Increased Kidney Size and Glomerular Filtration Rate in Early Juvenile Diabetes

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SUMMARY

Glomerular filtration rate (GFR), renal plasma flow (RPF) and roentgenographic kidney size were measured in twelve normal young male subjects and in twelve juvenile diabetics with a mean duration of diabetes of 4.9 years. GFR but not RPF was significantly elevated in the diabetics. Furthermore, calculated kidney weight corrected to 1.73 m.^{2} body surface was increased in the diabetics, being 391 gm. ± 46.2 (S.D.) [normal value 321 gm. ± 54.6 (S.D.) ($p < 0.01$)]. When GFR was expressed per gram calculated kidney weight practically identical values were found in normals and diabetics. Moreover, there was a clear positive correlation between GFR, RPF and kidney size in both normals and diabetics ($p < 0.01$ in all cases). There was no statistically significant change in RPF per gram calculated kidney weight. These results suggest that there is a basal connection between enlarged kidneys and the elevated GFR of early diabetes. DIABETES *22*:706-12, September, 1973.

In a number of studies it has been demonstrated that the glomerular filtration rate (GFR) is markedly elevated in early juvenile diabetes.[1-6] It has been shown that this abnormally high filtration rate is associated with the metabolic derangement,[3] but the mechanism behind the abnormality has not been fully clarified. Glomerular permeability to high molecular weight dextran was found to be normal in these patients.[3] Furthermore, urinary albumin excretion is normal in short-term diabetic patients without proteinuria.[7] These findings suggest that abnormal filter properties are not the mechanism behind the high filtration rate. High filtration fraction has been found in juvenile diabetics with high filtration rate, suggesting that increased filtration pressure might be present in these patients. However, increased renal size might also be the mechanism responsible for the high GFR.[3,4] These topics have recently been surveyed.[8]

The purpose of the present study was to investigate whether the elevated GFR of early diabetes was associated with increased kidney size as measured on roentgenograms.

PATIENTS, CONTROLS AND METHODS

Subjects investigated

Twelve young male diabetic patients aged seventeen to thirty-three years were examined. Mean duration of diabetes was 4.9 years ± 3.3 (S.D.) and mean age 23.8 years ± 5.0 (S.D.). Pertinent data are given in table 1. The mean fasting blood sugar level on the day of the clearance test was 161 mg./100 ml. ± 48.0 (S.D.).

Twelve normal male subjects (medical students) served as controls. Their mean age was 25.3 years ± 2.0 (S.D.) (table 2).

Kidney function tests

Glomerular filtration rate (GFR) and renal plasma

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TABLE 1

Pertinent data, results of kidney function tests and roentgenographic kidney size in twelve young diabetic subjects

Subject	Age	Body surface	Blood sugar	Duration of diabetes	GFR	RPF	Filtration fraction	Roentgenographic kidney size: Right kidney length	Right kidney width	Left kidney length	Left kidney width	Area index (right +left)	Area index corrected to 1.73 m.^{2}
no.	yr.	m.^{2}	mg./100 ml.	yr.	ml./min.	ml./min.		cm.	cm.	cm.	cm.	cm.^{2}	cm.^{2}
13	18	1.60	192	5	156	697	0.22	12.8	7.0	13.5	7.3	188	204
14	17	1.61	181	2	155	592	0.26	13.2	6.2	14.6	7.4	190	204
15	18	1.75	200	1	122	462	0.26	12.4	7.4	12.2	7.6	185	182
16	21	1.96	124	12	140	603	0.23	13.5	7.2	14.7	6.7	196	173
17	25	1.79	152	3	159	767	0.21	13.7	8.0	15.0	8.4	236	228
18	29	1.62	196	9	157	703	0.22	14.0	8.0	13.0	6.0	190	203
19	25	1.99	74	7	139	603	0.23	13.5	7.0	14.7	8.5	220	191
20	30	1.74	250	2	133	598	0.22	14.5	6.5	15.5	7.5	211	209
21	23	1.86	114	3	139	576	0.24	14.2	7.5	14.0	8.5	226	210
22	23	1.90	120	6	136	522	0.26	13.0	7.5	13.3	7.2	193	176
23	33	2.02	153	6	128	444	0.29	14.5	7.2	13.0	7.7	205	176
24	24	1.95	180	3	174	705	0.25	15.0	8.5	15.5	8.5	259	230
Mean	23.8	1.816	161.3	4.9	144.8	606.0	0.241	13.69	7.33	14.08	7.608	208.3	198.8
S.D.	5.00	0.153	48.02	3.26	15.20	99.37	0.022	0.776	0.643	1.076	0.783	23.00	19.48

