Long-Term Follow-Up of Polyneuropathy in Diabetic Kidney Transplant Recipients

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Nerve conduction and electromyography (EMG) of insulin-dependent (type I) diabetic patients with end-stage nephropathy was studied before and up to 10 yr after kidney transplantation (KTx). A series of nondiabetic KTx patients served as a comparison group. Motor nerve conduction velocity (NCV) was measured in the ulnar, median, peroneal, and tibial nerves; sensory NCV was measured in the median nerve. EMG was performed in the first dorsal interosseus, flexor carpi radialis, anterior tibialis, and gastrocnemius muscles. In 68 pre-KTx diabetic patients, the mean NCV was below normal in all nerves, and the mean amplitudes of the evoked muscle action potential (MAP) were low normal in the upper extremity and below normal in the lower extremity. The values of the comparison group were within the normal range. At 1 (n = 57), 5 (n = 23), and 10 (n = 10) yr after KTx, the mean NCV of the diabetic patients remained essentially unchanged, but MAP amplitudes of all muscles had declined. EMG revealed progression of the denervation process, especially in muscles of the lower extremities. We conclude that diabetic neuropathy continues to progress by a progressive axonal loss after correction of uremia by KTx. *Diabetes* 37:1247–52, 1988

Progressive improvement over the past 15 yr in the results of kidney transplantation (KTx) for diabetic nephropathy has greatly prolonged the lives of the recipients (1–3). However, after KTx, the other secondary complications of long-standing diabetes persist and presumably advance in concert with continuation of the diabetic process. This is evidenced by the recurrence of diabetic nephropathy in renal allografts (4–6), the well-documented morbidity and mortality among diabetic KTx recipients from cardiovascular disease, and the incapacitating effects of diabetic retinopathy (4,7,8). The prevalence of polyneuropathy, with sensory loss, muscle weakness, and automatic symptoms, is high in diabetic patients with nephropathy (9), but little is known about the course of the polyneuropathy after KTx improves renal function (10). There are no reports of electrophysiological studies performed over many years on the same cohort of patients to describe either the natural history of progression of the neuropathy or its course after KTx. Likewise, the differential effects of diabetes and uremia on the neuropathy are not understood.

Herein we describe the results of nerve conduction and electromyography (EMG) examinations in diabetic patients who were among the first to elect KTx as treatment for end-stage nephropathy at the University of Minnesota between 1969 and 1975. Follow-up examinations extended for >10 yr in several patients.

MATERIALS AND METHODS

Patient population. During a 6-yr period from July 1969 to June 1975, we studied 68 patients with end-stage renal failure resulting from diabetic nephropathy who received a renal allograft at the University of Minnesota Hospitals. The mean age of the 38 men and 30 women at the time of KTx was 33.6 yr (range 18–54). A diagnosis of insulin-dependent (type I) diabetes mellitus was made at a mean age of 12.9 yr (range 1–34). A comparison group consisted of 14 nondiabetic uremic patients (9 men, 5 women; mean age 24.9 yr, range 16–46) who received a renal allograft in the same period.

Patient management has been described elsewhere (1). All patients received azathioprine, prednisone, and antilymphocyte globulin. Rejections were treated with increased doses of prednisone plus methylprednisolone. Strict regimens for glycemia control were not used in these patients.

Clinical evaluation of neuropathy. The admission examinations showed that all but two diabetic patients had signs or symptoms of polyneuropathy. In 53% there was a history

