Muscular Endurance in Long-Term IDDM Patients

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OBJECTIVE — To determine the short-term muscular endurance and working capacity of leg muscles in long-term IDDM patients in relation to neuropathic complications, muscle strength, and metabolic control.

RESEARCH DESIGN AND METHODS — The muscular endurance of extensors and flexors at the ankle and knee was assessed in 44 IDDM patients and in 44 matched control subjects during 30 maximal isokinetic movements. The endurance index was the work performance of the last 5 movements relative to the first 5 movements. Total work was the summated work of all movements. All patients underwent a neurological evaluation, nerve conduction studies, and quantitative sensory tests.

RESULTS — The combined endurance index of the ankle extensors and flexors was 70% (51–88) (median [range]) in the diabetic group and 65% (55–82) in the control group ($P < 0.01$). For knee extensors and flexors the combined endurance index was 65% (55–103) for the diabetic patients and 63% (48–75) in the control subjects ($P < 0.01$). The endurance index related neither to the severity of neuropathy nor to the metabolic control (blood glucose and HbA_{1c}) for any of the muscle groups. Diabetic patients had reduced strength of all muscle groups (14–24%, $P < 0.02$) and impaired total work performance (15–20%, $P < 0.01$) for ankle movements.

CONCLUSIONS — Long-term IDDM patients have increased endurance but reduced strength and work performance of leg muscles. The combined effect of the motor abnormalities is suggested to give rise to functional impairment, including an increased risk of falls and injuries.

Patients suffering from diabetic neuropathy have instability of posture and walking and an increased incidence of falls and injuries, including fractures at the hip (1–3). In long-term IDDM patients (diabetes duration >20 years) with polyneuropathy, muscle strength at the ankle and knee is impaired (4), which probably contributes to the frequent falls (5). Decreased muscular endurance has been reported in patients with neurogenic muscle weakness and was explained as an accelerated reduction in membrane excitability (6). Therefore, in addition to muscle weakness, impaired muscular endurance in diabetic patients could give rise to functional shortcomings during daily activities.

In healthy subjects, isokinetic muscular endurance increases with age, whereas maximal muscle strength decreases (7,8). These changes most likely reflect an increase in the proportion of fatigue-resistant type 1 muscle fibers. Also, in healthy young men, a positive relationship between muscular endurance and the proportion of type 1 fibers has been observed (9). In NIDDM patients, a higher proportion of the least fatigue-resistant type 2b muscle fibers has been described (10), whereas in genetically diabetic mice with hypoinsulinemia, a lower proportion of type 2b fibers is found (11). The changes in muscle fiber distribution relate closely to insulin concentration, and it is suggested that hyperinsulinemia induces the increase in number of type 2b fibers (10). Quantitative studies of fiber composition in IDDM patients in relation to motor performance and diabetic complications have not been performed.

IDDM patients adapt normally to exercise training with increased muscular strength and endurance and with a corresponding increase in cross-sectional muscle fiber area (12). However, short-term dynamic muscular endurance has not been evaluated thoroughly in diabetic patients, and its relationship to neuropathic complications and metabolic control is unknown. The aim of the present study was to determine the muscular endurance and working capacity of leg muscles in long-term IDDM patients with and without neuropathy.

RESEARCH DESIGN AND METHODS

Patients and control subjects

All IDDM patients at the diabetes outpatient clinic aged <65 years and with a diabetes duration >20 years were invited to participate in the study. Fifty-five IDDM patients agreed to participate. Excluded from the study were 11 patients with blood glucose outside the range 3.5–15 mmol/l at the isokinetic test (see below). In the remaining 44 patients (16 women and 28 men), the duration of diabetes was 28 years (20–47) (median [range]). Fourteen patients received insulin injections twice a day, 29 patients were treated with multiple injections, and one patient had an insulin pump. The daily dose of insulin was 26 U (6–50) of short-acting insulin and 22 U (6–80) of long-acting insulin. Patients were tested during a postprandial period from 10:00 A.M. to 4:00 P.M. Patients were classified according to their urinary albumin excretion: <20 μg/min (normoalbuminuria), between 20 and 200 μg/min (incipient nephropathy), and >200 μg/min (overt nephropathy). Furthermore, the retinal status of the patients was classified by an ophthalmologist as no, simplex, or proliferative retinopathy. The frequency of retinopathy

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Abbreviations: CV, coefficient of variation, MNCV, motor nerve conduction velocity; NDS, neurological disability score; NSS, neuropathy symptom score; ROM, range of motion; SNCV, sensory nerve conduction velocity; VPT, vibratory perception threshold.

