Altered energetic properties in skeletal muscle of men with well-controlled insulin-dependent (type 1) diabetes

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Crowther, Gregory J., Jerrold M. Milstein, Sharon A. Jubrias, Martin J. Kushmerick, Rodney K. Gronka, and Kevin E. Conley. Altered energetic properties in skeletal muscle of men with well-controlled insulin-dependent (type 1) diabetes. Am J Physiol Endocrinol Metab 284: E655–E662, 2003;10.1152/ajpendo.00343.2002.—This study asked whether the energetic properties of muscles are changed by insulin-dependent diabetes mellitus (or type 1 diabetes), as occurs in obesity and type 2 diabetes. We used 31P magnetic resonance spectroscopy to measure glycolytic flux, oxidative flux, and contractile cost in the ankle dorsiflexor muscles of 10 men with well-managed type 1 diabetes and 10 age- and activity-matched control subjects. Each subject performed sustained isometric muscle contractions lasting 30 and 120 s while attempting to maintain 70–75% of maximal voluntary contraction force. An altered glycolytic flux in type 1 diabetic subjects relative to control subjects was apparent from significant differences in pH in muscle at rest and at the end of the 120-s bout. Glycolytic flux during exercise began earlier and reached a higher peak rate in diabetic patients than in control subjects. A reduced oxidative capacity in the diabetic patients’ muscles was evident from a significantly slower phosphocreatine recovery from a 30-s exercise bout. Our findings represent the first characterization of the energetic properties of muscle from type 1 diabetic patients. The observed changes in glycolytic and oxidative fluxes suggest a diabetes-induced shift in the metabolic profile of muscle, consistent with studies of obesity and type 2 diabetes that point to common muscle adaptations in these diseases.

glycolysis; mitochondrial oxidative phosphorylation; tibialis anterior muscle

SKELETAL MUSCLE IN OBESE and non-insulin-dependent (type 2) diabetic patients shows insulin resistance (4, 26) and adaptations in muscle properties associated with energy metabolism (19). In both diseases, a reduction in the oxidative enzyme activity and an increase in the lipid content of all fiber types are found relative to control subjects (19). This pairing of a reduced oxidative capacity and an increased lipid content is unusual compared with the elevation in both factors with chronic physical exercise (15, 21). A trend toward a rise in muscle glycolytic enzyme activity relative to oxidative enzyme activity is also found in these two diseases (19, 42). Consistent with these findings in muscle fibers are reports of reduced maximal O2 consumption (V02 max) and elevated muscle lactate during exercise in obese and type 2 diabetic patients relative to age- and activity-matched control subjects (30, 36, 37). These changes in muscle properties represent a shift in the metabolic profile of the muscle fibers that has been suggested to be reflective of diseases involving insulin resistance (19).

Insulin resistance is also found in humans with insulin-dependent (type 1) diabetes (47), but little information is available on whether energetic properties such as glycolytic flux and oxidative capacity are also affected. Assays of a key glycolytic enzyme, phosphofructokinase, showed no difference between type 1 diabetic patients and control subjects (45). However, measurements during exercise provide evidence that the lower oxidative and higher glycolytic fluxes found in obesity and type 2 diabetes are also common to type 1 diabetes; specifically, V02 max is reduced (34) and blood lactate levels are elevated (48) in exercising type 1 patients compared with age- and activity-matched control subjects. In addition, an increased glycolytic flux in a rodent model of uncontrolled type 1 diabetes was apparent from a greater drop in muscle pH during stimulation, indicative of increased lactate generation compared with control muscle (6). Thus the few in vivo studies of active muscle affected by type 1 diabetes point to an alteration of metabolic properties indicative of a shift in the metabolic profile of the muscle.

The key energetic and metabolic properties of muscle can be evaluated in vivo with new noninvasive methods that measure chemical fluxes during exercise. The combination of phosphorus magnetic resonance spectroscopy (31P MRS) and exercise protocols that fully recruit muscle fibers permits quantification of the major components of energy metabolism, oxidative and glycolytic ATP supply and contractile ATP demand, in exercising muscle in vivo (2, 7). Validation of these measurements comes from isolated and intact muscle.
studies that have shown a close agreement between MRS-determined fluxes and direct measurements of O$_2$ consumption and lactate during exercise (17, 27). These measurements are sensitive enough to detect individual differences in muscle properties (3), account for declines in muscle function with aging (8, 9), and reveal adaptations of elderly muscle to exercise training (24).