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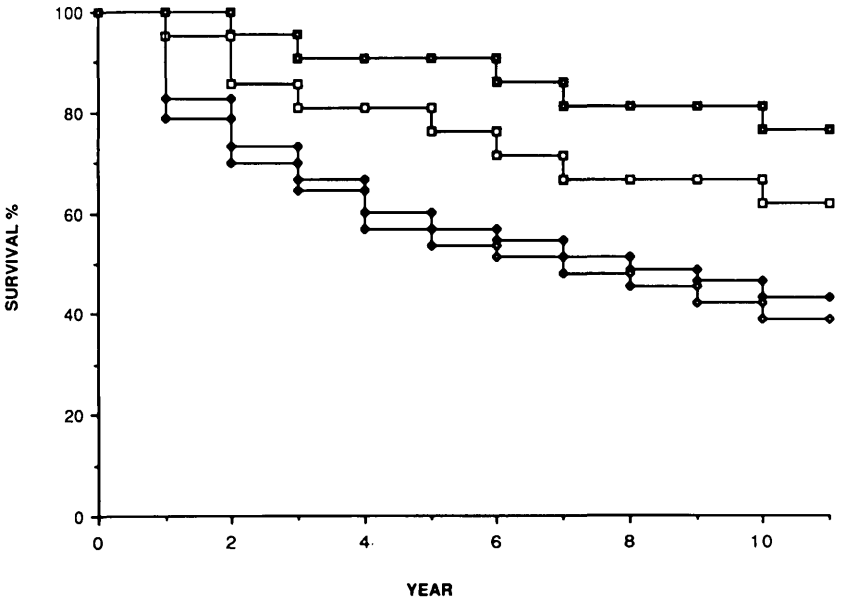

FIG. 1. Actuarial survival curves after kidney transplantation. ■, Nondiabetic patients; □, nondiabetic grafts; ◆, diabetic patients; ◆, diabetic grafts.

of sensory loss in the lower extremities. Autonomic dysfunction symptoms, e.g., repeated vomiting, constipation, and diarrhea, and impotence were present in 24%. Muscle strength in the lower extremities was impaired in 41%. The biceps, quadriceps, and Achilles tendon reflexes were decreased or absent in 38, 65, and 87%, respectively. The only abnormalities in the nondiabetic patients before KTx were mild sensory complaints (n = 2), male impotence (n = 2), and slight distal weakness (n = 1).

Comparison on the motor performance of a subset of the patients was made by simple tests of leg muscle strength before KTx and at yearly intervals thereafter, with direct observation by one of two investigators (J.J.B. or F.C.G.); these included 5 knee bends, 5 elevations on tiptoes, and 10 steps of heel-walking. Strength was scored as normal, impaired, or very weak (unable to perform the movement at all).

Electrophysiological studies. At yearly intervals, motor nerve conduction velocity (NCV) was measured in the right ulnar, median, peroneal, and tibial nerves. The amplitude of the evoked muscle action potential (MAP) was recorded from the hypothenar, thenar, extensor digitorum brevis, and abductor digiti quinti muscles, respectively. The latency and amplitude of the sensory nerve action potential (NAP) were recorded over the right median nerve at the wrist after stimulation of the index finger. When an evoked motor or sensory response was not obtained after nerve stimulation, NCV and latency were considered as missing values, and the amplitude was recorded as 0. The examinations were performed in a warm room, and the patients were warmed with an electric blanket if cool.

EMG was performed with a concentric needle electrode in the first dorsal interosseus, flexor carpi radialis, tibialis anterior, and gastrocnemius medialis muscles to detect evidence of denervation and collateral reinnervation. The findings were graded following an arbitrary scale: presence of few (+) or abundant (+ +) fibrillation potentials and mild (1), moderate (2), or severe (3) abnormalities in the amplitude, number, and phase components of the motor-unit action potentials.

Analysis of results. Patient and graft survival rates were calculated by actuarial techniques. Graft loss was defined as either return to dialysis or death with a functioning graft. Wilcoxon's test was used to analyze survival data, whereas the paired t test was used to analyze electrophysiological data. To avoid errors of improper patient selection due to patient death or nonreturn, statistical analysis of the nerve conduction data was performed only for patients who presented themselves for follow-up examinations at each of the previously studied intervals. Thus, some patients who returned at irregular intervals were not included. Because the population seen at 5 and 10 yr was only a portion of that seen before KTx, the baseline values in Table 2 differ slightly for the 1-, 5-, and 10-yr follow-up periods.

RESULTS

Patient and graft survival. Figure 1 shows the patient and graft survival. At 5 and 10 yr after KTx, 57 and 43% of the patients in the diabetic group survived, and graft survival was 54 and 39%, respectively. In the comparison group, 90 and 76% of the patients survived at 5 and 10 yr ($P < .005$), and graft survival was 76 and 61% (P NS).