flow (RPF) were measured by I-125 iothalamate and by 131-I-hippuran clearance, respectively, using a classic constant infusion technic as described in detail previously.[4] Three or four clearance periods lasting twenty minutes were performed during each test. It has been shown that labeled iothalamate and hippuran are reliable substances for measuring GFR and RPF, respectively.[4,9-12] Results were corrected to 1.73 m.^{2} body surface. Plasma glucose was measured using a glucose oxidase method. The tests were performed in the morning on patients

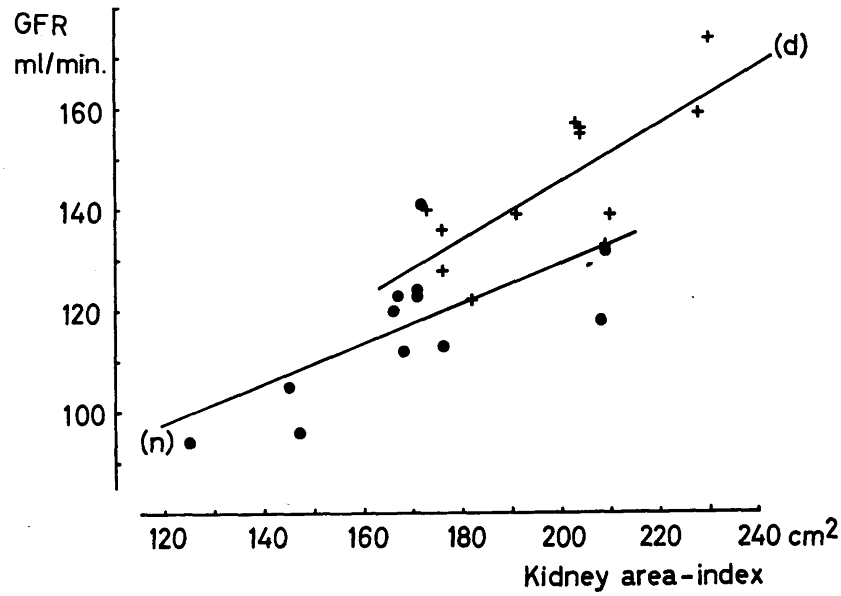
TABLE 2

Pertinent data, results of kidney function tests and roentgenographic kidney size in twelve young normal subjects

Subject	Age	Body surface	GFR	RPF	Filtration fraction	Roentgenographic kidney size: Right kidney length	Right kidney width	Left kidney length	Left kidney width	Area index (right+ left)	Area index corrected to 1.73 m.^{2}
no.	yr.	m.^{2}	ml./min.	ml./min.		cm.	cm.	cm.	cm.	cm.^{2}	cm.^{2}
1	24	1.65	132	769	0.17	14.5	6.2	15.2	7.2	199	209
2	23	1.85	123	638	0.19	13.7	7.0	13.2	6.6	183	171
3	24	1.96	94	412	0.23	12.0	5.8	12.2	5.9	142	125
4	23	1.91	118	622	0.19	13.7	8.0	15.0	8.0	230	208
5	30	1.78	113	609	0.19	14.5	6.0	13.8	6.8	181	176
6	26	1.94	112	565	0.20	14.0	6.8	13.3	7.0	188	168
7	25	1.74	123	480	0.26	13.0	6.0	13.8	6.5	168	167
8	25	1.87	105	453	0.23	12.5	6.3	13.0	6.0	157	145
9	26	1.85	141	697	0.20	13.3	7.0	12.4	7.3	184	172
10	28	1.95	120	517	0.23	14.7	6.5	13.5	6.8	187	166
11	26	2.11	124	491	0.25	13.6	7.5	14.0	7.6	208	171
12	26	1.99	96	356	0.27	13.2	6.0	14.2	6.3	169	147
Mean	25.5	1.883	116.8	550.8	0.218	13.56	6.59	13.63	6.83	183.0	168.8
± S.D.	2.02	0.122	13.77	121.30	0.032	0.818	0.682	0.911	0.629	23.19	23.74

FIGURE I

Glomerular filtration rate plotted against kidney area index in normal (●) and diabetic (+) subjects.