and nephropathy is given in Table 1. None of the patients had significant heart, lung, or musculoskeletal disorders. Neither did the patients suffer from any other neurological or endocrine diseases nor from symptomatic macroangiopathy. Among patients with neuropathic manifestations, only those with findings typical of distal symmetrical diabetic polyneuropathy were included. For comparison of the motor performance with healthy subjects, 44 healthy subjects (16 women and 28 men) matched for age, height, weight, and weekly physical activity were recruited from among hospital employees, blood donors, and relatives of the patients. All patients and control subjects gave informed consent to the study, which was approved by the local ethical committee.

Table 1—*Clinical data for IDDM patients and control subjects*

	n	Age (years)	Weight (kg)	Height (cm)	Nephropathy (none, incipient, overt)	Retinopathy (none, simplex, proliferative)
Diabetic patients	44	46 ± 9.1	76 ± 14.1	175 ± 8.5	21, 8, 15	6, 20,18
Control subjects	44	46 ± 10.9	74 ± 11.5	175 ± 8.7	—	—

Data are means ± SD or *n*.

Clinical evaluation, quantitative sensory examination, and electrophysiological studies

All patients were evaluated according to a neuropathy symptom score (NSS) (13) and a neurological disability score (NDS) by a trained neurologist (14). HbA_{1c} (normal range 4.4–6.6%), blood glucose (normal range 3.5–5.5 mmol/l), and serum creatinine (normal range 55–110 (mol/l) were determined with standard laboratory methods. Blood glucose was determined before the isokinetic tests. If the value was <3.5 mmol/l or >15 mmol/l, that patient was excluded. Vibratory perception threshold (VPT) was evaluated at dominant index finger pulp and nondominant dorsum of the great toe using forced-choice techniques (CASE IV, WR Medical Electronics, Stillwater, MN). The threshold was determined with the 4, 2, and 1 stepping algorithm (15). The VPTs for each patient were compared with a normative database, and the corresponding percentiles were determined. Nerve conduction studies were performed with an electromyograph as described elsewhere (DANTEC Counterpoint, Skovlunde, Denmark) (16). Motor nerve conduction velocity (MNCV) was measured in the dominant forearm segment of the median (elbow-capitulum fibulae-ankle) nerve. Sensory nerve conduction velocity (SNCV) was measured in the nondominant sural nerve with orthodromic activation and in the dominant median nerve (wrist-finger II and III) with antidromic activation. For MNCV, Z-scores were calculated from the values of healthy volunteers obtained with similar techniques (16). For SNCV, normal values previously determined in age-matched normal control subjects were adopted.

Isokinetic muscle testing

Isokinetic muscular endurance, work (joules), and maximal isokinetic muscle strength (peak torque [Newton meters]) were assessed for extensors and flexors at the ankle and knee of the nondominant leg with an isokinetic dynamometer (Lido Active Multijoint II, Loredan Biomedical, West Sacramento, CA). Before the study, all subjects received instructions about the procedures and performed a warm-up session. For correction of limb weight, a passive movement sequence provided by the LIDOACT software was performed throughout the defined range of motion (ROM), and subsequently the maximal muscle strength was determined. In a previous study, the peak torques of largely the same patients were examined at an angular velocity of 60 and 90 degrees/s. In the present study all isokinetic performances were performed at 180 degrees/s (17). Subjects were instructed to push and pull "as hard and fast as possible" through the full available ROM at every trial. In the ankle test, the full ROM was 48 degrees ranging 24 degrees from the neutral position in both dorsal and plantar directions. In the knee test, the full ROM was 70 degrees (from 80 to 10 degrees flexion of the knee). The verbal instructions of one of the examiners were tape recorded and used in all examinations. Every test included eight reciprocal trials at maximal effort with a 10-s rest interval after every trial. To exclude submaximal performance, data were only accepted if the coefficient of variation (CV) for torque values did not exceed 10%. If the CV exceeded 10%, the subject was retested once. If at the second test the CV still exceeded 10%, data were excluded if no outlier torque curve could be identified.

After a few minutes of rest, subjects were instructed to perform 30 maximal reciprocal isokinetic movements at the same ROM and velocity applied for determination of maximal strength. The subjects were asked to exert maximal effort in every single movement and were carefully instructed not to economize the muscle exertion. Subjects were positioned and tightly fastened as previously described (4,17) and received standardized tape-recorded verbal instructions during the exercise.