The goal of this study was to determine whether muscle energetic properties are altered in humans with type 1 diabetes. We assessed the properties of the ankle dorsiflexors muscles of men with well-controlled diabetes and control subjects matched to the diabetic subjects by age and activity level. Our $^{31}$P MRS measurements of the three major energetic properties revealed significant alterations of the major pathways of ATP supply in muscle: a higher glycolytic flux and lower oxidative capacity in diabetic subjects relative to control subjects.

**METHODS**

**Subjects.** We selected diabetic patients on the basis of three criteria. The first was good clinical control, as defined by two criteria set by the American Diabetes Association (25): 1) hemoglobin A$_1c$ levels of ≤7% and 2) a lack of glucose in the urine. The second was an absence of serious medical conditions such as cardiovascular or musculoskeletal disease. The third was an age range of mid-20s to mid-40s. It was not possible to recruit 10 inactive subjects with these three recruitment constraints from our pool of volunteers. Instead, we formed sedentary and active groups of subjects and matched control subjects to the diabetic patients on the basis of age and activity levels. The physical characteristics of our groups are listed in Table 1. The age range of subjects was 23–45 yr, and the mean age difference within each patient-control pair was 2.5 ± 0.6 (SE) yr. Our sedentary group had no habitual physical activity and no job with physical demands (5 pairs). Our active group had two activity levels: 1) they were recreationally active 1–2 times/wk or had a job with physical demands (2 pairs), or 2) they were active 2–9 h/wk (2 pairs) or competitive athletes (1 pair).

All subjects were in good health, and type 1 diabetes was the predominant malady of the patients. Minor and varied complications were present in four diabetic patients (1 patient had 2 complications); sensory neuropathy (2 subjects), hypothyroidism (1 subject), arthritis (1 subject), or well-managed hypertension (1 subject) for which appropriate medications were taken. Because the age of diabetes onset of the diabetic subjects was 17 ± 2.9 yr (range: 4–40 yr), diabetes was present in our subjects for an average of 18 yr. All diabetic subjects used insulin injections (average: 65 ± 13.5 U/day; range: 27–150 U/day) to keep their blood glucose levels under good clinical control (25).

The experimental protocols described in the next section were approved by the Institutional Review Board of the University of Washington, and voluntary, written informed consent was obtained from each subject. Subjects were asked to continue their normal dietary routine before testing and, in the case of diabetic subjects, to take their insulin as usual. Most experiments were performed in the afternoon.

**Experimental setup and data acquisition.** Our setup was essentially the same as previously described (12), except that six subjects (3 diabetic and 3 control subjects) were studied with a General Electric Signa 1.5 Tesla spectrometer, and the

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<th>Table 1. Physical characteristics of experimental subjects</th>
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<td><strong>Control</strong></td>
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<td>Age, yr</td>
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<td>Height, cm</td>
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Values are means ± SE for $n = 10$ in each group. BMI, body mass index.

rest were studied with a Bruker 4.7 Tesla spectrometer. Each subject lay supine with his right leg (4.7 T spectrometer) or entire body (1.5 T spectrometer) in the bore of the magnet. The right leg and foot were placed in a plastic holder to which a strain gauge was attached. The strain gauge measured the force exerted by the ankle dorsiflexors muscles and was linked to a computer running LabView data acquisition software (National Instruments, Austin, TX). A surface coil tuned to the resonating frequency of phosphorus was placed over the anterior compartment of the right leg. $^{31}$P MR spectra of the ankle dorsiflexors were then acquired with the surface coil, as previously reported (10). Briefly, a high-resolution control spectrum of the resting muscle was acquired under conditions of fully relaxed nuclear spins (interpulse delay: 16 s). Sequential spectra were then obtained under partially saturating conditions (interpulse delay: 1.5 s) throughout the experimental protocols (see Exercise protocol). The spectrum for each time point consisted of four summed acquisitions taken over 6 s or eight summed acquisitions taken over 12 s.

