Strength Training Increases Insulin-Mediated Glucose Uptake, GLUT4 Content, and Insulin Signaling in Skeletal Muscle in Patients With Type 2 Diabetes

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Strength training represents an alternative to endurance training for patients with type 2 diabetes. Little is known about the effect on insulin action and key proteins in skeletal muscle, and the necessary volume of strength training is unknown. A total of 10 type 2 diabetic subjects and 7 healthy men (control subjects) strength-trained one leg three times per week for 6 weeks while the other leg remained untrained. Each session lasted no more than 30 min. After strength training, muscle biopsies were obtained, and an isoglycemic-hyperinsulinemic clamp combined with arteriofemoral venous catheterization of both legs was carried out. In general, qualitatively similar responses were obtained in both groups. During the clamp, leg blood flow was higher (P < 0.05) in trained versus untrained legs, but despite this, arterio-venous extraction glucose did not decrease in trained legs. Thus, leg glucose clearance was increased in trained legs (P < 0.05) and more than explained by increases in muscle mass. Strength training increased protein content of GLUT4, insulin receptor, protein kinase B-α/β, glycogen synthase (GS), and GS total activity. In conclusion, we found that strength training for 30 min three times per week increases insulin action in skeletal muscle in both groups. The adaptation is attributable to local contraction-mediated mechanisms involving key proteins in the insulin signaling cascade. Diabetes 53:294–305, 2004
Blood biochemistry is fasting values measured in plasma, except glucose, which is measured in whole blood, and insulin and C-peptide, which were measured in serum. *Of cholesterol; †P < 0.05 (type 2 diabetic vs. control subjects at corresponding time).

**RESEARCH DESIGN AND METHODS**

**Subjects and experimental protocol.** We recruited 10 Caucasian patients with type 2 diabetes with fasting plasma glucose concentrations (means ± SE) of 8.4 ± 0.6 mmol/l and 7 Caucasian healthy control subjects with fasting plasma glucose concentrations of 5.6 ± 0.1 mmol/l and without a family history of type 2 diabetes. The study was approved by the ethical committee of Copenhagen and Frederiksberg (reference no. KF 01-204/99). Time since diagnosis of type 2 diabetes ranged from 2 to 11 years. All of the patients were treated with diet recommendations, and in addition some patients were treated with tolbutamide 1,000 mg/day (n = 2), glibenclamide 7 mg/day (n = 1), metformin 1,700 mg/day (n = 1), amlopidin 5 mg/day (n = 1), and cerivastatin 200 mg/day (n = 1). On the experimental day, no medication was taken. None of the control subjects took any medication. The diabetic patients were similar to the control subjects with respect to age (62 ± 2 vs. 61 ± 2 years) and body weight (85 ± 5 vs. 78 ± 3 kg), but height (172 ± 1 vs. 178 ± 2 cm, P < 0.05) was higher in control subjects compared with type 2 diabetic subjects. Thus, BMI was different (P < 0.05) between control (24.5 ± 0.8 kg/m²) and type 2 diabetic (28.3 ± 1.2 kg/m²) subjects.  

Resting arterial blood pressure covered a wide range and is therefore given as 25% quartile, median, and 75% quartile as follows: for control subjects, values were 133, 146, and 159 mmHg for systolic blood pressure and 69, 73, and 76 mmHg for diastolic blood pressure; for type 2 diabetic subjects, values were 136, 154, and 171 mmHg for systolic blood pressure and 70, 79, and 92 mmHg for diastolic blood pressure. Thus, both groups included normo- and hypertensive subjects. Other characteristics of the subjects are given in Table 1.

In one of the healthy control subjects, femoral venous catheterization in one leg proved to be very difficult, and for ethical reasons it had to be given up. Nevertheless, the experiment was continued without a venous catheter in one leg. Thus, paired comparisons between the legs could not be performed and therefore n = 6 for all leg balance data.

**Training program.** All subjects participated in a 6-week strength training program. The focus of the program was to have one leg perform strength training exercises while the other leg remained sedentary. The leg to be trained was chosen by drawing lots. Training sessions were all supervised and took place three times a week, with each training session lasting no more than 30 min. This included time for warm-up, which were light exercises for the upper body plus a warm-up set of 10–12 repetitions with a light load in each leg followed by a 2-min rest period. During the first and the last training session, the subject's 3 repetition maximum (3-RM) were measured. We calculated 1-RM as 106% of the measured 3-RM for each leg exercise (leg press, knee extension, and hamstring curl).  

