabetes mellitus. In general, the effects on glucose metabolism have been moderate, of short duration, or even lacking (1–3), in spite of the now well-established fact that increased levels of plasma insulin are clearly lowered by physical training due to an increased peripheral insulin sensitivity (4). These findings suggest that, at best, only a subgroup of Type 2 (non-insulin-dependent) patients benefits from physical training.

In the present work this possibility was elucidated by subjecting sufficiently large groups of diabetic and obese subjects and controls to physical training to allow an analysis of effects in subgroups, characterized in terms of glucose intolerance as well as secretion, peripheral uptake and effectiveness of insulin. Changes in these variables were registered after physical training in an attempt to explain how alterations in glucose tolerance are brought about.

Subjects and methods

Subjects examined

Study I. Fifty-five obese women were recruited from the Obesity Outpatient Clinic at the University Hospital. They were all in a non-dieting, weight-stable condition, body weight changing less than 2 kg

within the preceeding three months. They all had a non-diabetic glucose tolerance test (for definition, see below). Non-obese control women ($n=15$) were found among volunteers obtained by an advertisement in a local newspaper. They were weightstable, healthy and non-dieting. Most of these women were physically active to some extent, but none was training regularly. No subjects were taking contraceptive drugs or any other drugs of known importance for the examined variables. All the controls had normal glucose tolerance tests. The body composition and other characteristics of these subjects are seen in Table 1.

Study II. Forty-six subjects, 34 women and 12 men, were recruited from the Diabetes or Obesity Outpatient Clinics at the University Hospital or by an advertisement in a local newspaper for participation in the study. The general characteristics of the patients are summarized in Table 2. The subjects had a history of weight stability ($\pm$-2 kg body weight) during at least the preceeding 3 months. They were then observed for about two months to ensure weight stability by body weight recordings at least twice during this period. All were actively employed but had a rather sendentary way of life, not training regularly or being engaged in any kind of sports activity. None was on a diet except patients with known Type 2 diabetes (12 men and 12 women). These subjects were also treated with sulfonylurea drugs for at least 1 year. This medication was not changed during the period of physical training, and no subject was on insulin treatment. No subject had obvious signs or symptoms of diabetic complications, and the mean diabetes duration was 5.1 years. Of the 46 subjects participating in study II glucose tolerance tests revealed that 13 had a normal glucose tolerance (for definition, see below), while the remaining ($n=33$) had decreased glucose tolerance of varying degrees including overt clinical diabetes mellitus ($n=24$) and were examined in one group.

Five days prior to, as well as after the physical training period, the patients were placed on a diet estimated to give caloric balance, viz. 35 kcal per kg ideal body weight. Ideal body weight was taken from the Metropolitan Life Insurance tables as the mean of the value given at medium frame. The diet consisted of about 15, 40 and 45% of protein, fat and carbohydrate, respectively, and was identical before and after the period of physical training. Glucose tolerance tests and the euglycaemic glucose clamp were performed under these conditions on the fourth day or later after the last exercise session. All participants were instructed not to change their ordinary diet during the training period.

All participants gave their informed consent before entering into the examinations. The study was approved by the Ethical Committee at the University of Göteborg.

Oral glucose tolerance test (OGTT). One hundred grams glucose, dissolved in 200 ml lemon flavoured water, were taken orally in the morning in the overnight fasting state. The subjects were asked not to smoke that morning and arrive to the laboratory without rush. Blood samples were drawn before and at 30, 60, 90 and 120 min after glucose ingestion from an indwelling catheter in an antecubital vein for enzymatic determination of blood glucose (GLOX, Kabi, Sweden), plasma insulin and connecting C-peptide by commercially available radioimmunoassay methods (Phadebas Pharmacia, Uppsala, Sweden and Novo, Copenhagen, Denmark respectively). The error of these methods are <0.05% in the mean range of the analysed results. With this test the subjects were classified as diabetic if at least three glucose values exceeded the ranges proposed by the Diabetes Data Group [5].

Body composition determinations

Body weight was recorded to the nearest 0.1 kg and height to the nearest cm. Total body potassium was measured in a whole body counter, after correction for the shielding effect of body fat [6]. Lean body mass (LBM) and body fat were then calculated as described by Forbes et al. [7].

Subcutaneous needle biopsies of adipose tissue were performed in the epigastric, hypogastric, femoral, gluteal and upper arm regions for determinations of fat cell weight with a microscopic method [8]. These

values were averaged. Total fat cell number was estimated by dividing body fat with the average fat cell weight.

Exercise test and determination of maximal oxygen uptake (VO_2 max)

A Monark (Varberg, Sweden) mechanically braked bicycle ergometer was used for the exercise tests. The maximal oxygen uptake measurements were performed by stepwise work load increase until exhaustion [9] with continuous ECG and frequent blood pressure recordings. Expired air was collected in Douglas bags, and the volume and O_2-content measured in a Beckman OM-11 instrument during the last minutes of the maximal work load. The test was repeated once at another occasion to ensure reproducibility, which was $\pm 3\%$.

Heart rate and blood pressure at predetermined submaximal work loads (50 W and 100 W) were also recorded for comparisons before and after the physical training programme.

