The lack of an appropriate animal model that spontaneously develops diabetic nephropathy has been a significant limitation in the search for genetic factors underlying this disease and the development of new therapeutic strategies to prevent progressive renal disease in diabetes. We introgressed the mitochondria and some passenger loci from the FHH/EurMcwi rat into the genetic background of diabetic GK rats, creating a new rat strain, T2DN (T2DN/Mcwi). Despite the high degree of genetic similarity between T2DN and GK rats (97% at 681 loci), diabetes ensues earlier and progresses more severely in T2DN rats. T2DN rats exhibit proteinuria by 6 months of age, accompanied by renal histologic abnormalities such as focal glomerulosclerosis, mesangial matrix expansion, and thickening of basement membranes. These characteristics progress over time, and nearly all T2DN rats exhibit diffuse global glomerulosclerosis with nodule formation and arteriolar hyalinosis by 18 months of age. The histologic changes in the kidney of T2DN rats closely mimic the changes seen in the kidney of patients with diabetes. These results indicate that the T2DN rat is a suitable model for investigating diabetic nephropathy. Here we report the initial genetic and physiological characterization of this new rat model of diabetic nephropathy. Diabetes 53: 735–742, 2004

One of the major morbidity and mortality factors confronted by patients with diabetes is an increased risk of developing diabetic nephropathy that often progresses to end-stage renal disease (ESRD) (1–3). A long-standing question pertaining to the development of renal disease in diabetes concerns the mechanisms involved in this process. A wealth of data have been generated on possible mechanisms by which diabetes and its ancillary metabolic, hemodynamic, growth, and glomerular cell injury–related alterations may modulate the progression of diabetic nephropathy (4–7). Nevertheless, the observation that approximately two-thirds of patients with diabetes do not develop renal disease indicates that hyperglycemia is a permissive factor in diabetic nephropathy, but elevated plasma glucose levels alone do not fully account for renal injury (1). Thus, genetic factors are thought to play an important role in the susceptibility for diabetic nephropathy, with several clinical and epidemiologic studies supporting this hypothesis (8–10).

The complex interplay between diabetes-dependent and -independent factors in determining the progression of renal disease could become more amenable to study if there were adequate animal models that spontaneously develop diabetes and renal lesions that mimic those seen in patients with diabetic nephropathy. However, to date, no rodent model of diabetes that fully recapitulates the chronology of events and histologic changes in the kidney that are characteristic of patients with diabetic nephropathy has been developed. Several rodent models of spontaneous diabetes, such as the Zucker rat, BB rat, and DB mice, exhibit glomerular hypertrophy, thickening of basement membranes, and diffuse expansion of the glomerular mesangial matrix that resemble some of the histologic changes seen in diabetic nephropathy (11–14). However, these models, unlike human diabetic nephropathy, do not exhibit progressive expansion of mesangial matrix leading initially to focal glomerulosclerosis and proteinuria, continuing with the development of severe diffuse, global glomerulosclerosis with nodule formation and ESRD, characterized by elevations in plasma urea and creatinine levels and decreased GFR.

One strain of a spontaneously diabetic rat that may harbor genetic factors predisposing them to renal disease is the GK rat, a nonobese, normotensive model of non–insulin-dependent diabetes (type 2 diabetes). GK rats display glucose intolerance as early as 2 weeks of age (high basal plasma insulin levels) and exhibit elevated plasma glucose levels after the administration of a glucose load by 4 weeks of age (15–17). By 12 weeks of age, GK rats exhibit frank type 2 diabetes characterized by elevated fasting glucose and insulin levels and a prolonged elevation in plasma glucose levels after an oral glucose load.