During the first 2 weeks of the exercise, the subjects performed three sets of 10 repetitions, utilizing a load equivalent to 50% of 1-RM. During weeks 3–6, the subjects performed four sets of 8–12 repetitions utilizing 70–80% of 1-RM. During the last 2 weeks of the 6-week period, the load was adjusted so that all sets were exhaustive within 8–12 repetitions. The subjects rested for >90 s between sets and for >2 min between lifting stations. For further details of the leg resistance training program, see Table 2.

**Experimental procedures.** At 16 h after the last training session (i.e., in the trained state, “between” sessions), an isoglycemic-hyperinsulinemic clamp combined with arterio-venous catheterization of both legs was performed. Having fasted since midnight, the subjects arrived in the laboratory in the morning. Leg volume was measured by water displacement, and thigh circumference (20 cm proximal to the patella) was measured. The subjects were weighed and had their height measured, and then they were placed in bed. Electrocardiogram and heart rate were monitored by precordial electrodes. A catheter was inserted in a medial cubital vein for infusions of insulin (20%) and glucose (20%), and an arterial cannula was inserted in the radial or brachial artery for sampling of blood and continuous monitoring of blood pressure. In both femoral veins, Teflon catheters were inserted for sampling of blood and measurements of leg blood flow (thermodilution technique) as previously described (20).

**TABLE 2**

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Working loads refer to the weight used. A working load of, for example, 12 repetition maximum (RM) means that the load (weight used on the equipment) is so high that 12—but not 13—repetitions can be performed correctly.
subsequent adjustment of the glucose infusion rate. Arterial and femoral measurements in each leg at each time point) were performed at t = −30 and −15 min and then 105, 120, and 150 min in each clamp step. Before infusion of the clamp, muscle biopsies were obtained from both legs.

Calculations and analytical procedures. Leg uptake and release of glucose, β-hydroxybutyrate, glycerol, and free fatty acids (FFAs) were calculated as arterio-venous concentrations in whole blood or plasma (FFA) difference multiplied by blood flow. Plasma concentrations of FFAs were converted to whole-blood concentrations by multiplying with (1 + hematocrit). Leg balance was calculated relative to leg mass, assuming that the volume of 1 l corresponds to 1 kg of leg. All samples were stored at −80°C until analysis, except for C-peptide, FFA, and muscle biopsies, which were stored at −80°C.

A detailed description of the stabilization of blood samples and analysis of hormones, metabolites, and gasses was previously described by us (21). Glucose uptake rates in the whole body (M-values, calculated as the averaged glucose infusion rate during the final 30 min of each clamp step) and specifically in the legs were transformed to clearance rates (glucose uptake divided by the prevailing arterial glucose concentration), allowing for comparisons between the groups who were clamped at their prevailing glucose concentration (isoglycemic clamp).

After excision, the muscle biopsies were quickly cleaned from visible blood and fat and were then frozen immediately in liquid nitrogen. Biopsies were stored at −80°C until analyzed. Before fluorometric measurements of citrate synthase (CS) activity and the percent G6P-independent activity (referred to as the %I form 100 times the activity in the presence of 0.02 mmol/l G6P divided by the activity at 8.0 mmol/l G6P [saturated]), respectively.

Muscle fiber types and capillary density. All procedures were performed on 5-μm unfixed cryosections of human skeletal muscle specimens, essentially as described previously (24). Primary antibodies were mouse anti-skeletal fast myosin antibody (clone MY32; Sigma, St. Louis, MO) and mouse anti-skeletal slow antibody (clone WB-MHCs; Novocastra, Newcastle, U.K.). Capillaries were localized by immunostaining for the endothelial surface marker CD31, using mouse anti-CD31 (Dako, Glostrup, Denmark). Immunohistochemically stained sections from each biopsy specimen were analyzed in a Cast Grid system (Olympus, Copenhagen, Denmark). In each section, >20 fields (each 0.1134 mm² in size) including >100 muscle fibers were automatically randomly sampled for analysis. In each field the fibers were counted and their diameter determined as the lesser diameter. The mean fiber diameter for each fiber type was calculated as the average of measured fiber diameters for this fiber type in each section. The fractions of slow and fast fibers were calculated as the number of counted, typed fibers divided by the total number of fibers. The number of capillaries were counted per field and expressed as capillaries per square millimeter.