**Analysis of spectra.** Free-induction decays were summed, baseline-corrected, line-broadened, and Fourier-transformed into spectra. Areas of phosphorus peaks in the fully relaxed spectra were measured using Omega software (GE Medical Systems, Waukesha, WI). Resting phosphocreatine (PCr)/ATP and P/ATP ratios were determined from the relative areas of the appropriate peaks. PCr peaks of partially saturated spectra were analyzed with the “Fit-to-Standard” program (20), and absolute PCr concentrations were then calculated using the PCr/ATP and P/ATP ratios of the fully relaxed spectra with the assumption that the muscle [ATP] was 8.2 mM (18). The sum of P, + phosphomonoesters was assumed to increase stoichiometrically with decreases in PCr, as previously demonstrated (1, 7, 12). The chemical shift of the P, peak relative to PCr was used to calculate muscle pH (44). Because the P, peak was often split during exercise, the “MRUI” protocol was used to fit two peaks to the P, signal in all spectra, and the average muscle pH was computed as a weighted average of the pH values of the two peaks.

**Exercise protocol.** Subjects exercised by performing voluntary isometric dorsiflexions against the resistance of the plastic footholder. Subjects attempted to maintain a constant force of 70–75% of their maximal voluntary contraction (MVC) force using visual feedback from a light-emitting diode display. All subjects performed a single sustained contraction lasting 120 s, during which contractile costs and glycolytic flux were quantified. Glycolytic H+ production during this contraction drove muscle pH to levels known to inhibit oxidative phosphorylation (17, 46); therefore, oxidative phosphorylation was quantified during recovery from a shorter (30-s) contraction, during which the muscle pH remained close to 7.0. Fourteen subjects (7 diabetic and 7 control subjects) performed this 30-s contraction in addition to the 120-s one. These subjects performed the 30-s and 120-s
contractions on the same day. They were given >12 min of recovery time between exercise bouts.

Calculations. Contractile cost was quantified as the decline in [PCr] during the first 15 s of exercise, during which time there was little PCr resynthesis by glycolysis. We assumed oxidative ATP production during this period to be negligible, because intense continuous contractions occlude blood flow and thus prevent O2 delivery to the muscle (5, 16).

Glycolytic H+ production during exercise was calculated as the observed change in H+ concentration plus the H+ consumed in the breakdown of PCr, as previously described (7)

$$\Delta H_{\text{glycol}} = \Delta pH + \beta_{\text{tot}} + (\gamma) \times \Delta [\text{PCr}]$$  \hspace{1cm} (1)

where $\Delta pH$ is the change in muscle pH, $\beta_{\text{tot}}$ is the total muscle buffer capacity (which includes buffering due to P, and PME), $\gamma$ is the proton stoichiometric coefficient of PCr hydrolysis (29), and $\Delta [\text{PCr}]$ is the change in [PCr]. Estimates of individuals’ nonphosphate buffer capacities were similar for diabetic and control subjects (14.7 ± 1.5 vs. 14.5 ± 2.7 Slykes), so all individuals were assigned a nonphosphate buffer capacity of 14.6 Slykes.

Oxidative phosphorylation after the 30-s contraction was quantified by fitting each subject’s PCr recovery data to a monoexponential curve. The oxidative recovery rate constant $k_{\text{VPCr}}$, was then calculated as the reciprocal of the time constant of the curve. $k_{\text{VPCr}}$ is independent of the extent of PCr depletion (31) and directly proportional to the oxidative capacity of the muscle (9, 33). Oxidative capacity was estimated for each subject by use of $k_{\text{VPCr}}$ and the [PCr] in resting muscle, as previously described (9)

$$M_{\text{ox-cap}} = k_{\text{VPCr}}[\text{PCr}]_{\text{rest}}$$ \hspace{1cm} (2)

Statistics. Values reported are means ± SE. Differences between groups were assessed for statistical significance with two-tailed paired t-tests unless otherwise indicated. We tested for the effects of activity level on our group comparisons using a two-factor ANOVA. The time of the significant rise of glycolytic flux above zero was determined using one-tailed t-tests with a sequential Bonferroni correction for multiple comparisons (38). Significance was assigned at the 0.05 level.