Several studies have reported that GK rats also exhibit common histologic changes in the kidney seen in other animal models of diabetes, including thickening of the glomerular basement membranes, mild mesangial matrix expansion, and glomerular hypertrophy (18,19). Neverthe-
Genetic comparison of the T2DN and GK<sub>FL</sub> rats. For determining the degree of genetic relatedness between GK and T2DN rats, a second colony of GK rats, termed GK<sub>FL</sub> (purchased from Dr. Robert Farace, Tampa, FL), had to be used, given our inability to obtain more animals from the Swedish colony. A genome-wide scan with 681 SSLPs distributed across the genome was carried out to assess the degree of the FHH genome retained in the T2DN strain, as well as differences between T2DN and GK<sub>FL</sub> rats. The SSLPs selected were polymorphic between GK and FHH rats and exhibited a high degree of strain, as well as differences between T2DN and GK<sub>FL</sub> rats. The SSLPs selected for this scan were provided by serial backcrossing to this animal of female rats from the ongoing GK-FHH cross. Using a modified speed congeneric strategy, female rats in each generation were selected on the basis of the genotypes of 180 simple sequence–length polymorphisms (SSLPs), polymorphic between GK and FHH, along the 20 autosomes and X chromosome. The percentage of GK alleles retained in each rat was determined and female rats carrying the most GK alleles (~2 SD) were subsequently chosen to backcross with the same male GK rat. This breeding strategy allowed for the rapid fixation of most of the original GK genome, except for the mitochondrial DNA, inherited from the female FHH rat. In the sixth backcross generation, male and female T2DN rats were intercrossed, and strict brother–sister mating was maintained in the colony thereafter. The present studies were done on rats from the 9–12 generations after the GK-FHH intercross. The rederived strain is named the T2DN/Mcw/i, in accordance with the rat nomenclature guidelines. Genotyping. DNA was extracted from a 1-mm<sup>3</sup> section of tail that was incubated in 500 µl of lysis buffer overnight at 55°C, followed by an isopropanol precipitation and resuspension in TE buffer. DNA was diluted to a final concentration of 5 ng/µl. The rats were genotyped using PCR. Before PCR, the primers were radiolabeled with ³²P-ATP. PCR was carried out, and the products were electrophoretically separated in 6% polyacrylamide gels, as previously described (22).

Characterization of diabetes and glucose intolerance. Male BN, FHH, T2DN, and GK<sub>FL</sub> rats were subjected to an intraperitoneal glucose tolerance test (IPGTT) at 3, 6, 9, and 12 months of age. Before the test, all animals were subjected to two to three training sessions. After the determination of fasting (12 h) glucose levels, the animals received an injection of 1 g/kg of a 2.8-mol/l glucose solution, intraperitoneally. Approximately 10-µl blood samples were collected from an incision in the tail at 30, 60, 90, and 120 min after the glucose load. Plasma glucose levels were measured using reagent strips read in a glucose meter (Bayer, Elkhart, IN).

Proteinuria and albuminuria. Male BN, FHH, T2DN, and GK<sub>FL</sub> rats were placed on standard cages at 1, 3, 6, 9, 12, and 18 months of age, and urine was collected for 24 h. Total protein concentration in the urine was determined colorimetrically using the Bradford method (BioRad, Hercules, CA) (23). Albumin was measured using the albumin blue 580-fluorescence assay (24).

Creatinine. Serum creatinine levels were determined at 12 and 18 months in male T2DN and GK<sub>FL</sub> rats (22 months as well for this strain), using a modification of the Jaffe color reaction.

Determination of lipid profiles. Serum cholesterol and triglyceride concentrations were measured in BN, T2DN, and GK<sub>FL</sub> rats at 6 and 12 months of age. For this procedure, the rats fasted overnight, and 500–700 µl of blood was collected from the tail vein. Total cholesterol and triglycerides were determined using kits from Sigma Diagnostics (St. Louis, MO).

Histology. Renal histology was assessed in T2DN and GK<sub>FL</sub> rats at 6, 12, 18, and 22 (GK<sub>FL</sub>) only months of age. The right kidney was removed, weighed, and then fixed in 10% formalin solution followed by embedding in paraffin. Two 4-µm-thick sections were prepared and stained with periodic acid–Schiff. The sections were examined by light microscopy for the degree of vascular injury, renal interstitial fibrosis, and the degree of glomerulosclerosis and expansion of the mesangial matrix in the glomerulus. Lesions in individual glomeruli were scored on a 0 to 4+ scale with 0 representing a normal glomerulus, 1+ representing a 1–25% loss of capillaries in the tuft, 2+ representing a 26–50% loss, 3+ representing a 51–75% loss, and 4+ representing >75% of the tuft sclerosed. A total of 30–35 glomeruli per kidney were analyzed, and an average score ( sclerosis index) was calculated for each animal. Glomerular diameter and volume were also determined using a modification of the Maximal Planar Area method (25).

For electron microscopy, kidneys were removed and placed in cold 3% glutaraldehyde fixative in 0.1 mol/l cacodylate buffer (pH 7.4). Tissue was cut in 1-mm<sup>3</sup> blocks and further fixed overnight at 4°C. After postfixation, tissues were embedded in Epon/Araldite, and sections were cut from epoxy blocks. Sections were mounted on 200-mesh copper grids and observed and photographed at 11,000×.