Nerve conduction studies. Before KTx, the mean motor NCV of the 68 diabetic patients tested was below normal in all four nerves (Fig. 2). The mean MAP amplitudes were below normal in the lower extremity and just above the limits of normal in the upper extremity. The mean sensory NAP amplitude in the median nerve was decreased and the latency increased (Fig. 3). Abnormal NCV or MAP amplitudes in either upper or lower extremity before KTx were not correlated with reduced patient survival (r = .18, P NS).

Fifty-seven of the 68 diabetic patients (all the living patients with a functioning graft) examined before KTx were reexamined 1 yr later (Table 1). The motor NCV was not significantly changed, except for a small increase in the median nerve. However, statistical analysis showed a significant worsening (increase) of the distal latencies and reduction of the evoked MAP for peroneal and tibial nerves. The parameters for median nerve sensory conduction were unchanged.

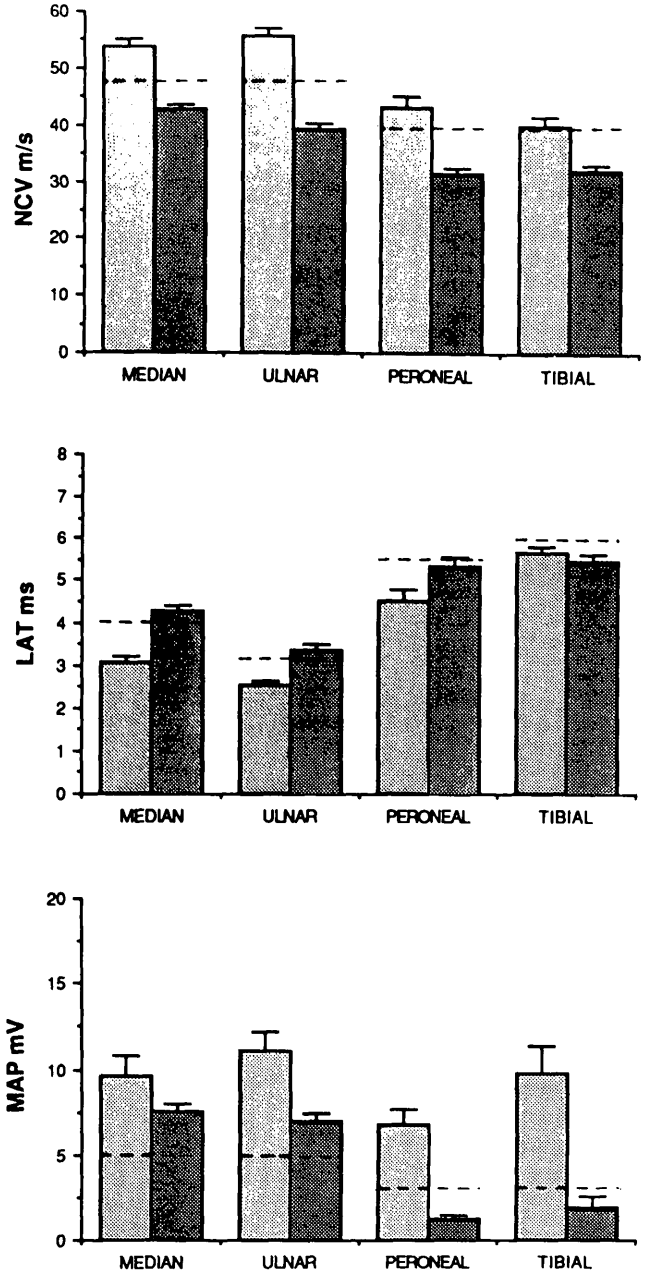

FIG. 2. Parameters of motor nerve conduction in diabetic (*dark bars*, *n* = 68) and nondiabetic (*light bars*, *n* = 14) patients before renal transplantation. Columns represent mean values with standard error. NCV, nerve conduction velocity; LAT, distal latency; MAP, muscle action potential amplitude. Normal limits are shown as *dashed lines*.

Of the 57 diabetic patients seen at 1 yr, 29 were retested 5 yr after KTx. There were 8 other living patients with a functioning graft who did not return at a time appropriate for inclusion in the study. With the exception of an increased NCV in the median nerve and a decrease in the MAP amplitude of the hypothenar and extensor digitorum brevis muscles, other results were not significantly changed compared with before KTx. The decline of the MAP amplitude seen in the abductor digiti quinti muscle did not reach statistical significance (P = .067). Sensory latency tended to increase. Sensory NAP decreased in amplitude (20% for the mean).