RESULTS

Resting muscle. No differences were seen in resting PCr/ATP ratios for the muscle of control subjects [4.08 ± 0.12 (CON)] vs. muscle of diabetic patients [4.16 ± 0.11 (DIA)] or in resting P/ATP ratios [0.45 ± 0.05 (CON) vs. 0.40 ± 0.02 (DIA)]. Figure 1A shows spectra of resting muscle in single subjects from each group. The P1 peak is expanded in Fig. 1B to show the significant difference in resting muscle pH between the groups [7.02 ± 0.02 (CON) vs. 6.96 ± 0.01 (DIA)].

Muscle force, metabolite, and pH changes. The MVC force was not significantly different between the two groups [301.2 ± 24.2 N (CON) vs. 334.3 ± 32.4 N (DIA)]. Figure 2, A-C, shows the isometric force, [PCr], and pH during the 120-s isometric contraction of individual muscles for a representative matched pair of a control subject and a diabetic patient. The decline in force below the target level (70–75% of MVC force) indicates that the two groups fatigued to a similar extent by the end of exercise [Fig. 2A; 33.6 ± 4.9% of MVC (DIA) vs. 40.6 ± 3.0% of MVC (CON); $P = 0.28$]. The [PCr] decline was similar during exercise for the control and diabetic muscles and resulted in similar end-exercise values [Fig. 2B; 6.3 ± 1.4 mM (DIA) vs. 6.7 ± 1.2 mM (CON); $P = 0.97$]. Figure 2C shows that pH dropped more rapidly with exercise in the DIA compared with CON muscle, with the result that the end-exercise muscle pH was significantly lower in DIA (6.44 ± 0.07) than in CON (6.64 ± 0.04; $P = 0.0164$). Figure 1C shows that the P1 peak at the end of exercise expanded to demonstrate the chemical shift differences that reflect the disparity in intracellular pH between the control subject and the diabetic patient. Four DIA and two CON subjects showed a splitting of the P1 peak, indicative of different pH levels among distinct populations of fibers. The pH value for these subjects was the pH of each P1 peak weighted by its respective area.

Glycolysis. The accumulated glycolytic flux as a function of time is shown in Fig. 3. The difference in muscle pH dynamics with exercise is due in part to an earlier onset of glycolytic flux during exercise in DIA relative to CON. A significant rise in glycolytic H+ production

![Figure 1](http://ajpendo.physiology.org/Downloaded_from/Http://ajpendo.physiology.org/10.1152/ajpendo.00006.2003)
was observed at 15 s of exercise for DIA and at 27 s of exercise for CON.

The highest glycolytic flux rate over any 24-s period of exercise significantly differed between CON (0.30 ± 0.03 mM H⁺/s) and DIA (0.43 ± 0.04 mM H⁺/s) in a paired comparison of subjects matched by age and activity (P < 0.02). Figure 4 shows the mean and individual values for low-activity subjects (i.e., sedentary or no regular physical activity) vs. high-activity subjects (i.e., weekly or more frequent activity >30 min duration) in each group. There was a significant difference in peak glycolytic flux between CON and DIA groups (P < 0.03) but no significant effect of activity level (P = 0.27) by a two-factor ANOVA. Thus the main factor affecting the peak glycolytic flux is the diabetic state, and this effect is significant whether the subjects are matched in a paired t-test or the groups are compared in an ANOVA.

**Contractile costs.** The similar PCr dynamics shown in Fig. 2B resulted in contractile costs for CON (0.71 ± 0.12 mM ATP/s) and DIA (0.98 ± 0.08 mM/s) that were not significantly different.

**Oxidative properties.** A second experiment, involving a shorter muscle contraction and a subset of subjects (n = 7), was used to deplete PCr without significantly changing pH. The end-exercise pH for both groups [7.04 ± 0.02 (CON) and 6.96 ± 0.05 (DIA)] was well above the pH (i.e., 6.8) at which PCr recovery rate is

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**Fig. 2.** Isometric force (A), phosphocreatine concentration ([PCr]) (B), and muscle pH (C) during the 120-s exercise bout. Values plotted are for a single subject from a representative matched pair.