Physical training

The groups were trained for 3 months, three times a week. The duration of each training session was 50 min, starting with 10-15 min warm-up including walking, jogging and calisthenics of light intensity, and including exercises with all parts of the body. The programme then continued with alternating heavy and light periods. The heavy intervals were performed on a bicycle ergometer, lasted for 4 min, and were standardized for each patient to reach 80-90% of the individual VO_2 max, commencing with a submaximal work load. This level was adjusted upwards as the conditioning of the participants increased during the training to be kept at an 80-90% level.

Euglycaemic glucose clamp measurements

Arterial blood was drawn from the radial artery and fed into an automatic, continuous glucose monitoring system (Gambro, Lund, Sweden), which measures the blood glucose levels every minute. A solution of 0.4 IU/ml of porcine insulin (Actrapid, Novo, Copenhagen, Denmark) dissolved in isotonic saline was infused into the subclavian vein through a catheter introduced into a brachial vein with a constant infusion pump (IMED 922 H, San Diego, Calif., USA).

The insulin was given at two infusion rates (0.08 and 0.60 IU·kg body weight^{-1}·min^{-1}). The plasma insulin levels obtained by these infusions were not different before and after training (105.5 ± 7.2 and 107.3 ± 7.4 at low level and 1357.6 ± 103.9 and 1410.3 ± 69.9 mU/l at high level - means $\pm$ SEM, before and after training respectively). Blood glucose levels were kept constant by the infusion centrally of a 40% (w/v) solution of glucose containing 100 mmol/l of potassium, 20 mmol/l of magnesium and 30 mmol/l of phosphate. Blood for plasma insulin levels was drawn every 5 min. When steady state was reached, determined by the coefficients of variation (mean $\pm$ SD) for insulin and glucose, the glucose disposal rate was calculated during the last 20-min period of the low and high insulin infusions respectively. The duration of each of these periods was 60 min. These studies were performed in a subgroup of 13 control and 10 diabetic subjects who gave their informed consent.

Adipose tissue studies

After fasting overnight, a subcutaneous adipose tissue biopsy was taken from the hypogastric region in local anaesthesia (Lidocaine, Astra, Sweden). Care was taken not to infiltrate the tissue to be excised.

Insulin binding

Fat cells were liberated by incubating the biopsies in medium 199 containing collagenase (1.5 mg/ml) and 50 g/l of bovine serum albumin

Table 1. Characteristics of examined groups (Study I)

	Control subjects ($n = 15$)	Obese subjects ($n = 55$)	
		Before training	After training
Age (years)	37.1 ± 1	38.5 ± 2.0	–
Height (cm)	169.0 ± 2	165.9 ± 1.3	–
Weight (kg)	62.0 ± 1.8	93.1 ± 2.6 ($p < 0.001$)	94.0 ± 2.8
Whole body potassium (Meq)	2781 ± 88	3499 ± 88 ($p < 0.001$)	3462 ± 83
Body fat (kg)	20.0 ± 2.1	41.8 ± 2.1 ($p < 0.001$)	42.1 ± 2.1

Means ± SEM. Comparisons between controls and obese subjects

Table 2. Characteristics of examined groups (Study II)

	Control subjects ($n = 13$)		Diabetic subjects ($n = 33$)	
	Before	After	Before	After
Age (years)	46.2 ± 3.3	–	49.8 ± 2.1	–
Body weight (kg)	92.3 – ± 3.2	91.2 ± 3.2	87.5 ± 3.1	88.0 ± 3.1
Body cell mass (kg)	27.3 ± 0.8	27.0 ± 0.7	31.6 ± 1.3 ($p < 0.05$)	38.1 ± 1.3
Body fat (kg)	44.2 ± 2.3	43.8 ± 2.4	31.1 ± 1.9 ($p < 0.05$)	31.2 ± 2.0
Fat cell number (10^{10})	6.8 ± 0.5	–	4.8 ± 0.5 ($p < 0.05$)	–
Fat cell weight (μg)	0.65 ± 0.02	–	0.65 ± 0.03	–

Means ± SEM. Comparisons between controls and Type 2 diabetic subjects

for 1 h at 37 °C as previously described [10]. After filtration, the cells were carefully washed four times in fresh medium. Insulin binding to the cells was then measured using the method of Gammeltoft and Gliemann [11]. The cells were incubated for 45 min at 24 °C with 0.5–1.0 ng/ml monocomponent ^{125}I-insulin. Cold insulin added was present at the indicated concentrations. Tracer binding in the presence of 4.17 ng/ml (100000 μU/ml) unlabelled insulin was considered nonspecific and subtracted from the results. Mean fat cell size was determined according to Smith et al. [10]. Mean fat cell surface area was calculated according to the formula:

$SA = [\bar{d}^2 + SD^2] \pi$: where SA = surface area, $\bar{d}$ = mean fat cell diameter, and SD the standard deviation.

Lipolysis and glucose incorporation into triglycerides

After preincubating tissue fragments (average weight 10 mg) for 30 min, the incubations were performed for 2 h at 37 °C in fresh medium 199 containing 1 mmol glucose, 40 g/l bovine serum albumin, 0.15 μCi/ml (U-^{14}C)-glucose and noradrenaline (10^{-5} M), and different concentrations of insulin. Glycerol release to the incubation medium, analyzed according to Laurell and Tibbling [12], was taken as an index of lipolysis. Triglycerides were extracted according to Dole [13] and the radioactivity counted. These studies were performed in 12 control and 18 diabetic subjects who gave their informed consent.