Statistics. Results are presented as the means ± SE. ANOVA for repeated measures was used for detection of differences between the trained and the untrained legs in the two groups. When a significant main effect was observed, the Student-Newman-Keuls test was used post hoc. In comparisons with a single measurement (e.g., glycogen content in the untrained and in the trained leg), Wilcoxon’s signed-rank test was used. The SigmaStat version 2.03 software package was used for all statistical calculations. P < 0.05 was considered significant in two-tailed testing.

RESULTS

Leg size and strength. After the strength training program, leg volume was 12.9 ± 1.0 vs. 13.4 ± 1.0 l for untrained versus trained legs (P < 0.1) and 12.5 ± 0.7 vs. 12.7 ± 0.6 l for untrained versus trained legs (NS) in control and type 2 diabetic subjects, respectively. Percent difference between untrained and trained legs was 4.1 ± 1.5 and 2.3 ± 2.2% in control and type 2 diabetic subjects, respectively. Thigh circumference was 52.8 ± 3.1 vs. 53.4 ± 2.7 cm for untrained versus trained legs (NS) and 52.5 ± 1.5 vs. 54.3 ± 1.9 cm for untrained versus trained legs (P < 0.05) in control subjects (n = 4) and type 2 diabetic subjects (n = 8), respectively. Percent difference between untrained and trained legs was 1.5 ± 1.6 and 3.4 ± 1.1% in control and type 2 diabetic subjects, respectively. No differences in these parameters were present between control and type 2 diabetic subjects.

Muscle strength increased in all subjects with training. Thus, in type 2 diabetic subjects, knee extension and leg press increased by 42 ± 8 and 75 ± 7% (both P < 0.05), respectively, and in control subjects they increased by 29 ± 1 and 77 ± 15% (both P < 0.05), respectively (Fig. 1). Muscle strength and the training-induced improvements were similar in the two groups.

Whole-body glucose metabolism. Type 2 diabetic subjects exhibited considerable insulin resistance, with whole-body glucose clearance rates approximately half the rates measured in control subjects (2.5 ± 0.6 and 8.9 ± 0.7 vs. 5.7 ± 0.9 and 14.4 ± 0.7 ml·min⁻¹·kg body wt⁻¹ in the two clamp steps, respectively; both P < 0.05). In absolute values, whole-body glucose uptake rates were not significantly different between type 2 diabetic and control subjects (clamp step I: 3.5 ± 0.7 vs. 5.8 ± 0.9 mg·min⁻¹·kg body wt⁻¹, P = 0.06; clamp step II: 13.8 ± 1.5 vs. 15.4 ± 0.5 mg·min⁻¹·kg body wt⁻¹, P = 0.40).

Leg glucose clearance. During the experiment, arterial blood glucose concentrations remained quite constant (Fig. 2), with a coefficient of variation of 6.1 ± 0.9 and
4.5 ± 0.9% in control and type 2 diabetic subjects, respectively. The arterio-venous glucose concentration difference was not different between trained and untrained legs in any of the groups. A difference between type 2 diabetes and control subjects approached statistical significance at clamp step II ($P < 0.1$) (Fig. 2).

Glucose clearance rates in the legs were not significantly different in the basal state between type 2 diabetic and control subjects. However, during clamp step I and II, clearance rates in the untrained legs ($P = 0.041$ and $P = 0.002$, respectively) as well as in the trained legs ($P = 0.002$ and $P < 0.001$, respectively) were decreased in type 2 diabetic subjects compared with control subjects (Fig. 3). In both groups a significant training effect was seen during clamp step II, whereas the difference between untrained and trained legs during clamp step I only approached significance (control subjects: $P = 0.062$) or was not different (type 2 diabetic subjects: $P > 0.05$) (Fig. 3).