**Fig. 3.** Onset of glycolytic flux during exercise in muscles of CON and DIA subjects. Asterisks mark the first data point to be significantly greater than zero, according to a 1-tailed t-test with a sequential Bonferroni correction for multiple comparisons (38). Values are means ± SE; n = 8 for DIA group and n = 10 for CON group. (Timing differences in data collection prevented inclusion in Fig. 3 of 2 DIA patients and their matched CON subjects.)

**Fig. 4.** Peak glycolytic flux rate during exercise in the muscle of individual CON subjects (open symbols) and DIA patients (closed symbols) with low chronic activity (□) and high chronic activity (○) subgroups. Horizontal bars are means for each subgroup. Asterisk denotes that 2 groups significantly differed between CON and DIA whether subjects are matched (paired t-test; P < 0.02) or groups are compared without matching (ANOVA; P < 0.042).
affected (33, 46). Figure 5 shows the oxidative PCr recoveries following this 30-s contraction for individual muscles from a representative matched CON and DIA pair. Each individual’s recovery was fit to a monoexponential curve from which the oxidative recovery rate constant ($k_{PCr}$) was derived as previously described (9). Figure 6 shows the mean and individual values for low- vs. high-activity subjects in each group. The $k_{PCr}$ was significantly higher for CON (0.025 ± 0.003 s⁻¹) vs. DIA (0.017 ± 0.002 s⁻¹) in a paired comparison ($P < 0.05$). This disparity in oxidative properties was also reflected in the oxidative capacity of the muscles [0.80 ± 0.07 mM/s (CON) and 0.61 ± 0.09 mM/s (DIA)].

**DISCUSSION**

The key findings of this paper are significant differences in energetic fluxes during exercise in muscle of type 1 diabetic patients vs. control subjects. Altered glycolytic metabolism was evident both at rest and during exercise. A significantly lower pH at rest and at the end of exercise indicated a greater reliance on glycolytic metabolism in the muscles of the diabetic patients. In addition, oxidative recovery was slower after exercise, indicating a lower oxidative capacity in the diabetes-affected muscles. These alterations in metabolic flux are the first reported differences in muscle energetic properties in type 1 diabetes vs. control subjects, but they are consistent with the increased ratio of glycolytic to oxidative enzyme activity reported in obesity and type 2 diabetes. Thus muscle from type 1 diabetic patients under good clinical control shows significant alteration in energetic properties with changes in common with obesity and type 2 diabetes.

Subjects. Our diabetic patients were screened for well-managed disease and an age range that avoided subjects with a high risk of cardiovascular complications. These criteria prevented us from recruiting 10 sedentary patients from our volunteer population. Instead, we matched our patients to control subjects to reduce the effects of two factors known to affect muscle properties: age and activity. Prior studies of diabetic muscle properties have typically selected patients without carefully screening for activity (23, 42) or included active patients with “no more than two exercise sessions weekly on a regular basis” (19). We chose to closely match patients to control subjects to eliminate any bias due to activity and used a sample size similar to that in other studies of muscle properties in types 1 and 2 patients (42, 45, 47). This matching permitted us to take into account the role of chronic activity level in the variation in the energetic properties of a muscle. The variation in properties apparent in Figs. 4 and 6 is somewhat greater than the nearly twofold range for contractile costs and oxidative recovery rates that we have found among normal individuals (3) and reflects the range of chronic activity levels in this study. The fact that we could distinguish muscle properties between the two groups with a sample size of 10 subjects emphasizes the effectiveness of matching to activity level to reduce this contribution to the individual variation in muscle properties. We avoided additional screening factors such as body mass, which is not known to affect muscle properties (except in obesity, and our patients’ average body mass index (BMI = 28) was well below the threshold for this malady (i.e., BMI >30)). We also did not match subjects by VO2 max to avoid obscuring the diabetes-induced differences in the muscle oxidative properties that we sought to study.