Glucagon-poor insulin was generously supplied by Eli Lilly and Co, (Indianapolis, Ind., USA). Medium 199 was obtained from Stat-

ens Bakteriologiska Laboratorium, (Stockholm, Sweden). Collagenase, type I, bovine serum albumin, fraction V, and norepinephrine bitartrate were from Sigma (St. Louis, Mo., USA). U-^{14}C-glucose (4 mCi/mmol) was obtained from New England Nuclear Corporation (Boston, Mass., USA), and ^{125}I-monocomponent insulin (specific activity about 190 μCi/ug) was a generous gift from Dr. S. Ivarsson, Malmö, Sweden.

Statistical methods

Intra-individual differences, comparing results before and after the training period as well as differences between groups, were tested using the Student's t-test.

Results

Study I

As seen in Table 1, physical training was not followed by any changes in body composition. All subjects following the training programme showed increases in VO_2 max. and/or decreases of heart rate on a submaximal work load (not shown).

Table 3 shows that the fasting glucose values and sum of the glucose values during glucose tolerance test were higher in the group of all obese subjects than in controls ($p < 0.05$). The sum of insulin values during glucose tolerance test was also higher in the obese group ($p < 0.01$) but the C-peptide values were not.

Physical training in the entire group of obese subjects was not followed by any changes in glucose or insulin, while the sum of C-peptide concentrations decreased.

Figure 1 a shows the C-peptide values before and after physical training (r: 0.72 $p < 0.01$) and Figure 1 b the correlation between the changes in C-peptide and the pretraining values (r: 0.28, $p < 0.05$). There were no correlations between the changes of insulin and glucose concentrations with their respective pretraining values (not shown).

To further analyse this phenomenon the obese subjects were divided into three groups with low, normal or high insulin secretion, utilizing the sum of C-peptide values of the controls as dividing line. The obese subjects with C-peptide concentrations within the mean ± 2 SD of the controls were called normal insulin secretors (NIS), those below or above these limits were low high insulin secretors (LIS and HIS groups respectively). As seen in Table 3 these groups did not differ in glucose tolerance, but the obesity HIS group had higher insulin values than the other groups ($p < 0.05$). With physical training no changes occurred in neither blood glucose nor insulin values in any of these groups. C-peptide values decreased in the HIS group and NIS group (only sum of C-peptide values), and increased in the LIS group (Table 3). There were no differences in body weight, body fat and total body potassium between the groups and no changes with physical training (not shown).

Table 3. Effects of physical training on glucose tolerance and plasma insulin and C-peptide concentrations (Study I)