The same comparison was made at 10 yr (n = 10). Again, several patients did not return at the appropriate interval. By this time, a significant decrease in the MAP ampltiude from thenar and hypothenar eminence muscles and from the extensor digitorum brevis muscle was found, without significant change in the NCV or in the sensory conduction parameters.

In nondiabetic patients (n = 14), the pre-KTx mean nerve conduction results from the median and ulnar nerves were within the normal range (Figs. 2 and 3). The mean NCV for the peroneal and tibial nerves, however, were only just above the lower normal limits, reflecting the abnormal values recorded from 3 patients. Mild progression was seen in only 1 of 12 patients tested again the 1st yr after KTx. Unfortunately, only 4 patients returned at 5 yr and 1 at 10 yr after KTx. All values recorded from these patients were normal.

EMG. Before KTx, fibrillation potentials were more frequently found in the first dorsal interosseus than in the flexor carpi radialis (Table 2). They were more abundant in lower-extremity muscles and were present in about one-fourth of the patients. The number of fibrillation potentials fluctuated over the course of the study, reflecting the progressive denervation and collateral reinnervation process that existed.

The most consistent changes were abnormalities of the motor-unit action potentials. Before KTx, these were observed in over one-half of the muscles tested, except for a lower percentage in flexor carpi radialis. Several patients had clinical, NCV, and EMG evidence of an ulnar neuropathy. Some of the abnormalities listed for the first dorsal interosseus resulted from this mononeuropathy, superimposed on those from the polyneuropathy. Motor unit action potential abnormalities were found with increasing frequency and severity during the follow-up period. Tibialis anterior was the most severely involved muscle. We used a combination of the above abnormalities to judge the evolution of the neuropathy. Of diabetic patients tested at 1 yr (n = 52), 19 (32%) were considered worse and 11 (22%) better compared with pre-KTx. At 5 and 10 yr, 43 and 59% were worse compared with the previous examination; none had improved.

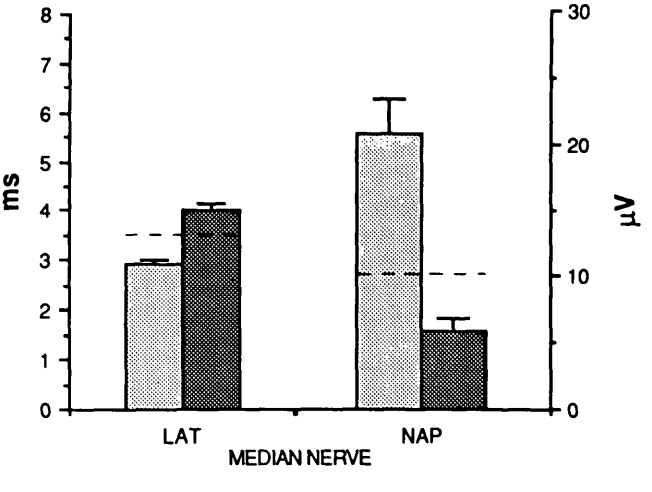

FIG. 3. Parameters of sensory nerve conduction in diabetic (*dark bars*, *n* = 68) and nondiabetic (*light bars*, *n* = 14) patients before renal transplantation. Columns represent mean values with standard error. LAT, distal latency; NAP, nerve action potential amplitude. Normal limits are shown as *dashed lines*.

TABLE 1
Parameters of motor and sensory nerve conduction in diabetic patients who had complete electrophysiological examination before and at 1, 5, and 10 yr after renal transplantation