RESULTS

Development of the T2DN rat. The strategy of using marker-assisted selection to identify animals carrying the least number of heterozygous donor-FHH and maximum number of homozygous recipient-GK genomic segments (D/R) allowed for the rederivation of the GK genome in fewer generations as compared with a standard congeneric breeding strategy (26), as well as limiting the number of passenger loci (FHH alleles). To search for passenger loci, we increased the number of SSLPs screened from 180 to 681 microsatellites. This scan identified only six FHH passenger loci—one on chromosome 2 (D2Rat12), one on chromosome 11 (D11Rat93), one on chromosome 16 (D16Rat15), one on chromosome 19 (D19Rat59), and two on chromosome X (DXMit4 and DXRat42)—that were still present in the rederived T2DN strain. Given the genomic interval between these and the closest microsatellite markers, these polymorphisms correspond to a maximum of 1% of FHH genome retained in the T2DN strain. Because a female FHH rat was used to produce the F1 rats in this cross and female rats were used to rederive the T2DN rats, they harbor mitochondrial DNA of FHH rats, which has been sequence verified (data not shown).

Genomic comparison of T2DN and GK<sub>FL</sub> rats. A genome-wide scan with 543 polymorphic markers from the 681-marker set was carried out for comparison between T2DN and GK<sub>FL</sub> rats. The results indicate that the two strains of GK rats are 98% identical (535 of 543 markers). Of the eight markers that were different (these are not FHH alleles but alleles that differ between the GK substrains from Sweden and Florida), three were on independent chromosomes: 3 (D3Rat157), 11 (D11Mgh5), and 12 (D12Rat22). Five additional polymorphic markers were identified on chromosome 1: D1Rat291, D1Mit18, D1Mit34, and D1Mgh12 within 30 cm from each other. The fifth difference at D1Rat185 mapped 57 cm from the telomere on chromosome 1 (Fig. 1). Together with the genomic segments carried over from the FHH rats, the genotyping results indicate that T2DN and GK<sub>FL</sub> strains are 97% identical at the microsatellite level across the entire genome.

Physiological comparison of T2DN and GK<sub>FL</sub> rats. We next physiologically characterized the new T2DN strain in
Development of diabetes and glucose intolerance. Baseline fasting glucose levels were elevated to >200 mg/dl by 3 months of age in both T2DN and GKFL rats and were significantly greater than the values seen in nondiabetic BN and FHH rats (Fig. 2). However, no significant difference in fasting glucose levels was seen between GKFL and T2DN rats at any point during the study. Both GKFL and T2DN exhibited glucose intolerance as indicated by the increased area of the plasma glucose clearance curve after an IPGTT. The degree of glucose intolerance was greater in T2DN than in GKFL at 3 months of age, but no significant difference was observed in 6- and 9-month-old rats. After 12 months of age, the degree of glucose intolerance in T2DN rats was 20–30% greater than that seen in age-matched GKFL rats.

Proteinuria and markers of progressive renal disease. A longitudinal screening of proteinuria in T2DN rats shows that at 1 month of age, proteinuria is similar in T2DN, GKFL, FHH, and control BN rats (Fig. 3). It becomes significantly elevated in 3-month-old FHH, T2DN, and GKFL rats. The degree of proteinuria progresses in T2DN rats over time, reaching 297 ± 17 mg/day at 12 months and 528 ± 51 mg/day at 18 months. In contrast, GKFL rats do not develop severe proteinuria even at 12 months of age. Similarly, albuminuria progressively increased in 6- vs. 12-month-old T2DN rats, but it did not increase significantly in GKFL rats (Table 1). Urine flow rate was higher in

FIG. 1. Schematic diagram of the rat chromosome 1. Arrows display the chromosomal projections of the five microsatellites identified as polymorphic between T2DN and GKFL in this chromosome. The genomic interval linked to the Niddm1 QTL is also highlighted (27–29).

FIG. 2. Progression of type 2 diabetes in T2DN (○) and GKFL rats (▲) measured by IPGTT. Glycemic profiles of nondiabetic BN (●) and FHH rats (□) are also shown. Six to seven animals per group were tested at all ages. *P < 0.05 T2DN vs. GKFL (repeated measures ANOVA with a Duncan’s multiple range pairwise post hoc comparison).
RAT MODEL OF DIABETIC NEPHROPATHY

T2DN rats than in GKFL or BN rats, at both 6 and 12 months of age (Table 1).