|	Control subjects ($n=15$)	Obesity all ($n=55$)	Obesity HIS ($n=15$)	Obesity NIS ($n=22$)	Obesity LIS ($n=14$)
Fasting glucose (mmol/l)					
Before	3.9 ±0.1	4.4 ±0.1	4.6 ±0.2	4.4 ±0.2	4.2 ±0.1
After	–	4.3 ±0.1	4.6 ±0.2	4.3 ±0.2	4.1 ±0.2
p		NS	NS	NS	NS
Sum of glucose (mmol/l)					
Before	22.8 ±1.1	31.5 ±1.1	32.6 ±1.8	32.4 ±2.2	29.4 ±1.6
After	–	30.5 ±1.2	32.5 ±2.6	31.3 ±2.3	28.1 ±1.4
p	–	NS	NS	NS	NS
Fasting insulin (nmol/l)					
Before	0.11±0.06	0.12±0.01	0.16±0.02	0.11±0.01	0.09±0.01
After	–	0.11±0.01	0.16±0.02	0.10±0.01	0.08±0.01
p	–	NS	NS	NS	NS
Sum of insulin (nmol/l)					
Before	1.00±0.10	2.30±0.13	2.99±0.28	2.06±0.15	2.04±0.22
After	–	2.12±0.14	2.89±0.33	2.00±0.20	1.70±0.16
p	–	NS	NS	NS	NS
Fasting C-peptide (nmol/l)					
Before	0.32±0.03	0.39±0.03	0.67±0.04	0.40±0.03	0.13±0.02
After	–	0.36±0.03	0.61±0.04	0.35±0.04	0.19±0.05
p	–	NS	$0.10>p>0.05$	NS	$0.10>p>0.05$
Sum of C-peptide (nmol/l)					
Before	5.11±0.31	4.86±0.42	8.91±0.32	4.84±0.33	1.51±0.18
After	–	4.15±0.46	7.51±0.60	3.78±0.63	2.35±0.67
p	–	$p<0.05$	$p<0.05$	$p<0.05$	$p<0.05$
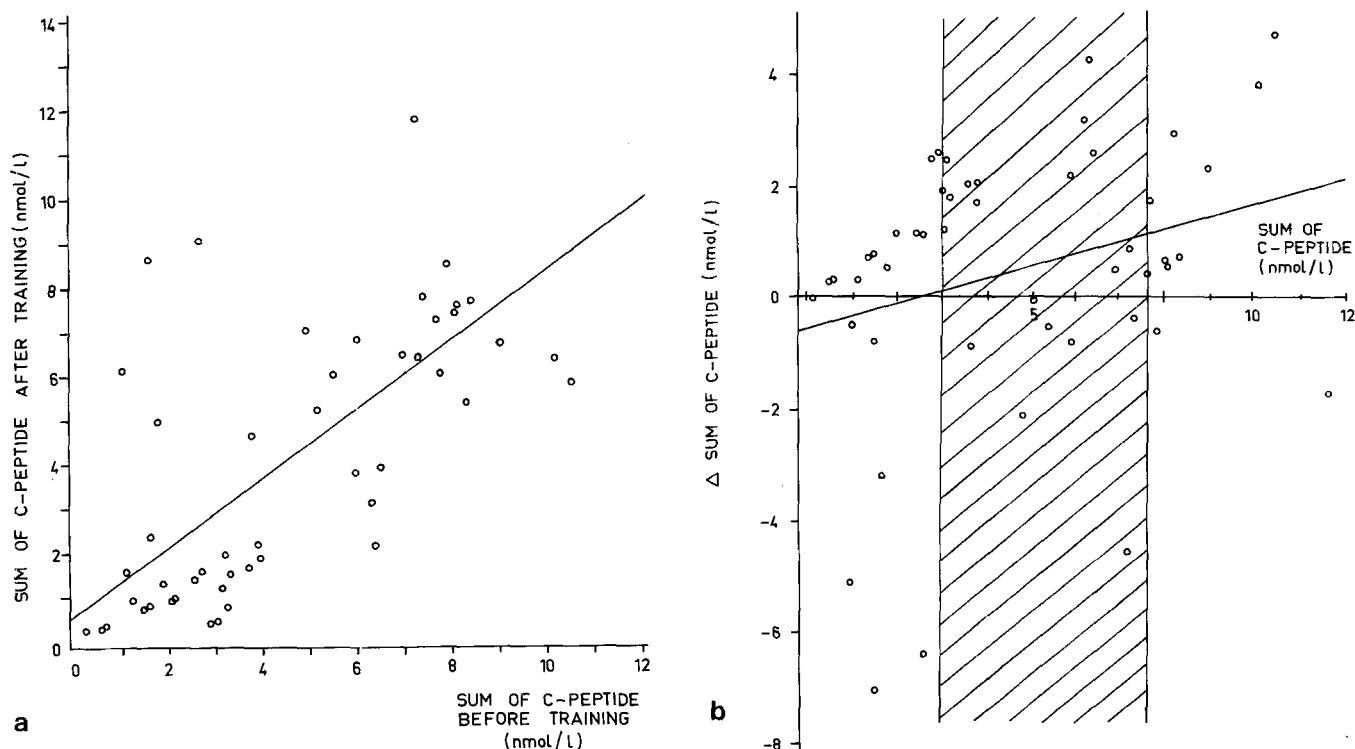
Fig. 1. a The relationship between the sum of plasma C-peptide concentrations during glucose tolerance test before and after physical training in obese subjects. $y=0.55+0.78\ x$; $r: 0.72$; $p<0.01$ (Study I). **b** The relationship between the sum of plasma C-peptide concentrations during glucose tolerance test before training and the change in these values with physical training in obese subjects. $y=-0.55+0.22\ x$; $r: 0.28$; $p<0.05$. Shaded area: Mean ±2 SD of values for nonobese controls (Study I)

Study II

Table 2 shows that age, body weight and average fat cell size did not differ between the non-diabetic and diabetic subjects. The diabetic subjects had higher body cell mass, less body fat and fewer fat cells than the non-diabetic subjects. None of these variables changed with physical training.

A mean increase was seen in maximal oxygen uptake following training, while heart rate and blood pressure decreased both at rest and during submaximal work (Table 4). Examining individual data, five diabetic subjects did not show any evidence of physical training in neither VO_2 max nor heart rate during submaximal

work load. These subjects were therefore excluded from further analyses.

The blood glucose levels were higher in the diabetic than the non-diabetic subjects (Table 5). Plasma concentrations of C-peptide as well as of insulin during OGTT were lower in the diabetic group. Plasma lipids were not different.

With physical training the plasma C-peptide concentrations during the glucose tolerance test decreased in the nondiabetic subjects. In contrast, in the diabetic group, C-peptide concentrations increased. Glucose intolerance improved in the diabetic group. Insulin or lipid values did not change in any of the groups.

Comparisons between the diabetic subjects who were treated with sulfonylurea or not showed higher glucose values and lower C-peptide values in the former, but otherwise no differences were found. Both showed the same response to physical training. Furthermore, no difference in response to physical training was seen between men and women (not shown).

Analogous to the non-diabetic obese subjects in Study I the change in sum of C-peptide values during OGTT correlated significantly with the C-peptide values before commencing the training program as seen in Figure 2. It is also seen that this correlation was mainly due to an increase during physical training of low values, particularly those which before training were below the normal range. Here the average values increased dramatically from 1.93 ± 0.14 nmol/l before training to 6.09 ± 1.43 nmol/l after training ($p < 0.001$). There were no significant changes in insulin in this subgroup or in the remaining subjects.