	1-yr follow-up (n = 57)		5-yr follow-up (n = 29)		10-yr follow-up (n = 10)	
	Before	1 yr	Before	5 yr	Before	10 yr
Motor nerve						
Median						
NCV (m/s)	42.9 ± 0.6 (98)	44.7 ± 0.6* (100)	43.3 ± 1.2 (100)	46.3 ± 0.9* (100)	42.8 ± 1.4 (100)	42.8 ± 1.7 (100)
LAT (ms)	4.2 ± 0.1	3.9 ± 0.1*	4.3 ± 0.1	4.2 ± 0.1	4.2 ± 0.2	4.5 ± 0.2
MAP (mV)	7.8 ± 0.4	8.8 ± 0.5	8.8 ± 0.6	8.3 ± 0.6	9.9 ± 1.0	6.3 ± 0.7*
Ulnar						
NCV (m/s)	39.4 ± 1.1 (100)	39.5 ± 1.0 (100)	40.5 ± 1.5 (100)	42.7 ± 1.2 (100)	39.1 ± 2.1 (100)	43.3 ± 2.0 (100)
LAT (ms)	3.4 ± 0.1	3.4 ± 0.1	3.2 ± 0.1	3.1 ± 0.1	2.9 ± 0.2	3.4 ± 0.2*
MAP (mV)	7.0 ± 0.5	6.6 ± 0.5	7.7 ± 0.8	6.5 ± 0.6*	10.0 ± 1.0	5.2 ± 1.2‡
Peroneal						
NCV (m/s)	33.3 ± 1.1 (73)	32.1 ± 1.0 (46)	32.7 ± 1.5 (78)	36.1 ± 1.3 (52)	32.4 ± 2.1 (80)	33.5 ± 3.2 (40)
LAT (ms)	5.1 ± 0.3	6.2 ± 0.4†	5.3 ± 0.4	5.8 ± 0.5	4.9 ± 0.4	5.5 ± 1.1
MAP (mV)	1.5 ± 0.3	0.8 ± 0.2*	1.6 ± 0.5	0.9 ± 0.3*	1.3 ± 0.6	0.6 ± 0.3*
Tibial						
NCV (m/s)	34.1 ± 1.0 (71)	34.1 ± 0.9 (54)	34.5 ± 1.6 (78)	33.2 ± 1.3 (65)	35.7 ± 3.1 (50)	35.0 ± 5.6 (50)
LAT (ms)	5.4 ± 0.2	6.4 ± 0.4*	5.6 ± 0.4	6.2 ± 0.4	5.2 ± 0.3	6.6 ± 0.7
MAP (mV)	2.6 ± 0.8	1.4 ± 0.5*	2.9 ± 1.2	0.9 ± 0.3	3.2 ± 2.1	0.2 ± 0.1
Sensory nerve						
Median						
LAT (ms)	3.8 ± 0.1 (61)	3.7 ± 0.1 (57)	3.9 ± 0.2 (76)	4.2 ± 0.2 (75)	3.9 ± 0.3 (60)	4.3 ± 0.3 (60)
NAP (μV)	5.9 ± 1.1	7.2 ± 1.6	8.7 ± 1.6	6.9 ± 1.2	7.0 ± 2.3	4.7 ± 1.5

Due to the different composition of subgroups, pretransplant values in table are not identical. Values are means ± SE. Percentage of response in parentheses. NCV, nerve conduction velocity; LAT, distal latency; MAP, muscle action potential; NAP, nerve action potential. *$P < .05$; †$P < .005$; ‡$P < .0005$.

The EMG was mildly abnormal in only 2 of the 14 nondiabetic patients before KTx. Both showed minimal progression 1 yr later.

Tests of leg muscle strength. It became obvious in the first few years of follow-up of the diabetic patients that some who had been unable to walk before KTx had regained this ability. Paired observations at baseline and follow-up were made in 29 diabetic (Fig. 4) and 12 nondiabetic kidney recipients. Although many of the diabetic subjects had good strength in all three maneuvers tested, nearly half of them were moderate or markedly weak before KTx. More patients showed improvement than deterioration 1 yr after KTx. Improvement was observed more often for knee bends than for the other two tests. The nondiabetic patients all showed good muscle strength at baseline and at 1-yr follow-up.

DISCUSSION

The regular acceptance of diabetic patients with end-stage renal disease into the transplantation program at the University of Minnesota since 1969 allowed us to make this long-term neurophysiological study. Although the patient and graft survival data of this early group of uremic diabetic patients were not comparable with those of the nondiabetic patients, as is currently the case (11), the number of patients available for analysis was adequate to draw meaningful conclusions.

Sufficient clinical and electrophysiological evidence existed to justify the pre-KTx diagnosis of polyneuropathy in almost all diabetic patients. This is in accord with other reports that found neuropathy to be a major cause of morbidity in patients with long-standing diabetes (9,12,13).