For comparing the onset and rate of progression of renal disease between T2DN and FHH rats, proteinuria was measured longitudinally in FHH rats (Fig. 3). The onset of overt proteinuria occurs much earlier in FHH rats, being evident already at 3 months of age, followed by a rapid progression, reaching 790 ± 11 mg/dl by 12 months of age. Death ensues between 12 and 15 months of age, as a result of ESRD, as previously described (30–32).

To determine whether T2DN rats develop progressive renal disease leading to ESRD, we measured plasma creatinine concentrations at 12 and 18 months in BN, GKFL, and T2DN rats. Serum creatinine concentration did not increase in GKFL rats compared with age-matched BN rats (Fig. 3), indicating that GKFL rats do not exhibit progressive renal disease leading to ESRD. In contrast, in T2DN rats, serum creatinine levels rose from 0.58 ± 0.01 at 12 months to 1.66 ± 0.26 mg/dl at 18 months (five times the normal level for a rat), indicating that T2DN rats exhibit a progressive decline in renal function.

**Dislipidemia.** Given the strong correlation between proteinuria and dyslipidemia in human diabetic nephropathy (33,34), we compared serum cholesterol and triglyceride levels in T2DN and GKFL rats (Table 1). Serum cholesterol levels in 12-month-old male T2DN rats averaged 170.4 ± 14.0 mg/dl and are four times higher than the levels measured in age-matched male BN rats (41.7 ± 1.4 mg/dl). Serum triglyceride concentration was also elevated in 12-month-old T2DN rats (157.6 ± 23.8 mg/dl) compared with the values seen in age-matched control BN rats (34.0 ± 5.1 mg/dl). In 12-month-old male GKFL rats, both serum triglyceride (108 ± 3 mg/dl) and cholesterol levels (66 ± 6 mg/dl) are elevated as compared with BN rats but are still significantly lower than the corresponding values obtained in age-matched T2DN rats. Proteinuria and dyslipidemia are strongly correlated in T2DN rats with a correlation coefficient between proteinuria and serum cholesterol levels of 0.80 (P < 0.01) and that between proteinuria and serum triglycerides levels of 0.77 (P < 0.01) at 12 months.

**Histologic changes in the kidney.** Histologic analysis of the kidneys of T2DN rats revealed an extensive pattern of progressive renal disease characterized by glomerular, tubular, and renal interstitial injury. As illustrated in Fig. 4, the predominant form of glomerular alteration at 12 months of age in T2DN rats is glomerular hypertrophy (Fig. 4B) and focal segmental glomerulosclerosis, with regional adhesion of the glomerular tuft to Bowman’s capsule associated with expansion of the mesangial matrix and filling in of capillaries (Fig. 4C and D), is more severe than that seen in age-matched BN (Fig. 4A) and GKFL rats (Fig. 4E). Electron microscopy reveals a similar pronounced thickening of both glomerular and tubular basement membranes in the kidneys of both GKFL and T2DN diabetic rats (Fig. 4G and H) relative to BN rats (Fig. 4F).

At 12 months of age, glomeruli in T2DN rats also exhibit expansion of mesangial matrix and appearance of periodic acid-Schiff–positive material. This expansion of the mesangial matrix is even more prominent at 18 months of age, with nearly complete obliteration of glomerular capillaries in the majority of glomeruli, indicative of severe global