Methodology. Our exercise protocol was designed to achieve a high rate of muscle energy use, to eliminate blood flow without the possible complications of a tourniquet, and to minimize any effect of blood-borne substrates or hormones. A continuous contraction resulted in a high contractile ATP use above the oxidative capacity (see Muscle glycolytic properties) and ensured cessation of O2 delivery, since blood flow ceases at force levels as low as 30% of MVC force (5, 16). This high exercise flux has been shown to rely nearly entirely on intracellular and not blood-borne substrates (11). For example, indirect calorimetry studies of control and
diabetic subjects at 70% of \( V_{O2\max} \) show that muscle glycogen and lipid comprise >80% of the fuel for contraction (35). This intracellular substrate use and the lack of blood flow mean a negligible contribution of blood-borne substrates and hormone effects on substrate flux in our protocol.

Muscle ischemia during the continuous contraction ensured a negligible contribution of oxidative metabolism to our glycolytic flux measurements. The ATP generated from intracellular \( O_2 \) stores is rapidly consumed (~2.7 mM ATP from stored \( O_2 \)) supports only ~4 s of contraction at the measured ATP demand, >0.7 mM/s; see Fig. 5), so mitochondrial respiration and oxidation of pyruvate cease after a few seconds of exercise in our protocol. The measured change in \( pH \) during exercise, therefore, reflects the generation of \( H^+ \) and lactate in an anoxic muscle.

**Muscle glycolytic properties.** A difference in glycolytic metabolism in the diabetic vs. control muscle is apparent both at rest and in exercise. At rest, muscle \( pH \) was significantly lower by a small amount (\( \Delta pH = 0.06 \)) in the diabetic muscle (Fig. 1). A similar, small disparity was reported in resting diabetic rodent muscle (6) and in vitro cells deprived of insulin (32). Moore (32) suggests that this disparity seen in cells in vitro reflects the role of insulin in ion transport in cells. Such a role of insulin in muscle is also plausible given recent findings that glycolysis is linked to ion pumping in isolated skeletal muscle (23).

The difference in the diabetic patients’ and control subjects’ resting muscle \( pH \) is exacerbated by exercise, with end-exercise \( pH \) differing by an average of 0.2 units (Fig. 1). The similarity in \( PCr \) breakdown during exercise in the muscles means that the uptake of \( H^+ \) in the creatine kinase reaction is similar, and therefore the observed \( pH \) difference directly reflects the disparity in glycolytic flux. This measurement of \( H^+ \) flux has been validated against a direct assay of lactate generation, confirming that we have a quantitatively accurate measurement of glycolytic flux by MR (27).

The early disparity in \( pH \) between the muscles reflects an earlier onset of glycolysis in the muscle of diabetic patients compared with control subjects (Fig. 3). In addition, Fig. 4 shows that the peak glycolytic flux also differs in the muscles between the two groups. These results indicate significant differences in glycolytic metabolism in diabetic muscle under both resting and exercising conditions. The differences in resting muscle \( pH \) may reflect a perturbation in ion exchange, whereas the lower \( pH \) and higher glycolytic fluxes in exercise indicate significantly elevated glycolytic capacity in well-managed type 1 diabetic muscle.

These results are particularly striking because of the small difference in glycolytic flux during exercise as a function of age (9) and exercise training (13) in our previous studies. Both studies found significant differences in oxidative properties between adult and elderly quadriceps muscle but no difference in glycolytic flux. Thus neither age nor activity alone can account for the large differences in glycolytic flux found here. Finally, the minor complications found in 4 of 10 diabetic participants did not critically affect our results, since the difference in peak glycolytic flux remained significant when these affected patients were removed from the analysis.

**Oxidative capacity.** We performed a short (30-s) exercise bout with a subset of our subjects \( (n = 7/group) \) to follow the recovery of \( PCr \) after exercise as a measure of the muscle oxidative capacity (Fig. 5). The short exercise bout of this experiment avoided the large \( pH \) drop known to inhibit \( PCr \) recovery (33, 46) that occurred in our longer exercise protocol. The \( PCr \) recovery rate constant in our control subjects’ muscles \( (0.025 s^{-1}) \) was similar to that obtained by Kent-Braun and Ng (28) in male control subjects with no chronic activity and of similar age \( (0.027 s^{-1} \text{ (converted to } k_{PCr} \text{ from half-time)}) \). However, these \( k_{PCr} \) are well below the values reported in the tibialis anterior of collegiate athletes specializing in sprint \( (0.032 s^{-1}) \) and distance running \( (0.050 s^{-1}) \) (13). Thus the \( k_{PCr} \) in our type 1 diabetic subjects \( (0.017 s^{-1}) \) is low compared with age- and activity-matched control subjects, and well below athletic subjects, indicating a reduced oxidative capacity as a result of the diabetes (Fig. 6).