Euglycaemic glucose clamp studies

The results of the euglycaemic glucose clamp studies are shown in Fig. 3. The glucose disposal rate was simi-

Table 4. Circulatory variables of examined groups before and after physical training (Study II)

	Control subjects (n = 13)		Diabetic subjects (n = 33)	
	Before	After	Before	After
VO₂ max (l/min)	2.23 ± 0.14	2.62 ± 0.20^b	2.27 ± 0.14	2.59 ± 0.13^c
Heart rate (beats/min)				
Rest	86 ± 4	77 ± 4^a	83 ± 3	72 ± 3^c
Work (50 W)	116 ± 4	115 ± 4	113 ± 4	105 ± 4^a
Work (100 W)	147 ± 5	141 ± 4	140 ± 4	123 ± 4^b
Systolic blood pressure (mm Hg)				
Rest	140 ± 4	131 ± 4^a	144 ± 4	143 ± 4
Work (50 W)	150 ± 3	145 ± 4	160 ± 4	152 ± 4^a
Work (100 W)	179 ± 5	157 ± 6^a	188 ± 6	178 ± 5^a

Means ± SEM. Comparisons between results before and after physical training.
$^a p < 0.05$; $^b p < 0.01$ $^c p < 0.001$

Table 5. Metabolic variables of examined groups before and after physical training (Study II)

	Control subjects (n = 13)		Diabetic subjects (n = 28)	
	Before	After	Before	After
Fasting glucose (mmol/l)	4.7 ± 0.2	4.7 ± 0.2	7.8 ± 0.4 ($p < 0.001$)	7.8 ± 0.4
Sum of glucose values during OGTT (mmol/l)	32.1 ± 1.8	31.5 ± 2.6	62.8 ± 4.0 ($p < 0.001$)	59.4 ± 4.3^a
Fasting C-peptide (nmol/l)	0.64 ± 0.08	0.53 ± 0.05	0.50 ± 0.05 ($p < 0.05$)	0.60 ± 0.05
Sum of C-peptide values during OGTT (nmol/l)	8.34 ± 0.74	6.85 ± 0.81^a	4.64 ± 0.46 ($p < 0.01$)	6.10 ± 0.57^a
Fasting insulin (nmol/l)	0.16 ± 0.03	0.14 ± 0.02	0.13 ± 0.01	0.13 ± 0.01
Sum of insulin values during OGTT (nmol/l)	2.76 ± 0.29	2.67 ± 0.36	1.58 ± 0.14 ($p < 0.01$)	1.53 ± 0.15
Triglycerides (mmol/l)	1.9 ± 0.2	2.0 ± 0.3	1.7 ± 0.2	1.7 ± 0.2
Cholesterol (mmol/l)	6.2 ± 0.3	6.0 ± 0.3	6.1 ± 0.2	6.1 ± 0.2

OGTT: Oral glucose tolerance test
Means ± SEM Comparisons between control and diabetic subjects (within parentheses) and between results before and after physical training.
^{a} $p < 0.05$

lar in the diabetic and non-diabetic groups at both low and high insulin infusion rates. Physical training increased the glucose disposal rate in both groups, and at both insulin infusion rates. There was a positive, significant correlation between improvement in glucose tolerance (sum of glucose values during OGTT before - after) and the glucose disposal rate (per kg LBM) in the glucose clamp studies in the diabetic group (r: 0.65, $p<$ 0.01).

Adipose tissue studies

Figure 4 depicts the data of insulin binding to adipocytes. There were no significant differences in insulin binding between the groups, neither before nor after physical training. There was no change in binding after the training period.

Figure 5 shows the insulin effect on glucose incorporation into triglycerides before and after training. Adipocytes from diabetic patients showed less incorporation than from controls before training ($p<0.05$). The non-diabetic group showed no change with training. In the diabetic group, however, the insulin stimulated glucose incorporation was significantly increased after physical training.

Basal and noradrenaline-stimulated lipolysis as well as the antilipolytic response of insulin, were similar in both groups, and were not significantly changed by the training period. Insulin sensitivity, evaluated as the insulin concentration giving half-maximal antilipolytic effect, was also unchanged following the training period (data not shown).

Discussion

C-peptide and insulin are released from the B cell in equimolar amounts [14, 15]. In contrast to insulin, C-peptide is not taken up by the liver in animals [16, 17] or in man [18, 19]. Measurements of C-peptide concentrations in peripheral blood therefore give a better estimate of insulin secretion than measurements of peripheral insulin concentrations. The validity of evaluating insulin secretion by C-peptide concentration measurements depends, however, on several additional prerequisites. First, metabolic clearance rate (MRC) has to be known to allow transformations of concentration to actual secretion of insulin and C-peptide. If this is not known, MCR has at least to be constant in different conditions, and comparable between different groups.