Definitions, calculations, and statistical analysis

The minimal criteria for diabetic neuropathy were adopted (18,19). Patients were defined as neuropathic if at least two of the following four categories were abnormal, with one as an abnormality of nerve conduction or of sensory examination: *1*) NSS ≥1; 2) NDS ≥2; 3) abnormal nerve conduction velocity in at least two of four nerves; 4) abnormal VPT at index finger and great toe (≥98th percentile).

To calculate the corrected individual muscle strength, multiple regression analysis including the strength, age, height, weight, and sex of the control subjects and 65 additional subjects was performed (4). To quantify the degree of neuropathy, a neuropathy rank-sum score was calculated for each patient. The neuropathy rank-sum score was the summated rank scores of the NSS, the NDS, the VPTs, the MNCV, and the SNCV as described previously (4).

The primary study parameter was the combined endurance index of the extensors and flexors of the ankle and the knee. The index was the work of the last five repetitions as a percentage of the work of the first five repetitions, a high index reflecting a high endurance. Differences of the endurance index between diabetic patients and control subjects were evaluated with Wilcoxon's signed-rank test using a 2.5% limit of significance (Bonferroni correction).

To evaluate whether there was any difference in the individual effort during the first part of the endurance test, peak torque determined before the endurance test (at the maximal-strength test) was compared

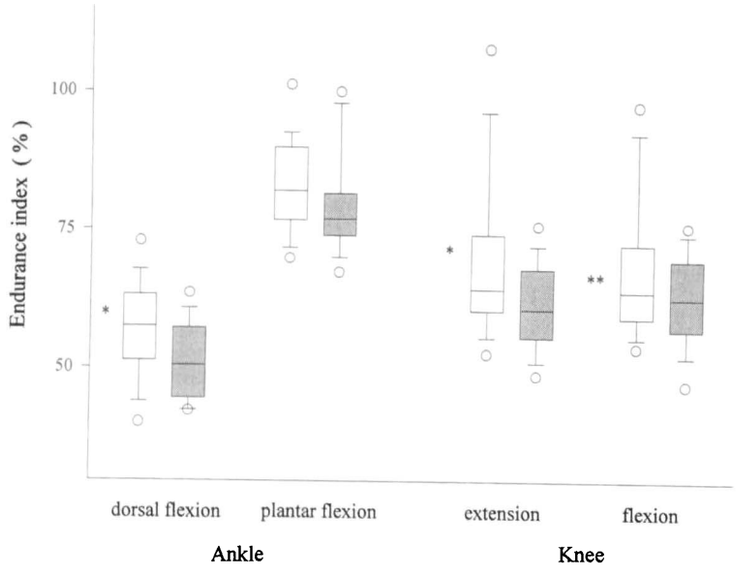

Figure 1—*The endurance index of extensors and flexors at the ankle and knee in 44 diabetic patients (□) and 44 matched control subjects (■). The endurance index is the work of movement 26–30 as a percentage of the work of movement 1–5. Box plots show median values (line), 25th and 75th percentiles (lower and upper boundaries of the box, respectively), 10th and 90th percentiles (lower and upper error bars, respectively), and 5th and 95th percentiles (lower and upper circles, respectively). *P < 0.005; **P < 0.05.*

with the maximal value during the first five repetitions of the endurance test. Differences (delta values) were calculated by subtraction of the highest torque value in the endurance test from those determined at the maximal-strength test.

To test the statistical significance of differences for each individual movement of work and peak torque between diabetic patients and control subjects, an unpaired Student's *t* test with a 5% limit of significance was applied. For comparison of endurance indexes for each individual movement, Wilcoxon's signed-rank test was used. To estimate the correlations between the muscular performance and the neuropathy rank-sum score, as well as the various laboratory findings, Pearson's product-moment correlation analysis was applied.