GFR and kidney area-index in 12 normal (•) and 12 diabetic (+) subjects.
Regression line for normals (n)
—— " —— diabetics (d)

in the fasting state. The diabetics had been given their last insulin injection in the morning or afternoon the day before the clearance test.

Kidney size measurements

The size of the kidneys was measured on intravenous pyelograms taken with ureteric compression. Conray

TABLE 3

Calculated kidney weight and RPF and GFR per gram kidney in twelve young diabetic subjects

Subject	Calculated kidney weight* grams	Renal plasma flow* per gram ml./min./gm.	Glomerular filtration rate* per gram ml./min./gm.
13	403	1.73	0.39
14	403	1.47	0.38
15	351	1.32	0.35
16	330	1.83	0.42
17	461	1.66	0.34
18	401	1.75	0.39
19	372	1.62	0.37
20	415	1.44	0.32
21	417	1.38	0.33
22	338	1.54	0.40
23	338	1.31	0.38
24	466	1.51	0.37
Mean	391.3	1.547	0.370
± S.D.	46.19	0.172	0.030

* Corrected to 1.73 m.[2] body surface.

TABLE 4

Calculated kidney weight and RPF and GFR per gram kidney weight in twelve young normal subjects

Subject	Calculated kidney weight* grams	Renal plasma flow* per gram ml./min./gm.	Glomerular filtration rate* per gram ml./min./gm.
1	415	1.85	0.32
2	323	1.98	0.38
3	223	1.85	0.42
4	413	1.51	0.29
5	338	1.80	0.33
6	319	1.77	0.35
7	317	1.51	0.39
8	267	1.70	0.39
9	329	2.12	0.43
10	314	1.65	0.38
11	326	1.51	0.38
12	271	1.31	0.35
Mean	321.3	1.713	0.368
± S.D.	54.58	0.229	0.041

* Corrected to 1.73 m.[2] body surface.

(20 to 40 cc.) 400 mg. iodine per cubic centimeter (Jodtalamin natrium) was used as contrast medium; the focus-film distance was 110 cm.

The length and width of the kidneys were measured on exposures taken ten minutes after contrast injection if the kidneys were well delineated. In a few cases measurements were made at a later time or on a tomogram. The following measurements were obtained: *length*—greatest distance from pole to pole in centimeters; *width*—greatest distance from lateral kidney surface to tangent line of medial borders of the kidney in centimeters; *kidney area index*—sum of product of length and width in square centimeters of both kidneys; *kidney weight* calculated on the basis of data presented by Moëll.[13] In addition the renal index as defined by Friedenberg et al.[14] was calculated according to the following formula:

$$\text{Renal index} = \frac{\text{Length (cm.)} \times \text{width (cm.)}}{\text{Body surface (m.}^2\text{)}}$$

The kidney size measurements were taken by one of us (M.J.F.A.) who did not know whether the subjects were diabetic or normal and who was also unaware of the results of the kidney function tests.

RESULTS

Results of kidney function tests and measurements of the roentgenographic kidney sizes are given in tables 1 and 2. The GFR was significantly increased in the diabetics, the mean value being 144.8 ml. per minute $\pm$ 15.20 (S.D.), compared to the value found in the normals, 116.8 ml. per minute $\pm$ 13.77 (S.D.) ($p < 0.001$). The mean value for RPF was 10 per cent higher in the diabetics but this difference is not statistically significant.

Both the kidney area index corrected to 1.73 $m.^2$ (sum of length x width of both kidneys) and the calculated kidney weight corrected to 1.73 $m.^2$ (tables 3 and 4) were significantly increased in the diabetics ($p < 0.01$ and 0.01 respectively).

In figures 1 and 2 the GFR and RPF are plotted against the kidney area index. In normal subjects a positive correlation with kidney area is found both for GFR ($r = 0.68$, $p < 0.01$) and RPF ($r = 0.80$, $p < 0.001$). For all the subjects there was also a clear positive correlation between GFR and kidney area ($r = 0.82$, $p < 0.001$) and RPF and kidney area ($r = 0.82$, $p < 0.001$). Also for the diabetics a significant positive correlation was found between kidney area and GFR ($r = 0.75$, $p < 0.01$) and RPF ($r = 0.77$, $p < 0.01$). Similar correlation coefficients were found between kidney function and calculated weight. Results are plotted in figures 3 and 4. The greatest indication that renal function in diabetes depends upon kidney size is shown by the finding that kidney function per calculated gram kidney weight is the same in diabetics and nondiabetics. These results are shown in tables 3 and 4. The mean RPF per gram calculated kidney weight is 10 per cent lower in the diabetics, but the difference is not statistically significant. Practically identical values are found for GFR per gram calculated kidney weight, also shown in figure 5.