MCR of C-peptide does not change with stimulation of insulin secretion. Uptake is apparently not occurring in muscle and adipose tissue, and the main excretory route is via the kidneys [20]. Urinary clearance of C-peptide is essentially independent of the plasma C-peptide concentration, and similar in normal weight, obese and diabetic subjects in relation to creatinine secretion [21, 22], and MCR of C-peptide is not different
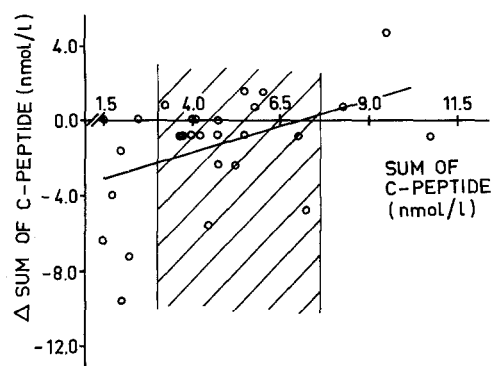

Fig. 2. The relationship between the sum of plasma C-peptide concentrations during glucose tolerance test before training and the change in these values with physical training in patients with Type 2 diabetes. $y= -4.26+0.603$ x; $=0.35$ ptb <0.01. Shaded area; Mean ± 2 SD of values for non-obese controls (Study II)
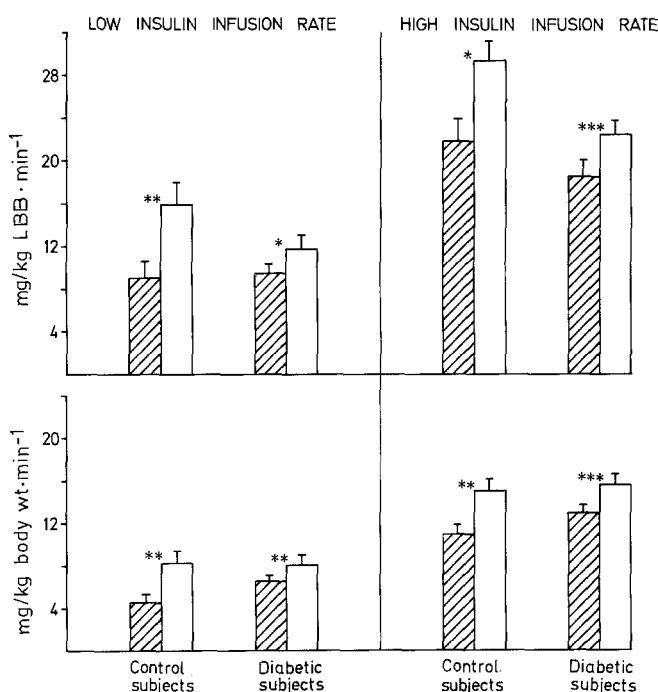

Fig. 3. Glucose disposal rate in diabetic and control subjects during euglycaemic clamp before (hatched bars) and after (open bars) physical training at two different insulin infusion rates (69–165 and 810–2350 mU/min, respectively).
$*p<0.05$; $**p<0.001$; $***p<0.001$. (Means $\pm$ SEM)
$n=13$ and $n=10$ for control and diabetic patients respectively (Study II)

between non-diabetic and diabetic subjects [23]. Taken together this information seems to make it possible to conclude that C-peptide secretion from the B cell is equivalent to insulin secretion, and that liver uptake does not invalidate estimation of insulin secretion from C-peptide determinations. In summary, this means that the plasma C-peptide concentrations in the present work probably are useful indices of insulin secretion.

The correlation between the decrease and initial value of C-peptide (Fig. 1b) is partly a statistical artefact
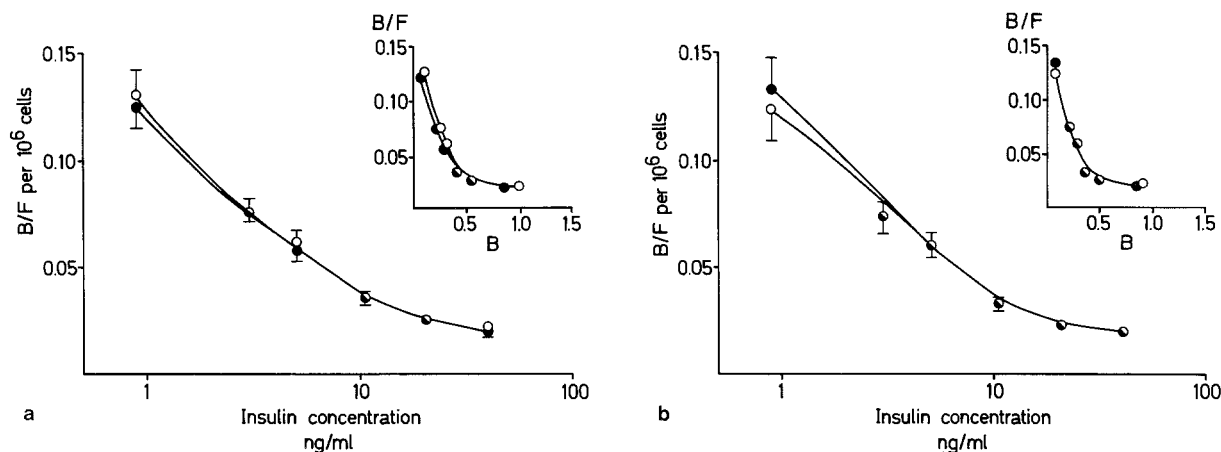
Fig.4a and b. Specific ^{125}I-insulin binding to adipocytes in **a** diabetic and **b** control subjects before (open circles) and after (filled circles) physical training. Inserted are shown the Scatchard plots. Bound insulin expressed as ng/10^6 cells. (Means ± SEM) $n = 12$ and $n = 17$ for control and diabetic subjects, respectively (Study II)
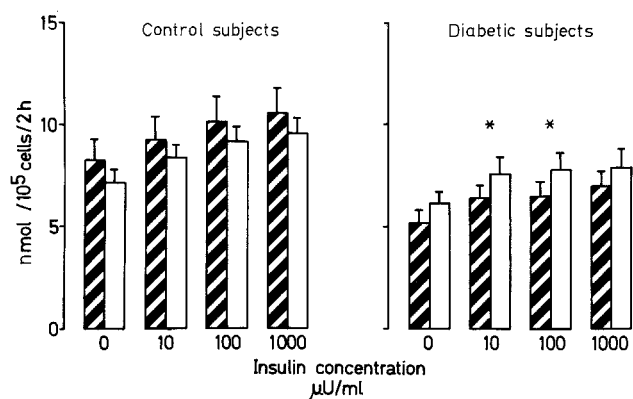