Insulin infusion increased leg blood flow in both groups (Fig. 3), and leg blood flow was higher in control subjects compared with type 2 diabetic subjects (main effect: $P = 0.034$). Among type 2 diabetic subjects, leg blood flow was increased in trained versus untrained legs during clamp steps I ($P = 0.012$) and II ($P = 0.005$), but in control subjects a difference was seen between untrained and trained legs only at clamp step II ($P = 0.016$).

Despite higher insulin-mediated leg blood flow in trained versus untrained legs, glucose extraction was not different in trained and untrained legs (Fig. 3). However, glucose extraction was decreased in type 2 diabetic subjects compared with control subjects (main effect: $P = 0.047$), and this was primarily attributable to differences between the groups at clamp step I, for both trained ($P = 0.004$) and untrained ($P = 0.006$) legs, because no significant difference between control subjects and type 2 diabetic subjects in glucose extraction was detected at clamp step II.

**Hormones, substrates, and metabolites.** Fasting glu-
cose, insulin, and C-peptide concentrations in plasma were higher in type 2 diabetic compared with control subjects, but in both groups these parameters were unaltered by training (Table 1).

On the experimental day, fasting plasma insulin concentration was higher in type 2 diabetic subjects (60 ± 11006 12 pmol/l) compared with control subjects (29 ± 4 pmol/l) (P < 0.05). Probably because of this, a higher plasma insulin concentration at clamp step I was achieved in type 2 diabetic compared with control subjects (377 ± 26 vs. 270 ± 20 pmol/l, respectively; P < 0.05), whereas similar insulin concentrations were seen during clamp step II (12,453 ± 856 vs. 11,066 ± 874 pmol/l, respectively). In clamp steps I and II, plasma C-peptide concentrations were 735 ± 102 and 563 ± 62 pmol/l, respectively, in type 2 diabetic subjects and 413 ± 86 and 344 ± 66 pmol/l, respectively, in control subjects.

Arterial concentrations of glycerol, FFAs, and D-3-hydroxybutyrate always decreased with insulin infusion (Fig. 4). Basal arterial concentrations of FFAs (P < 0.05) and glycerol (P < 0.1) were slightly higher in type 2 diabetic compared with control subjects. At the lowest insulin infusion (clamp step I), arterial glycerol and FFA concentrations were significantly higher (P < 0.05) in type 2 diabetic compared with control subjects, but at clamp step II, concentrations were similar in the two groups. Arterial concentrations of D-3-hydroxybutyrate were, especially in the basal state, quite variable, and no statistical difference between the groups could be detected. Leg balance data (net uptake and/or release in/from the leg) for glycerol and FFAs showed, in general, the same pattern in the two groups, with no difference between the trained and the untrained legs. Thus, the release was considerably reduced with insulin infusion, and as regards FFAs, sometimes not distinguishable from 0 (Fig. 4). Because of substantial variation, no apparent pattern for D-3-hydroxybutyrate leg balance was seen in control subjects, whereas in type 2 diabetes, the release was significantly reduced with increasing insulin concentrations (Fig. 4).

**Biopsy data**

**Glycogen.** Glycogen content in skeletal muscle was similar in type 2 diabetic and control subjects, and when data were analyzed separately, there was a tendency (P < 0.1) to an increase in trained (366 ± 27 and 358 ± 39 nmol · mg⁻¹ · dry wt⁻¹, respectively) compared with untrained (316 ± 19 and 285 ± 19 nmol · mg⁻¹ · dry wt⁻¹, respectively) muscle. When data from the two groups were pooled, a significant (P < 0.05) effect of training was seen.