The results calculated on the basis of the renal index as defined by Friedenberg are shown in table 5. Also using this index the difference in kidney size is highly significant ($p < 0.01$).

DISCUSSION

It is well established that GFR is increased in early juvenile diabetes.[1-6,8] It has also been shown recently that GFR is elevated to approximately the same extent in long-term diabetics without proteinuria.[15] In the present study it has been shown that the roentgenographic kidney size is increased to approximately the same amount as GFR in these patients. When the filtration rate is expressed per gram calculated kidney weight the same level is found in the twelve normal and the twelve diabetic subjects investigated. Elevated maximal tubular reabsorption capacity for glucose has also been found in early diabetes which suggests tubular hyperfunction.[5]

In the present study kidney size was determined after injection of the contrast media while urography was being performed. Moëll used plain roentgenograms for estimation of kidney size. Passage of the contrast media through the kidneys may cause swelling, resulting in increased roentgenographic size. Our normal values are also slightly higher than those reported by Moëll. The weight of the kidney may therefore be slightly overestimated when calculating kidney weight on the basis of the diagram presented by Moëll. However, for comparative purposes such a small overestimation is probably without significance.

The data of the normal subjects in our series correspond with the results of Friedenberg et al.,[13] since the mean index as defined by Friedenberg et al. in our study was 49.9 for the left kidney and 47.6 for the right kidney, compared with 47.2 and 45.2 in Friedenberg's study of eighty-eight males without renal disease aged fifteen to thirty-nine years.

The mean value for the RPF is 10 per cent higher

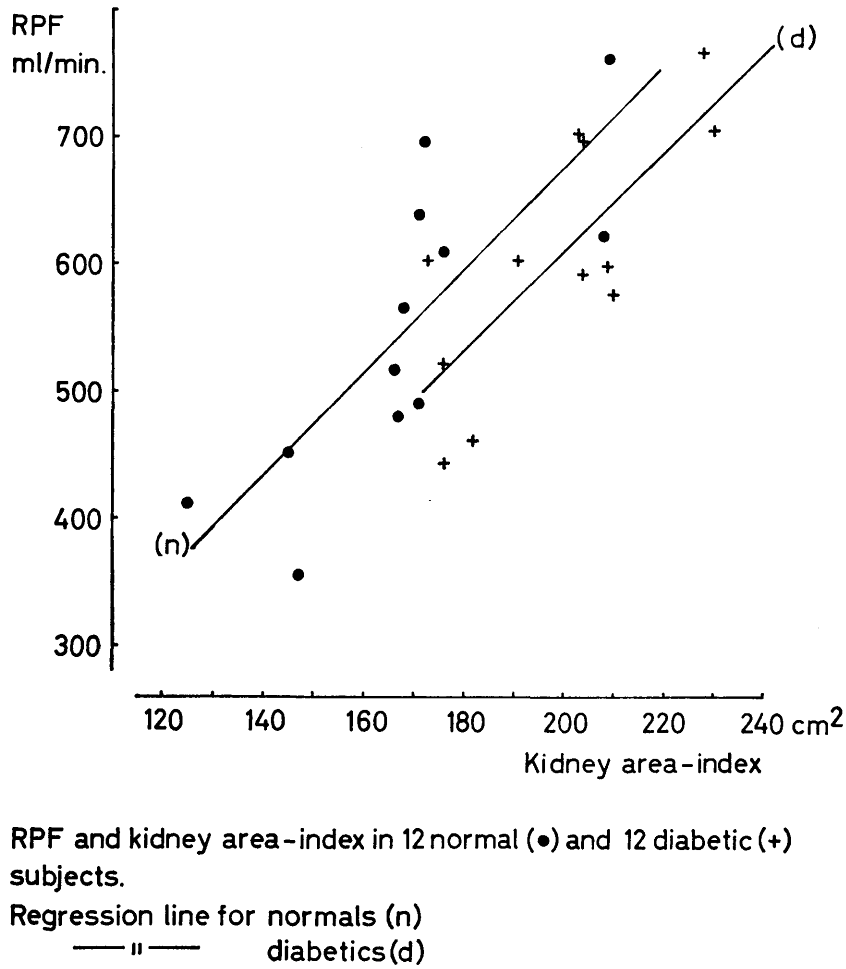


FIGURE 2

Renal plasma flow plotted against kidney area index in normal (●) and diabetic (+) subjects.

in the diabetics than in the normals but the difference is not statistically significant. When the plasma flow is expressed per gram calculated kidney weight no statistically significant difference is found.