Electrophysiological examination before KTx showed that the abnormalities of sensory and motor conduction and on the EMG were more marked in the lower than in the upper extremities, as found in other studies (14–17). After KTx, the NCV values remained unchanged for as long as 10 yr, but there was a decline in amplitude of the evoked MAP amplitude. Moreover, the EMG demonstrated the continuous occurrence of fibrillation potentials and a decreased number of motor units during voluntary contraction. Those motor units activated were of increased amplitude and duration. These results indicate that there was a progressive loss of axons of α-motoneurons that was incompletely compensated for by collateral reinnervation. These conclusions are based on the knowledge that fibrillation potentials arise after denervation of muscle fibers and decline after reinnervation. Re-

TABLE 2
Electromyography findings in diabetic patients before and after renal transplantation

	0 (n = 64)	1 yr (n = 52)	5 yr (n = 28)	10 yr (n = 16)
First dorsal interosseus				
FIB	14	27	14	27
MUAP	56	58	68	73
Flexor carpi radialis				
FIB	3	4	3	0
MUAP	19	17	29	20
Tibialis anterior				
FIB	27	30	33	38
MUAP	64	68	93	94
Gastrocnemius medialis				
FIB	24	37	32	38
MUAP	57	60	75	75

Numbers indicate the percentage of patients with fibrillation potentials (FIB) and with any degree of abnormalities in motor unit action potential (MUAP) in 4 muscles tested.