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**TABLE 1**

<table>
<thead>
<tr>
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<th>6 months</th>
<th></th>
<th></th>
<th>12 months</th>
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<tbody>
<tr>
<td></td>
<td>BN</td>
<td>GKFL</td>
<td>T2DN</td>
<td>BN</td>
<td>GKFL</td>
</tr>
<tr>
<td>Urine flow rate (ml/24 h)</td>
<td>12.2 ± 1.1</td>
<td>10.4 ± 1.7</td>
<td>18.8 ± 2.1†</td>
<td>10.8 ± 1.5</td>
<td>11.8 ± 0.8</td>
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<td>Albuminuria (mg/day)</td>
<td>0.7 ± 0.1</td>
<td>7.5 ± 2*</td>
<td>10.3 ± 3*</td>
<td>0.7 ± 0.3</td>
<td>29.8 ± 10*</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>45 ± 3</td>
<td>67 ± 2*</td>
<td>77 ± 3*</td>
<td>42 ± 2</td>
<td>66 ± 6*</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>37 ± 3</td>
<td>54 ± 2*</td>
<td>90 ± 5†</td>
<td>34 ± 5</td>
<td>108 ± 3*</td>
</tr>
<tr>
<td>Glomerular diameter (µm)</td>
<td>137 ± 3</td>
<td>161 ± 3*</td>
<td>172 ± 4*</td>
<td>140 ± 2</td>
<td>173 ± 5*</td>
</tr>
<tr>
<td>Lesion score</td>
<td>ND</td>
<td>0.5 ± 0.4</td>
<td>0.4 ± 0.02</td>
<td>ND</td>
<td>1.1 ± 0.08</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>340 ± 18</td>
<td>351 ± 13</td>
<td>375 ± 15</td>
<td>432 ± 18</td>
<td>421 ± 20</td>
</tr>
<tr>
<td>Kidney weight (g)</td>
<td>1.0 ± 0.03</td>
<td>2.0 ± 0.05*</td>
<td>2.2 ± 0.04*</td>
<td>1.3 ± 0.4</td>
<td>2.11 ± 0.04*</td>
</tr>
<tr>
<td>Kidney weight/body weight (×1,000)</td>
<td>2.85 ± 0.1</td>
<td>5.70 ± 0.2*</td>
<td>5.85 ± 0.2*</td>
<td>3.01 ± 0.1</td>
<td>5.01 ± 0.2*</td>
</tr>
</tbody>
</table>

Data are means ± SE; n = 6–27 each. *P < 0.05 GKFL or T2DN vs. BN; †P < 0.05 T2DN vs. GKFL.
glomerulosclerosis (Fig. 5A–C). These alterations are also accompanied by arteriolar hyalinosis (Fig. 5D). More importantly, many glomerular are filled with asymmetric, acellular nodules, resembling Kimmelstiel-Wilson nodules that are characteristic of human diabetic nephropathy (35,36) (Fig. 5). In contrast, even at 22 months of age, GKFL rats exhibit only a very modest degree of mesangial matrix expansion and a limited degree of focal glomerulosclerosis similar to that presented in Fig. 4E, which is not greater than that seen in age-matched, nondiabetic BN rats.

Glomerular hypertrophy and nephromegaly were evident in the kidneys of both T2DN and GKFL rats as early as at 6 months of age (Fig. 4, Table 1). However, glomerular hypertrophy was slightly greater in T2DN than in GKFL rats at any age. The degree of renal growth (given by the kidney weight and body weight ratio) was significantly correlated to the degree of proteinuria in 12-month-old T2DN rats ($r = 0.51, P < 0.01$). As shown in Table 1, 6-month-old GKFL and T2DN rats exhibited a similar degree of glomerulosclerosis (0.51 ± 0.04 and 0.41 ± 0.02, respectively). By 12 months of age, the degree of glomerular damage in GKFL rats increased to 1.1 ± 0.08, but it was significantly less than that found in T2DN rats (1.9 ± 0.20), representing an average of 50% damage on all glomeruli (Table 1).

**DISCUSSION**

The present study characterized the development of a new rat model that exhibits progressive diabetic nephropathy. The T2DN rat model arose by combining the genomes of GK rats that develop type 2 diabetes but not progressive renal disease and FHH rats that develop progressive renal
disease but not type 2 diabetes. After early-onset diabetes, overt proteinuria develops in T2DN rats at ~6 months of age, and the degree of proteinuria progressively becomes more severe as the rats age. This is accompanied by hypertrophy of the glomeruli, thickening of glomerular and tubular basement membranes, expansion of the mesangial matrix, and the development of focal followed by diffuse global glomerulosclerosis and the formation of glomerular nodules by 18 months of age. In contrast, GKFL rats exhibit a similar time course and severity of diabetes, but this strain does not develop progressive renal disease leading to ESRD, even though renal hypertrophy and thickening of glomerular and basement membranes are also observed in this strain. Because of the nonavailability of animals, we were unable to compare T2DN rats with GK rats of the Swedish colony from which they were re-derived.

In the present study, we demonstrated that T2DN rats are genetically identical to GKFL rats at 97% of the 681 SSLP markers tested across the genome. Of the 3% differences between the strains, only 1% is accounted for by passenger loci from the FHH genome retained in T2DN rats. None of these passenger loci overlap with genomic regions corresponding to quantitative trait loci (QTLs) reported to be modulating the development of proteinuria, renal morphologic abnormalities, or hypertension in FHH rats (30,37). Moreover, the renal histopathologic findings and time course of renal disease in T2DN rats are very different from those observed in FHH rats (30–32, 37). Together, these data suggest that diabetic nephropathy in T2DN rats is altogether a distinct pathological entity from the renal disease of FHH rats. We conclude that the differences in the development of diabetic nephropathy in T2DN and GKFL rats are likely due to small differences in their genomic background and/or their different mitochondria.