In previous studies it was shown that the high GFR of early diabetes was associated neither with an abnormal dextran clearance pattern nor with an abnormal urinary albumin excretion rate; this suggests that abnormalities of the filter properties of the glomerular membrane could not explain the high GFR in these patients.[3,7] On the basis of these studies it could not be known whether increased kidney and glomerular size or increased filtration pressure was responsible for the high GFR. Increased filtration fraction found in early diabetes suggested that increased filtration pressure might be present.[3,4] The results of the present study support the concept that increased kidney size is an important factor for the high GFR. The increased kidney size probably reflects increased size of the glomeruli also. Studies are in progress in our laboratory to elucidate this problem.

It is not known whether increased filtration pressure is found in early diabetes. The filtration fraction is elevated, but direct measurements of glomerular filtration pressure in either normal or diabetic human beings are not available in the literature; thus, conclusive data cannot be obtained at the present time. The increased kidney size would readily explain the elevated GFR, however.

The stimulus for renal enlargement in early diabetes mellitus remains unclarified. Increased growth hormone secretion is found in early diabetes[16] and growth hor-

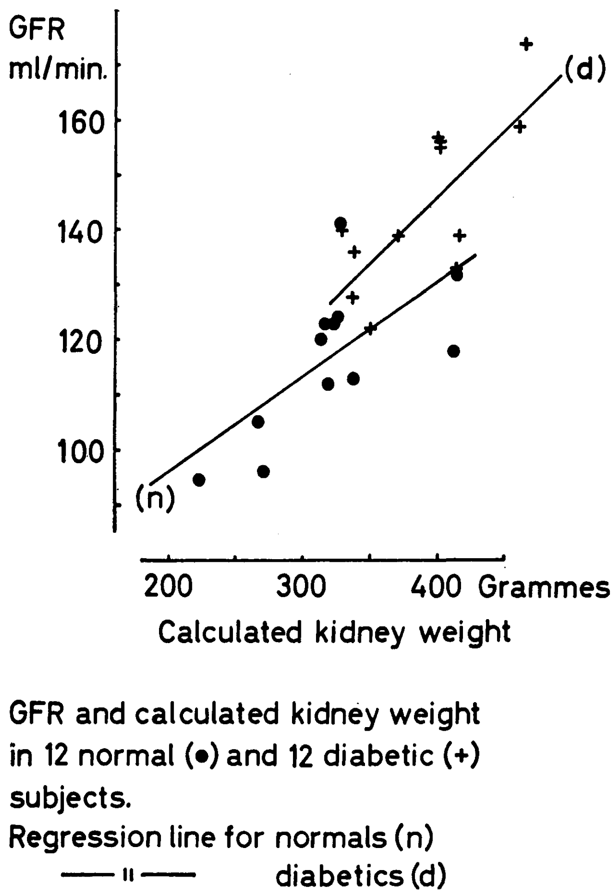


FIG. 3. Glomerular filtration rate plotted against calculated kidney weight (grams) in normal (●) and diabetic (+) subjects.

mone is able to stimulate renal growth, but it must be emphasized that a great number of substances are capable of stimulating renal enlargement.[17]

Ross and Goldman[18] found considerable renal enlargement after a few days of streptozotocin-induced diabetes in the rat. Renal function was not determined in these experiments, however. It is possible that long-term increased glucose transport in the kidney is capable of stimulating renal growth and thus enhancing kidney function. In short-term experiments no increase in renal function is found except minor changes which can probably be explained by the infusion per se.[6]

It has previously been shown that the increase in GFR in newly diagnosed diabetics could be normalized during strict insulin treatment.[3] Studies are now in progress to determine whether the increase in kidney size is a reversible phenomenon.