RESULTS — Detailed clinical data of the patients and their matched control subjects is given in Table 1. The amount of physical exercise per week was 0.7 ± 1.3 h for the patients and 0.8 ± 1.6 h for the control subjects. The diabetic patients had a median HbA_{1c} of 9.0 % (6.8–12.1), a serum creatinine of 89 μmol/l (61–153), and a blood glucose of 7.9 mmol/l (3.6–13.8). Twenty patients had at least one neuropathic symptom, whereas 24 did not have any neuropathic symptoms. Only three patients complained of muscle weakness. The median NDS, including manual muscle testing, was 15 (range 0–46) for all patients. The MNCV and the Z-score for the median nerve in all diabetic patients were 51.5 m/s (41.0–60.2) and −1.5 (−4.4 to 0.9), respectively. For the peroneal nerve, the same values were 39.8 m/s (23.0–49.4) and −2.1 (−6.5 to 0.2), respectively. In eight patients, the MNCV of the peroneal nerve could not be determined because of atrophy of the extensor digitorum brevis muscle. SNCVs of the median and sural nerve were 47.8 (36.2–60.0) and 44.8 m/s (33.4–55.8), respectively. No action potential could be obtained from the sural nerve in 22 patients or from the median sensory nerve in 8 patients. According to the minimal criteria for diabetic neuropathy, 10 patients were defined as non-neuropathic and 34 patients as neuropathic.

The measures of effort were not different in the diabetic group and the control group. The delta values for extension and flexion of the ankle in the diabetic patients were 1.2 ± 7.7 (mean ± SD) and −3.6 ± 14.9 N · m, respectively. The corresponding values for the control subjects were 2.5 ± 8.5 and −7.6 ± 9.3 N · m (NS). For knee extensors and flexors, the delta values were −7.1 ± 8.4 and −2.1 ± 13.3 Nm in the diabetic patients and −6.6 ± 5.4 and −3.6 ± 8.1 Nm in the control group, respectively (NS).

The combined endurance index for the extensors and flexors at the ankle was 70% (51–88) in the diabetic group and 65% (55–82) in the control group ($P < 0.01$). For knee extensors and flexors, the combined endurance index was 65% (55–103) in the diabetic patients and 63% (48–75) in the control subjects ($P < 0.01$). The endurance indexes for the individual muscle groups are shown in Fig. 1. The largest difference was found for ankle extension. At the ankle extension test, one patient could not move at a velocity of 180 degrees/s, and those data were omitted. The endurance index did not correlate to the neuropathy rank-sum score for any of the four muscle groups (Table 2 and Fig. 2). Nor did the indexes relate to the blood glucose or the HbA_{1c} for any of the four muscle groups (Table 2).

Total work performance of the diabetic patients was significantly lower for ankle extensors and flexors. For extensors and flexors at the knee, the reduction was not statistically significant (Table 3). The work of the first five and the last five movements is also given in Table 2. Muscle strength of all four muscle groups was decreased in the diabetic patients (Table 4). The muscle strength expressed as a percentage of the expected value was significantly related to the neuropathy rank-sum score for ankle extensors and flexors and knee extensors (Fig. 2). The correlation coefficients for

Table 2—***Relationship between the endurance index of the ankle and knee extensors and flexors and the neuropathy rank-sum score and metabolic variables***

	Neuropathy rank-sum score	Blood glucose	HbA_{1c}
Ankle extension	0.29 (0.06)	−0.06 (0.75)	0.08 (0.64)
Ankle flexion	0.07 (0.67)	−0.12 (0.54)	0.03 (0.86)
Knee extension	−0.16 (0.32)	−0.04 (0.82)	−0.09 (0.58)
Knee flexion	−0.26 (0.09)	−0.08 (0.69)	0.07 (0.68)

The relationship is given as the Pearson product moment correlation coefficient. *P* values are given in parentheses.