There is a major difference between T2DN and GKFL rats on chromosome 1, with five polymorphisms clustering around a 57-cM genomic segment. These polymorphisms, in an otherwise isogenic background, suggest that the last common progenitor of T2DN and GKFL rats carried different haplotypes in this genomic segment and that each GK strain eventually retained one allelic variant. This finding is of special importance in the light of previous studies that revealed a major QTL, termed Niddm1, mapping to this same genomic segment on chromosome 1, linked to diabetes in GK rats (25,28). This QTL was later confirmed in congenic strains to be a major factor determining hyperglycemia in GK rats (29), but its role in determining the development of renal disease is unknown. Future studies aiming at dissecting the genetic basis of renal disease in T2DN rats will reveal whether similar genes are responsible for their susceptibility to diabetes and renal disease. Given the genetic similarities between GKFL and T2DN rats and that both strains develop type 2 diabetes, it is feasible to envision a scenario in which the added susceptibility to progressive renal disease in T2DN rats is due to genetic factors independent from diabetes, that were exclusively captured in the T2DN strain.

Glomerular hypertrophy is evident in both T2DN and GKFL rats several months before the development of overt renal disease in T2DN rats. These findings seem to corroborate earlier reports that GK rats exhibit glomerular hypertrophy and thickening of basement membranes that is commonly reported in most experimental models of diabetes (18–21). Unlike these other models, the natural
course of renal disease in T2DN rats closely parallels that of human diabetic nephropathy. Renal structural abnormalities such as glomerular and tubular hypertrophy are already observed at early ages and precede the development of proteinuria. The most common presentations of glomerular damage in T2DN rats at 12 months of age are severe focal segmental glomerulosclerosis and expansion of the mesangial matrix, with obliteration of glomerular capillaries and the formation of nodular lesions in several glomeruli. By 18 months of age, there is further expansion of the mesangial matrix, leading to diffuse global glomerulosclerosis with the formation of many large, acellular nodules in many glomeruli. The presence of nodular glomerulosclerosis, clearly discernible in T2DN rats with long-standing type 2 diabetes, is a pattern consistent with the development of diabetic nephropathy in humans (5,36). GKFL rats did not develop severe focal glomerulosclerosis or nodules even at 22 months of age, in the face of lifelong diabetes. Thus, the T2DN rat represents the first reported rodent model of spontaneous diabetes that develops progressive renal disease with the formation of nodular glomerulosclerosis.

Both T2DN and GKFL develop mild dyslipidemia, as reflected by elevated levels of plasma cholesterol and triglycerides. In T2DN rats, proteinuria and dyslipidemia are strongly correlated. This is consistent with previous reports in diabetic patients that demonstrate a strong correlation between dyslipidemia and progression of diabetic nephropathy (33,34). It is interesting that GKFL rats display a milder form of dyslipidemia. This likely reflects the milder proteinuria and lack of renal disease observed in these rats. These data seem to support the notion that the loss of plasma proteins triggers abnormalities in lipid metabolism perhaps as a result of loss of protein binding and explains the close association between proteinuria and lipid abnormalities in most forms of ESRD (38–40). Nevertheless, there is mounting evidence that alterations in lipid metabolism may also contribute to the renal damage seen in diabetes (41,42).

In summary, the present study characterized the first rodent model of spontaneous type 2 diabetes (T2DN rats) that develops progressive proteinuria and glomerulosclerosis leading to formation of nodules and ESRD. It also identified a closely related control strain of GK rats (GKFL) that develops diabetes but is resistant to the development of progressive proteinuria and renal disease. Discrete and yet unidentified genetic differences between these two strains of rats likely determine the difference in the susceptibility to develop diabetic nephropathy between T2DN and GKFL rats. These small differences, with large phenotypic impact, make these two strains ideal models for genetic dissection of diabetes-associated renal disease, as well as the relationships between the duration and severity of diabetes and the later onset and progression of renal disease.

REFERENCES


ACKNOWLEDGMENTS

We are grateful to Meredith Skelton, Lisa Henderson, Camille Torres, and Luanne Kelly for assistance with the biochemical assays; Mark Sadowski for assistance with electron microscopy; and Dr. Holger Latham, from the Karolinska Institute, Sweden, for kindly providing the GK rat used for the rederivation of the T2DN strain.

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