**Muscle fiber types, diameter, and capillary density.** The fraction of slow type I to fast type II fibers was similar in untrained and trained legs in control subjects (n = 6; 0.52 ± 0.02 and 0.63 ± 0.05, respectively) and in type 2
diabetic subjects \( (n = 10; 0.56 \pm 0.05 \text{ and } 0.51 \pm 0.04, \text{ respectively}) \), with no significant difference between control and type 2 diabetic subjects. The diameter of the fast fibers was slightly increased in trained versus untrained muscle in both control subjects \( (64.6 \pm 1.1 \text{ vs. } 62.9 \pm 0.9 \mu m, \text{ respectively}; P < 0.05) \) and type 2 diabetic subjects \( (66.2 \pm 1.2 \text{ vs. } 62.5 \pm 1.8 \mu m, \text{ respectively}; P < 0.05) \). In contrast, the diameter of the slow fibers was similar in trained versus untrained muscle in control subjects \( (61.8 \pm 1.0 \text{ vs. } 60.3 \pm 0.7 \mu m, \text{ respectively}) \) and type 2 diabetic subjects \( (61.7 \pm 1.1 \text{ vs. } 59.3 \pm 1.7 \mu m, \text{ respectively}) \). Thus, the average diameter of the muscle fibers (i.e., including both slow and fast fibers, corrected for fiber type ratio) was \( 61.5 \pm 0.8 \mu m \) (untrained) and \( 63.0 \pm 0.7 \mu m \) (trained) in control subjects \( (P < 0.1) \) and \( 60.9 \pm 1.6 \mu m \) (untrained) and \( 64.1 \pm 1.2 \mu m \) (trained) in type 2 diabetic subjects \( (P < 0.05) \). The percentage difference in fiber diameter was \( 2.4 \pm 0.9 \text{ and } 5.4 \pm 1.7\% \) in control and type 2 diabetic subjects, respectively. A representative cross-sectional “picture” of fiber types is seen in Fig. 5.

The capillary density, measured as the number of capillaries per millimeter squared of muscle, was unchanged with strength training in both control subjects (untrained: \( 238 \pm 29 \); trained: \( 241 \pm 36 \)) and type 2 diabetic subjects (untrained: \( 228 \pm 27 \); trained: \( 225 \pm 29 \)). No significant difference existed in capillary density between the two groups.

**GLUT4.** The density of GLUT4 protein in the muscle homogenate was similar in type 2 diabetic and control subjects, i.e., the difference between GLUT4 protein content in the untrained \( (P = 0.209) \) and the trained \( (P = 0.591) \) legs was not significantly different between the two groups (Fig. 6). In type 2 diabetic subjects, a 40% increase of GLUT4 density in the trained muscle was seen \( (P < 0.05) \), but in control subjects the 13% increase did not achieve statistical significance (Fig. 6).
Insulin signaling. No significant differences existed between control and type 2 diabetic subjects in regard to protein content of the insulin receptor, IRS-1, the p85 subunit of phosphatidylinositol (PI) 3-kinase, PKB α/β (Akt 1/2), GS, GS total activity, or GS activity measured as % I-form in comparisons within either untrained or trained legs (data not shown). However, in response to training, significant increases were found in protein content of the insulin receptor (control subjects: 19 ± 7%; type 2 diabetic subjects: 21 ± 6%; both P < 0.05), PKB-α/β (Akt 1/2) (control subjects: 22 ± 9%; type 2 diabetic subjects: 12 ± 7%; main effect P < 0.05), GS protein content (control subjects: 12 ± 9%; type 2 diabetic subjects: 13 ± 9%; main effect P < 0.05), and GS total activity (control subjects: 9 ± 3%; type 2 diabetic subjects: 21 ± 4%; both P < 0.05) (Fig. 7). No effect of training was seen for the protein content of IRS-1, the p85 subunit of PI3-kinase, or percent GS activity in the % I-form in either group (Fig. 7).

Markers of oxidative capacity. The enzyme activities of CS, LDH, and HAD were similar in control and type 2 diabetic subjects, and no effect of the resistance training program was seen (Table 3).

DISCUSSION
There are several novel findings in the present study. First, we have shown that the resistance type of exercise training increases insulin action in skeletal muscle in patients with type 2 diabetes, an effect that was likely not caused solely by an increase in muscle mass. Thus, skeletal muscle also adapts qualitatively to a strength training program. Secondly, the study has revealed possible mechanisms behind the effect of training, i.e., changes in protein...
contents of GLUT4, PKB, and GS. Finally, we have shown that the adaptations occurred in response to a minimal training effort, which could easily be carried out on a larger scale.