Fig.5. Basal and insulin stimulated U-^{14}C-glucose incorporation into triglycerides in diabetic and control subjects before (hatched bars) and after (open bars) physical training.
* $p < 0.05$. (Means ± SEM).
$n = 12$ and $n = 18$ for control and diabetic subjects, respectively (Study II)

(regression towards the mean) caused by the random errors (measurement errors and intraindividual variation). If the standard deviation of the random errors were known it would be possible to compute to what extent the observed correlation is a biological reality. Lacking such precise information we can investigate whether the observed correlation can possibly be caused by the random errors alone. Such computations show that with the coefficient of variation of the random errors equal to 10% the (false) correlation would be 0.03 and with a variation of 20% the correlation would be 0.12. A correlation coefficient 0.28 can thus hardly be an effect of regression towards the mean. The observation must, however, be considered as a rather weak indication of a biological relationship since one has also to take into account the sampling errors in the correlation coefficient. The observed value differs from zero only at the 5% significance level.

These considerations thus make it unlikely that the observed correlation was explainable other than to a minor degree by a statistical artefact. Therefore further analyses were performed with the material of obese subjects divided into groups with normal, low and high C-peptide values using control values as guidance.

Hyperinsulinaemia was found in all the subgroups of obesity (Table 3). Hypersecretion of insulin was, however, found only in the HIS group, while in the LIS group the insulin secretion was markedly low. These findings indicate different causes to the hyperinsulinaemia in obesity. One possible explanation might be found in differences in the liver uptake of insulin. If this is the main explanation the molar ratios of insulin and C-peptide concentrations in Table 3 suggest that very little of secreted insulin is taken up in the liver in the LIS group, while the liver uptake in the NIS and HIS groups would be approximately 60% and 70% respectively (sum of values). These observations confirm previous reports [24, 25].

In the total group of obese, non-diabetic subjects (study I) physical training was followed by only limited changes in the metabolic and hormonal variables. When divided into subgroups according to the initial insulin secretion, as indicated by C-peptide concentrations, it was found, however, that high and normal insulin secretors showed a decreased secretion after physical training. This was also the case with the obese controls in study II, who were on an average high insulin secretors with similar C-peptide values as the obesity HIS group in study I. This has been observed repeatedly before by measurements of insulin [4, 26, 27] and C-peptide [28]. In obese subjects with low insulin secretion, however, physical training was followed by increased C-peptide values. Confirming previous studies [4, 28], no changes were seen in glucose tolerance or in body composition variables.

Patients with diabetes mellitus improved their glucose tolerance with physical training. This occurred

without changes in body composition and plasma insulin. C-peptide concentrations increased, however. A closer analysis of this phenomenon revealed that this increase was most pronounced in those patients who initially had the lowest C-peptide values, again indicating that physical training in this situation actually causes an increase of a low insulin secretion.

Taken together these data then indicate that in conditions with insulin hypersecretion, physical training results in a decreased insulin secretion. In contrast, in subjects with abnormally low insulin secretion this is elevated after physical training. Insulin hypersecretion is usually considered to be the result of a compensation for an increased peripheral insulin resistance. When this resistance is lowered by physical training, as evidenced here by the glucose clamp studies, then consequently insulin secretion decreases. It is less clear why insulin secretion increases after physical training in conditions with low insulin secretion. It has previously been shown that physical training is followed by an increased sensitivity in both the cholinergic [29] and B-adrenergic [30] nervous systems, both stimulating insulin secretion. It is therefore suggested that this increased sensitivity is the cause to the increased insulin production after physical training in conditions with low insulin secretion reported here.

The changes in C-peptide concentrations after physical training were much more pronounced than those in insulin. Neither when an elevated C-peptide concentration was lowered nor when C-peptide values were increased were insulin concentrations in the periphery different after training as compared with before. The unchanged peripheral insulin concentrations in spite of alterations in insulin secretion indicate that the uptake of insulin in the liver and/or periphery was altered.