Cardiovascular complications are common in type 1 patients even without overt symptoms. The vascular pathology in asymptomatic type 1 diabetic patients has been found to result in loss of local blood flow control, and higher blood flow is found at rest and exercise compared with controls (43). The reported higher blood flow upon recovery from exercise (i.e., hyperemia) means that our finding of a reduction in recovery rate in diabetic patients compared with control subjects (Fig. 6) is most likely due to altered muscle oxidative properties and not to a blood flow limitation.

We have reported that the reduction in \( PCr \) recovery with age is quantitatively linked to muscle mitochondrial content and therefore oxidative capacity (9). The aging results are consistent with the findings in animal muscle that recovery rate is directly proportional to oxidative enzyme activity (33). Thus the lower \( k_{PCr} \) in the muscle of diabetic patients points to a reduced oxidative capacity relative to the muscle of age- and activity-matched control subjects.

**Metabolic profile.** The higher glycolytic flux and lower oxidative capacity reported here are consistent with the greater lactate generation and reduced \( V_{O2\max} \) seen in age- and activity-matched type 1 diabetic patients (34, 48). These results suggest a shift in muscle enzymatic profile of muscle in type 1 diabetics patients similar to the increased glycolytic-to-oxidative enzyme activity ratio seen in muscle fibers of obese and type 2 diabetic individuals (19). This shift in metabolic profile is consistent with a greater predominance of the fast-twitch, glycolytic fiber type, but several studies indicate metabolic properties are more plastic than the fiber type. The increased lipid content and reduced oxidative enzyme activity found in obese and type 2 diabetic muscle was found in all fiber types (19). Similarly, an increase in oxidative capacity in all fiber types has been reported with endurance training (22).
Thus alteration of the metabolic profile found here does not require changes in muscle fiber type. The difference in the metabolic profile of muscle between well-maintained type 1 diabetic patients and control subjects could reflect either a genetic predisposition or a sign of the diabetes. Early onset type 1 diabetes (before 5 yr of age) has a significant genetic component, but the genetic link to the disease decreases with later age of onset (14). Thus the late average onset age of this malady in our patients (17 yr) indicates that a genetic predisposition for diabetes and for the measured metabolic profile is unlikely.

The second possibility is that the metabolic shift found here reflects signs of diabetes that remain in the well-controlled state. Simoneau and Kelley (42) suggest that the shift in metabolic profile in obesity and type 2 diabetes results from the insulin resistance common to both diseases. Significant insulin resistance is also present in type 1 diabetes (47) and is apparent in the decreased plasma glucose uptake during exercise in well-controlled type 1 diabetic patients in the presence of high blood insulin levels (35, 39). Thus insulin resistance is common to all of these diseases, including well-controlled type 1 diabetes, and may be the factor responsible for the metabolic profile shared by these diseases.

The mechanism suggested for triggering insulin resistance in obesity and type 2 diabetes is the rise in plasma free fatty acid (FFA) levels in these diseases (4, 26, 41). The elevated FFA levels and lipid availability are postulated to suppress glucose uptake, with the consequence of increased lipid accumulation and alterations in the insulin-signal pathway, leading to insulin resistance (4, 40, 41). The factors leading to these changes in insulin resistance may also underlie adaptations in muscle properties associated with energy metabolism. For obesity and type 2 diabetes, an association between greater intracellular lipid accumulation and insulin resistance has been established (4, 26). However, this pairing of intracellular lipid levels and insulin resistance has not been demonstrated in type 1 diabetes. Our results suggest the possibility that the accumulation of lipids and insulin resistance found in obesity and type 2 diabetes may also be found in this disease and underlie the shift in metabolic profile of well-controlled type 1 diabetic muscle.

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