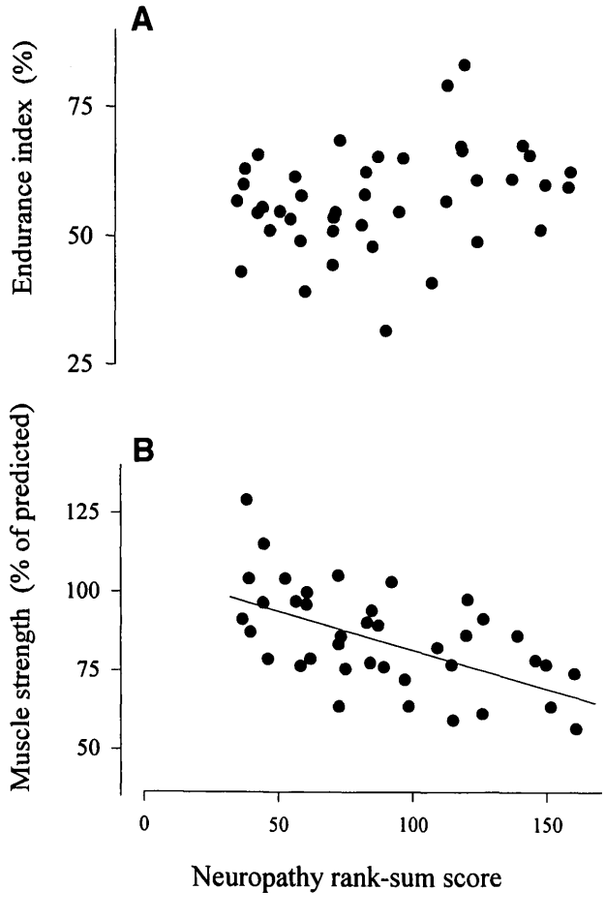

Figure 2—*The endurance index (A) and the normalized maximal isokinetic muscle strength (B) of ankle extensors in long-term IDDM patients in relation to the neuropathy rank-sum score.* A: r = *0.29;* P > *0.05.* B: r = *−0.57;* P < *0.0005.*

ankle extension, ankle flexon, knee extension, and knee flexion were $r = -0.57$ ($P < 0.001$) (Fig. 1), $r = -0.49$ ($P < 1 \times 10^{-6}$), $r = -0.44$ ($P < 0.001$), and $r = -0.26$ ($P = 0.09$), respectively. The muscle strength of ankle extension was related to the endurance index ($r = -0.39$, $P < 0.02$), whereas no significant correlation was found for the ankle flexors or the knee extensors and flexors.

CONCLUSIONS — The present study shows that long-term IDDM patients have increased short-term muscular endurance but reduced muscle strength and working capacity. The increased endurance is related neither to the severity of peripheral neuropathy nor to the metabolic variables HbA_{1c} and blood glucose.

A test for dynamic endurance was introduced by Thorstensson et al. (20) that consisted of 50 isokinetic knee extensions. In the present study, a smaller number of contractions was used, and in addition, endurance of reciprocal contractions was assessed. Performance of the exercises lasted only ~30–40 s, but a considerable decrease in work performance occurred in nearly all subjects (Fig. 1). The decline in work performance was lowest for the ankle flexors (Fig. 1), probably caused by a high proportion of fatigue-resistant type 1 muscle fibers in the triceps surae muscle (21). The increased endurance in long-term IDDM patients demonstrated in this study is an unexpected observation that cannot be explained by differences in degree of effort in the two groups. Thus the difference between the maximal peak torque at the start of the endurance test and at the test of maximal strength was not different in the diabetic and healthy control groups. In contrast to a previous report on patients with causes of neuropathy other than diabetes, we did not find an association between neuropathy and endurance (Table 2 and Fig. 2) (6). In the present study, only a limited number of patients with a very long diabetes duration were studied. Therefore, it is still unknown whether increased muscular endurance is also present in patients with short-term IDDM and patients with NIDDM.

Diabetic patients with neuropathy have decreased maximal O_2 uptake but normal cardiorespiratory response to exercise (22). IDDM patients with hypoinsulinemia have

Table 3—*Total work performance of 30 maximal isokinetic movements and the work performance at the first five and the last five movements of ankle and knee extensors and flexors in the diabetic patients and their matched control subjects*

	Work					
	Total work (J)		Movements 1–5 (J)		Movements 26–30 (J)	
Movement	Diabetic patients	Control subjects	Diabetic patients	Control subjects	Diabetic patients	Control subjects
Ankle						
Dorsal	220 ± 65*	260 ± 69	48 ± 17†	61 ± 16	27 ± 8*	32 ± 9
Plantar	740 ± 220‡	929 ± 277	134 ± 38†	176 ± 45	111 ± 31†	141 ± 42
Knee						
Extension	2,246 ± 647	2,416 ± 718	442 ± 136‡	506 ± 141	299 ± 86	312 ± 98
Flexion	1,377 ± 377	1,508 ± 442	272 ± 76‡	311 ± 87	181 ± 47	193 ± 59

Data are means ± SD. *$P < 0.01$; †$P < 0.005$; ‡$P < 0.05$ as compared with control subjects.