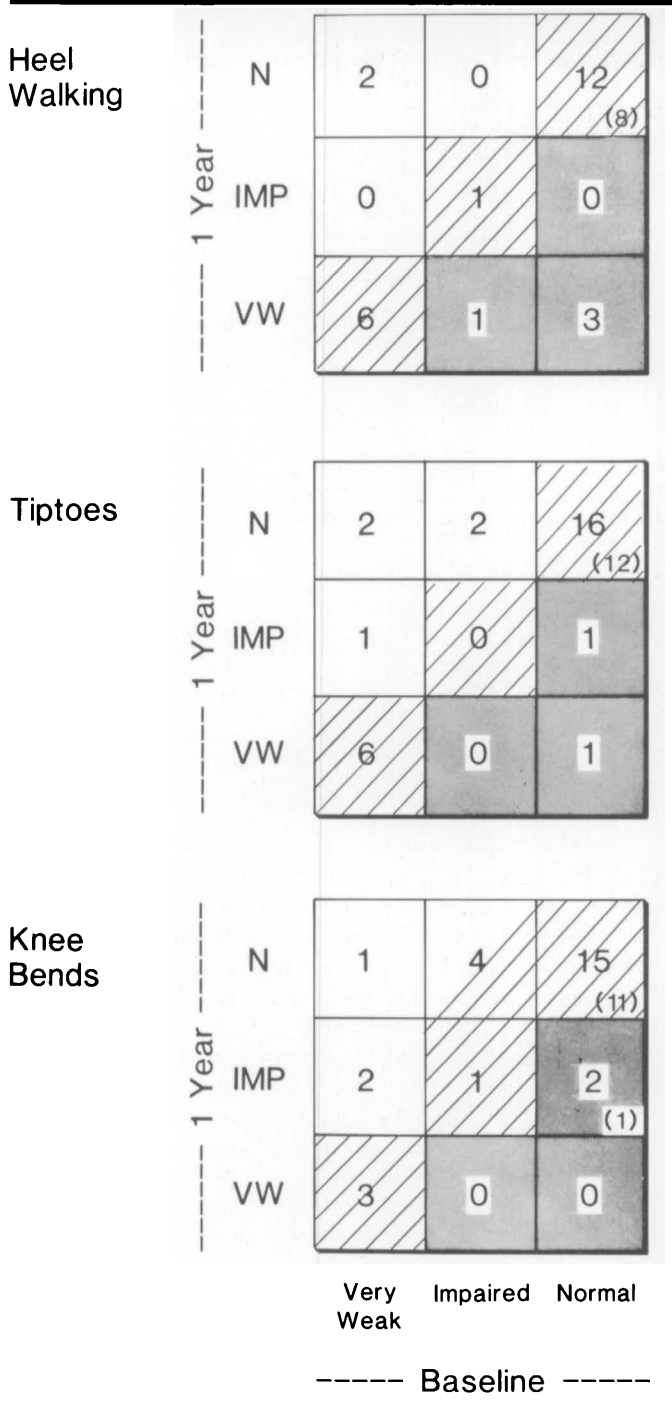

FIG. 4. Leg muscle strength in patients before and 1 yr after kidney transplantation. *n* = number of diabetic patients with given score of muscle strength at baseline vs. 1 yr later. Patients with better score at 1 yr than at baseline are counted in *open squares*, patients with deterioration of strength in *shaded squares*, and patients without change in *hatched squares*. *n* in parentheses = nondiabetic patients. N, normal; IMP, impaired; VW, very weak.

curring cycles of motor unit denervation and reinnervation result in the formation of progressively larger motor units that are recorded by EMG as high-voltage long-duration potentials that discharge more rapidly than normal for the strength of contraction. These compensatory mechanisms mask the extent of motor axon loss from clinical detection because strength and MAP amplitude are disproportionately maintained. A declining MAP indicates failure of collateral reinnervation to parallel the loss of motor axons. At this stage, the few surviving axons govern very large muscle territories, perhaps up to 4 or 5 times their original complement of muscle fibers (18). Therefore, the successively lower MAP amplitudes observed in this study represent a more significant progression of diabetic neuropathy than the percentage of reduction of the MAP amplitude.

The lowering of MAP amplitudes was not accompanied by lower NCV values; i.e., those motor axons that survived for 1, 5, or 10 yr conducted at the same velocity as the larger number of motor axons present at the beginning of the study. We conclude that NCV, although very useful for diagnosis of neuropathy early in the course of diabetes, is not a good index for measuring progression of neuropathy in patients with type I diabetes of long duration. The EMG findings were more sensitive for detecting denervation and partial collateral reinnervation, and the reduction in MAP was useful for following the overall progression of motor axon loss (19,20). Our data suggest that KTx prevented further reduction in NCV, but the unavailability of a long-term study of a cohort of untreated patients from our own clinic or in the literature prevents a more positive statement.

The amplitude of the sensory NAP measurements is a better indication of the number of axons in the measured nerve than the evoked MAP. However, NAP amplitude was not useful in this study because at the time of KTx, the NAPs of these long-term diabetic patients were already reduced by axon loss to a very low level. The further reductions found during the follow-up period (a few microvolts) were within the limits of variation of the method and therefore not statistically significant.

The effect of aging cannot be considered responsible for our findings. In adults, increasing age results in a slight decrease in NCV, only significant after 60 yr of age, whereas MAP amplitude is less affected and denervation evidence in the EMG is not seen normally (20). In fact, the age of the diabetic patients seen 10 yr after KTx ranged from 34 to 43 yr old.

The suggestion by Mitz et al. (22) that uremia plays a minor role to diabetes in the etiology of the neuropathy is supported by our demonstration that diabetic neuropathy continues to progress after KTx. This is complementary to the demonstration of advancement of retinopathy, cardiovascular disease, and nephropathy in the transplanted kidney (4–8). The influence of KTx on the rate of progression could not be shown, because there is no comparison group of uremic diabetic patients without KTx but with similar long follow-up. In our nondiabetic comparison patients, uremia alone was presumably responsible for the mild clinical and electrophysiological signs of neuropathy (22–24). The minimal nature of the findings in this group of patients and the short follow-up made it impossible to draw conclusions on the effect of the KTx on their neuropathy.

The effectiveness with which successful KTx reverses the complex effects of chronic uremia probably best explains the clinical improvement in performance abilities, mainly during the 1st yr after KTx, that were reported by some of our patients but not paralleled by improvement in the objective measurements of nerve function. Previous follow-up studies of this same group of uremic diabetic patients showed that KTx, even in the early days of this treatment, greatly improved

the length and quality of life (4,10). We attribute this apparent increase in general well-being and physical activity to improved renal function and changes in medication.

Our demonstration of progression of the neuropathy after KTx implies that careful control of hyperglycemia continues to be a requirement of post-KTx treatment, because clinical evidence suggests that this influences the development and progress of polyneuropathy (9,25–27).

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