It remains unclarified whether the increase in kidney size plays any role in development of the long-term lesions of diabetic nephropathy.

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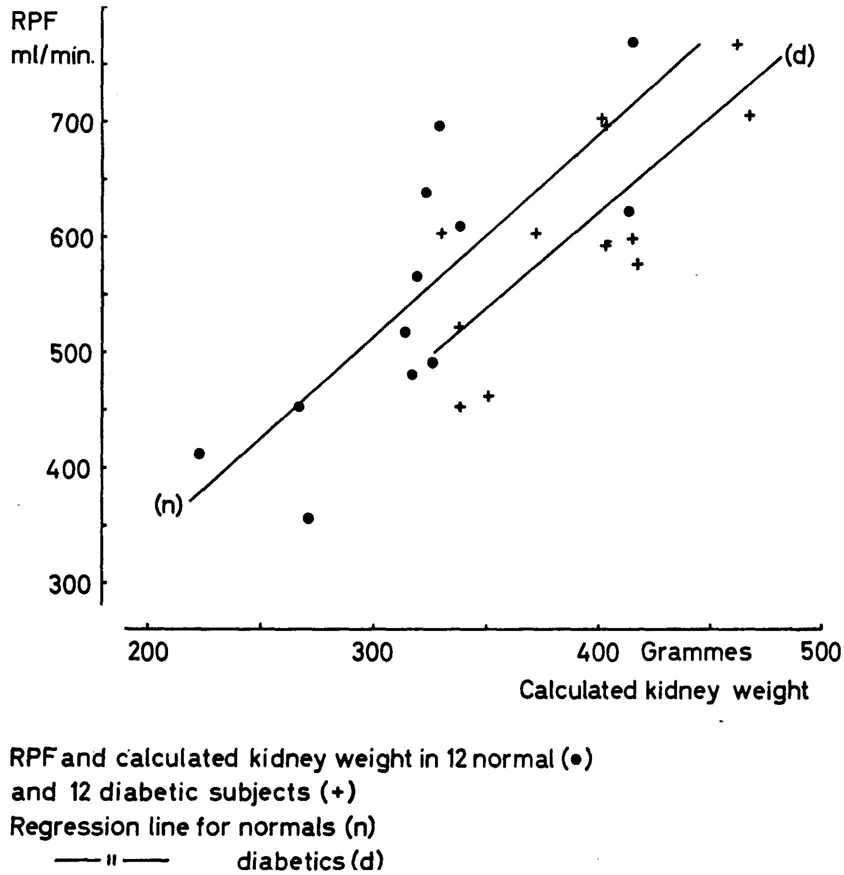

FIGURE 4

Renal plasma flow plotted against calculated kidney weight (grams) in normal (●) and diabetic (+) subjects.

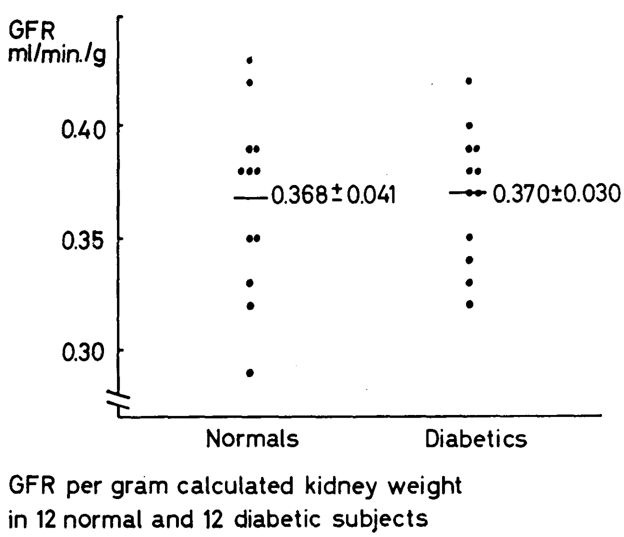

FIG. 5. Glomerular filtration rate per gram calculated kidney weight in twelve normal and twelve diabetic subjects.

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TABLE 5

Renal index according to Friedenberg et al.

	Left kidney Mean ± S.D.	Right kidney Mean ± S.D.
12 normal subjects	49.9 ± 8.2	47.6 ± 6.2
12 diabetic subjects	59.3 ± 8.4	55.5 ± 6.6
	$p < 0.01$	$p < 0.01$