The finding that the strength training–induced increase of insulin-mediated glucose clearance in the legs is independent of an increase in muscle mass is in line with our recent data in young, healthy men who abstained from strength training for 90 days, where accurate measures of changes in leg muscle mass was obtained by computed tomography scans (25). Strength training has previously been used in prospective studies in healthy subjects (26), subjects with impaired glucose tolerance (19), and subjects with type 2 diabetes (17), and in these studies 22–48% improvement in the $M$-value was found, generally attributable to increases in nonoxidative glucose metabolism. Data in two (17,26) of these studies were expressed relative to the fat-free mass, thus attempting to correct for the effect of a larger muscle mass in resistance-trained individuals. In two cross-sectional studies, no effect of resistance training on insulin-stimulated glucose uptake per kilogram muscle mass was found, and the positive effect of resistance training on the whole body were attributed solely the larger muscle mass (27,28). The data in the present study are in disagreement with these two latter studies, but our data are supported by the muscle biopsy data, speaking in favor of strength training–induced qualitative changes of the skeletal muscle. A very minor

FIG. 5. Representative light micrographs of portions of muscle bundles in transverse section of m. vastus lateralis in a patient with type 2 diabetes (A) and a healthy control subject (B). Cryosections of muscle biopsy tissue were immunostained for slow myosin as described in RESEARCH DESIGN AND METHODS. Immunoreactive muscle fibers appear dark.
contribution from an increase in muscle mass that we could not detect by water displacement is, however, possible. We did detect a 2–4% increase in leg volume by water displacement, and the more sensitive measure of muscle fiber diameter revealed only a marginally larger increase.

The present study is by design very different from all previous strength-training studies. We have used a one-legged training model and extended the traditional clamp experiments with arterio-femoral venous catheterization of both the trained and the untrained leg. By this model we are able to investigate both trained and untrained muscle in the same subject at the same time. The muscles are exposed to the same concentration of circulating humeral factors, and we are able to conclude that any measured difference between the two legs are due to local contraction-mediated mechanisms.

It is difficult for many patients with type 2 diabetes to engage in endurance-type training programs. With a previous sedentary lifestyle, strength training represents an attractive alternative, and the present study has provided proof for the effect. Furthermore, we have shown that the necessary training volume is of a magnitude that should present no major obstacle for putting the training into practice in the everyday life of most people. Altogether, each training session lasted no more than 30 min, and each session was only carried out three times per week. This training volume was sufficient and is in line with, but not
We do not know whether accumulation of, for example, moderate physical activity on most days of the week (29) is identical to, the general advice of accumulating 30 min of physical activity in a previous study using one-legged endurance training, muscle enzyme activities seem similar to those seen with endurance training. Thus, we found that both increased blood perfusion capillaries (nutritive), then the increased flow was directed into new capillaries (which we did not detect) or previously under-perfused capillaries (nutritive), then the increased flow could be a part of the explanation for increased glucose clearance in the trained muscle. For a detailed discussion of this issue, see the recent review by Clark et al. (32).

It is interesting to note that the effect of hyperglycemia on arterio-venous glucose concentration differences is not independent of the plasma insulin concentration (Fig. 2). At physiological plasma insulin concentrations (clamp step I, 0–240 min), arterio-venous glucose concentration differences were not different in type 2 diabetic compared with control subjects. However, at the high plasma insulin concentration (clamp step II, 120–240 min) the arterio-venous glucose concentration difference tended to be higher (P < 0.1) in type 2 diabetic compared with control subjects (Fig. 2). Thus, at the physiological insulin level, hyperglycemia cannot compensate for a defect in glucose extraction, and at high unphysiological insulin levels, only a partial compensation takes place.

The biochemical adaptations to training in skeletal muscle are many, and in the present study, we have focused on only some of the proteins, each of which could be partly responsible for the effects on glucose homeostasis. Thus, we found a training-induced increase in insulin receptor protein expression in both groups (Fig. 7). Our finding of increased glucose clearance at the supraphysiological insulin concentrations (Fig. 3) might be attributable to an increased insulin receptor number, but it is generally believed that insulin-sensitive tissues have more insulin receptors than necessary for eliciting maximal insulin effect (spare receptors). The finding of similar insulin receptor protein content in patients with type 2 diabetes and healthy control subjects confirms a previous finding (33), but to our knowledge the influence of exercise training on insulin receptor protein has not been carried out previously in patients with type 2 diabetes. In a cross-sectional study of 29- to 39-year-old endurance-trained and untrained men, in fact a decrease was found in the trained men (34), whereas in another study the gene expression seems unaltered by short-term endurance training in young men and women (35). In these two former studies, IRS-1 gene and protein expression followed the pattern of the insulin receptor (i.e., unchanged and decreased, respectively), whereas in the present study we found no effect on IRS-1 protein expression in response to strength training (Fig. 7). Similarly, we found that the protein expression of the p85 subunit of PI 3-kinase was unaltered by training in both groups (Fig. 7). Whether these contrasting results are caused by the type of training or the differences in age in the present and the aforementioned studies cannot be answered at the present time. The finding of similar IRS-1 and p85 protein content in patients with type 2 diabetes and in healthy control subjects is in line with findings from others (33,36).