Insulin clearance did not differ after as compared with before training as measured with the glucose clamp technique (data not shown), indicating that changes in the removal of insulin in the periphery was not changed by physical training. This in turn suggests that the uptake of insulin in the liver changed. In the case of an increased, low insulin secretion this then probably meant that the liver uptake of insulin had increased. This suggestion is supported by the fact that insulin uptake in the liver is dependent on the portal concentration of insulin [31], in turn dependent on insulin secretion. It seems reasonable to assume that this extra production of insulin after physical training, captured by the liver, contributed to the improvement of glucose intolerance seen in the diabetic subjects where the initial insulin secretion was subnormal.

Euglycaemic clamp studies

The glucose disposal rate estimated by the euglycaemic clamp showed no difference between the groups with or without diabetes mellitus, indicating a similar peripheral insulin effect on glucose uptake in these groups

which both were somewhat obese. The fact that the diabetic group did not appear resistant to insulin as compared to the non-diabetic group does not mean that they were normal with regard to insulin sensitivity and responsiveness. Rather insulin resistance was probably equally present in both groups. This was, however, improved by physical training to a similar extent in both groups. From other studies it is known that insulin sensitivity is increased in muscles during contraction [32, 33] or after physical training [34], while this does not seem to be the case in the liver [34]. The effects of physical training seen in the glucose clamp studies were then presumably mainly due to an increase of glucose uptake in muscles [35]. Although an increase of peripheral effectiveness of insulin occurred in both groups, it was only in the diabetic subjects that glucose tolerance improved. The improvement in glucose tolerance correlated with the increase in glucose disposal rate in the clamp measurement in the diabetic group. Whether these phenomena are causally related remains to be clarified, but this seems at least to be a reasonable possibility.

Adipose tissue studies

Adipose tissue only plays a minor role for total body glucose homeostasis, as compared to muscles and liver [36]. However, since insulin sensitivity and responsiveness in fat cells seem to reflect the severity of glucose intolerance in diabetic subjects [37, 38], it may be of interest to compare data obtained from adipocytes in vitro with those found with the glucose clamp technique. Therefore, to further elucidate the cellular mechanisms explaining the higher rate of glucose disposal following physical training, studies on abdominal fat cells were performed.

Insulin binding has been found not to deviate from normal in fat cells from obese and Type 2 diabetic patients [37, 38]. The present study confirms these results. Furthermore, insulin binding was not changed following physical training in accordance with previous reports [39, 40]. In monocytes an increased binding has been found [41, 42], but these cells are not natural target cells for insulin and, therefore, such data are less readily interpreted. Increased insulin binding to fat cells has been reported after physical training in rats [43]. A recent study seems to resolve this controversy showing that the increase in insulin binding, when found after physical training, is of such small magnitude that it has no obvious physiological significance in comparison with the increase in glucose transport [44].

Differences in insulin binding are reflected by a shift of the dose-response curve for insulin (altered insulin sensitivity) whereas a change in the maximal insulin effect (insulin responsiveness) mirrors postreceptor defect(s) [45]. Accordingly, insulin binding and insulin sensitivity, measured as the antilipolytic effect, were not changed in this study. In contrast, insulin responsive-

ness, as indicated by the maximal glucose incorporation into triglycerides, was significantly improved after physical training in the diabetic patients.

Increased glucose transport capacity has been found previously in fat cells from trained rats [44]. The glucose clamp data indicate that physical training results in an increased insulin responsiveness, because glucose disposal rate was increased both at the low (submaximal) and the high (maximal) insulin infusion rates. Adipose tissue data then also show that the effect of training on the insulin responsiveness of glucose metabolism is due to postreceptor changes, and with no changes in insulin binding. These parallel findings suggest that, following physical training, similar reactions are occurring in other tissues where glucose uptake is quantitatively more significant than in adipose tissue.

The insulin resistance in fat cells from Type 2 diabetic subjects is mainly due to a diminished insulin responsiveness of glucose metabolism, probably due to a post-receptor-defect of glucose transport [37, 38]. Hence, it is suggested that when physical training causes a reversal of this postreceptor defect, an improvement in glucose tolerance is obtained.

In conclusion, this study has shown that an improvement of glucose tolerance is obtained when moderately obese, diabetic subjects have been trained physically. Previous studies [1, 2] and studies appearing while this work was in progress [47–49] have shown varying results, which may be due to the fact that different subgroups of Type 2 diabetic patients react differently to physical training. The effect is probably partly due to an increase of the insulin effectiveness on peripheral glucose uptake, presumably of main quantitative importance in muscles. This improvement is accentuated by an increase of low insulin secretion, probably resulting in better insulinization of the liver. Taken together this then indicates that physical training improves glucose tolerance by increasing insulin effects both in the peripheral tissues (by increased tissue responsiveness, due to a reversal of a postreceptor defect), and in the liver (by uptake of an increased insulin secretion).

Finally, it should be emphasized that the present study has shown an improvement of glucose tolerance by physical training in the absence of body composition changes. When body fat decreases in physical training programs, the effects on glucose tolerance and glucose homeostasis are probably more pronounced [46].

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