Table 4—*Maximal isokinetic muscle strength of ankle and knee extensors and flexors in the diabetic patients and their matched control subjects*

Movement	Muscle strength (Nm)	
	Diabetic patients	Control subjects
Ankle		
Extension	19.4 ± 4.9*	22.9 ± 5.1
Flexion	55.6 ± 14.2*	73.0 ± 18.1
Knee		
Extension	117.2 ± 33.0†	136.1 ± 39.2
Flexion	67.3 ± 21.4†	80.1 ± 26.1

Data are means ± SD. *$P < 0.005$; †$P < 0.02$ as compared with control subjects.

decreased exercise tolerance at an exercise level of 60% maximal O_2 uptake. However, in short-term maximal muscle exercise as performed in this study, O_2 uptake and cardiovascular responses to exercise are of minor importance for local muscular fatigue. Alternatively, macroangiopathy with reduced blood supply in leg muscles could alter the strength and endurance of muscles in diabetic patients. After exclusion of symptomatic patients and patients aged >65 years, it seems unlikely that reduced blood supply can explain the difference in muscular performance. Future studies combining quantitative assessment of blood supply and muscular performance of leg muscles could provide information about the effect of smaller reductions in blood flow on endurance.

To ensure a sufficiently high frequency of diabetic neuropathy, only long-term diabetic patients were studied. In addition to neuropathy, differences in the glycemic level and the degree of insulinization could influence the muscular performance by effects on the metabolic state of the muscle fibers. However, no relationship was found between the endurance indexes and the blood glucose and the HbA_{1c}. To exclude the influence of such differences, patients with hypoglycemia and pronounced hyperglycemia were excluded. Furthermore, all patients were tested during postprandial periods at similar hours of the day.

The mechanisms underlying muscular fatigue during strenuous physical activity in healthy subjects are not fully understood. In older men, the increased endurance is in contrast to the concomitant decline in maximal muscle strength (7). Elderly people have a higher proportion of the fatigue-resistant type 1 muscle fibers. Correspondingly, in a group of younger men, a close positive relationship was found between the proportion of type 1 muscle fibers and dynamic endurance (9). Also, in the present study, a shift toward more type 1 muscle fibers could contribute to the increased endurance. In experimentally diabetic rats with hypoinsulinemia, muscle fiber composition is shifted toward type 1 predominance (11,23). Information about muscle fiber distribution in IDDM patients is sparse. In eight IDDM patients, Saltin et al. (24) found a normal distribution, but presence of diabetic complications was not stated, and the duration of diabetes was lower than in the present study, making a comparison between the two studies difficult. In striated muscles of NIDDM patients, Mårin et al. (10) found a higher proportion of the least fatigue-resistant type 2b muscle fibers closely related to the degree of hyperinsulinemia. Furthermore, they suggested that hyperinsulinemia is the primary event leading to a shift in fiber composition.

After a few seconds of contraction, lactate and H^+ accumulate intracellularly, and pH decreases (25). These changes impair contractile properties of the muscle fibers. In diabetic patients, the increased muscular endurance may be caused by a higher resistance against ischemia, which is a well-known finding in diabetic nerves (26). It has not yet been proven whether an increased resistance to ischemia also exists in diabetic muscle, but if present, this could contribute to the increased endurance. In experimentally diabetic rats, an increased sensitivity for Ca^{2+} of the contractile apparatus has been found (27). Since reduced Ca^{2+} sensitivity develops in fatiguing muscle fibers (28), an increased Ca^{2+} sensitivity could contribute to the increased endurance in the diabetic patients. Alternatively, the slowed fatigue process could be due to altered nerve function. However, deterioration in muscle mechanical capacity during fatigue is not closely related to the electrical changes of the neuromuscular system. In contrast, intracellular processes are believed to be the main cause of the fatigue process (29).

The increased endurance demonstrated in long-term diabetes is independent of degree of neuropathy. Treatment of diabetic patients, therefore, could aim at the prevention of neuropathy and, at the same time, preservation of the improved muscular endurance. An obstacle to such treatment goals is that the abnormalities responsible for the increased endurance are unknown.

The muscle weakness observed probably contributes to the more frequent falls and injuries in diabetic patients (1,5). Although physical exercise is a basic part of diabetic management, many diabetic patients avoid physical activity partly because of secondary complications (30). It remains to be studied whether regular physical exercise can improve motor performance. In the meantime, it seems reasonable to recommend moderate regular exercise for long-term IDDM patients, taking into consideration impairment of gait and balance.

In conclusion, long-term IDDM patients have increased endurance of leg muscles during short-term exercise but a reduced muscle strength and total work performance. The endurance is related neither to the severity of polyneuropathy nor to the glucose or HbA_{1c} levels. Impaired motor performance probably leads to an increased risk for falls and injuries. To elucidate the mechanisms underlying the increased muscular endurance, studies including assessment of distribution of muscle fiber type and tissue biochemistry are needed.

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