Further distal in the insulin signaling pathway, PKB protein expression increased in response to strength training (Fig. 7). PKB is involved in the insulin signaling to GS and might also be important in the regulation of insulin-mediated GLUT4 translocation and glucose uptake in skeletal muscle. Thus, the upregulation of this enzyme might be important for the improved insulin action after training. The finding of similar protein expression of PKB in the muscle of healthy subjects and patients with type 2 diabetes (36) or first-degree relatives to type 2 diabetic patients (37) has previously been observed, whereas the observation of increased expression after strength training in humans with and without type 2 diabetes is a new finding. In contrast to this are data from a study in which similar PKB expression was found in endurance-trained and untrained men (34). Many factors can be pivotal in these different responses, but the differences in age (range 29–39 vs. 52–71 years), type of training (endurance versus...
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strength training), and design (cross-sectional versus paired) in the aforementioned (34) and the present study are likely candidates.

GS protein expression increased with strength training (Fig. 7). Also, the gene expression increases with training (albeit endurance training) (10) in patients with type 2 diabetes and healthy control subjects. In all, this is compatible with the training-induced increase in glycogen activity also found in some (22,38,39) but not all (40) previous studies. The finding of similar levels of GS protein in the muscle of control subjects and patients with type 2 diabetes is in agreement with previous findings (33).

The strength-training-induced increase in GLUT4 protein expression also found in patients with type 2 diabetes training is novel and important. It extends the findings from endurance training studies in patients with type 2 diabetes (41) and two previous strength training studies in healthy humans (42,43).

In the present study, only content of signaling molecules and proteins (GLUT4 and GS) were measured. Thus, the functional significance of the changes in insulin receptor, PKB, GLUT4, and GS content in vivo are unclear. We may anticipate that a greater potential for signaling/activation is created by the changes, but whether these factors are limiting components during insulin stimulation (as applied in the present study) is not known. Thus, the data do not allow us to conclude that the expression changes per se are mediators of the increase in insulin action.

We have assumed that the predominant insulin-sensitive tissue in the leg is skeletal muscle. Adipose tissue in the legs may, although to a much lesser extent, also have contributed to the clearance of glucose from the blood. The specific effect of training on localized adipose tissue was not measured in this study, but it is reasonable to believe that insulin sensitivity in adipose tissue also increased in response to training (44–47). However, whether such an effect is restricted to the trained leg is not known. It does not seem that strength training influenced lipolysis, as judged from the net release of glycerol and FFAs (Fig. 4), results that are similar to those obtained after endurance training (10). Of note is the finding that in contrast to the healthy control subjects, in type 2 diabetic patients, arterial concentrations of both glycerol and FFAs was higher at basal and clamp step I, despite higher plasma insulin concentrations (Fig. 4). Only when plasma insulin concentrations were well above the physiological level were similar arterial concentrations in the two groups achieved. Altogether, this may reflect a resistance to the inhibitory effect of insulin on lipolysis in the patients with type 2 diabetes.

Markers of oxidative capacity (CS, HAD, and LDH) were measured to control for improvements that could be ascribed to endurance-like exercises. The training protocol used, with the relatively high number of repetitions, might for some of the subjects have endurance-like characteristics. If endurance was a major component of the training program, some or all of these would be expected to increase. However, this was not the case, and together with the major improvement in muscle strength, this indicates that the predominant type of exercise was indeed strength training.

In summary, we have reported that strength training, like endurance training, enhances insulin action in skeletal muscle in patients with type 2 diabetes. This effect was likely independent of increases in muscle mass and could be achieved with a low weekly training volume. The increases in muscle GLUT4 content and in various insulin signaling protein expressions and/or activity are part of the mechanism behind the improvement in insulin action, but each of them should probably not be attributed a single effect, but rather be looked on in concert.

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