Effect of Diet on Creatinine Clearance and Excretion in Young and Elderly Healthy Subjects and in Patients with Renal Disease[1,2]

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ABSTRACT

Thirty-seven young healthy subjects with normal renal function were studied to assess the quantitative effect of protein intake on creatinine clearance. A standard 24-h urine collection and blood sample at the end of the collection were obtained for creatinine and urea concentrations. Correlations between creatinine clearance and urinary urea nitrogen excretion ($r = 0.8$; $P < 0.0001$) and calculated protein intake ($r = 0.8$; $P < 0.0001$) were observed. A significant relationship between creatinine clearance and urea nitrogen excretion was also demonstrated in 28 elderly healthy subjects and 33 patients with renal disease. To demonstrate a cause and effect between urea nitrogen excretion and creatinine clearance in healthy subjects, 18 of the 37 healthy subjects repeated the 24-h urine collection and blood sample after ingesting 5 g of urea in addition to their usual diet. Mean urinary urea nitrogen excretion increased from a mean value of 9.8 ± 4.0 to 11.8 ± 4.0 g/day. There was a strong correlation between the changes in urea nitrogen excretion and the changes in creatinine clearance. In acute studies with oral protein loading, there was a significant correlation between creatinine clearance and urinary urea nitrogen excretion. It was concluded that protein intake has a direct and quantitative effect on creatinine clearance in healthy subjects. In normal humans, it is likely that GFR is not a fixed function. Thus, a low creatinine clearance is not a categorical sign of renal disease. A low creatinine clearance adjusted for urea nitrogen excretion may be a useful clinical tool to assess renal function.

Key Words: *Diet, creatinine clearance, urinary urea nitrogen, protein intake, elderly*

Several studies have demonstrated an important effect of diet on GFR (1–10). Acute and chronic experiments in animals and humans have established that an acute increase in protein intake induces a rapid and transient surge in GFR (1–13). These studies were conducted to establish a cause and effect between protein intake and creatinine clearance in healthy subjects. A quantitative relationship between these two variables has not been proposed as yet. The degree of functional impairment of the kidney has traditionally been based on GFR. It has been assumed that a low GFR represents parenchymal damage, and, over a period of time, there is further reduction in GFR. Inulin and iothalamate clearances or, more practically, the endogenous creatinine clearance have been used to measure GFR (14–20). Because diet is variable from day to day and from subject to subject, should the measured GFR be controlled for protein intake?

Diet has also been shown to influence creatinine excretion. Approximately 10% of daily urinary creatinine excretion is of exogenous origin (6). Long-term low-protein consumers, such as vegetarians, have urinary creatinine excretion that is lower than the 10% allowed for exclusion of exogenous creatinine sources (6). Plasma creatinine and its reciprocal value (21–23) are dependent on a constant urinary creatinine excretion rate for consistent interpretation when used to assess renal function or to follow the progression of renal disease. The manner in which dietary changes interfere with urinary creatinine excretion, especially in the face of acute dietary changes, renders the validity of such indirect parameters to assess GFR uncertain.

In this study, the relationship between urinary urea nitrogen excretion, as an indicator of protein intake, and creatinine clearance was determined in young and elderly healthy subjects and patients with renal disease. The concept of GFR that emerges from these studies is quite contrary to traditional views. We propose that GFR: (*1*) is not a fixed function, (*2*) changes over time, and (*3*) is not necessarily synon-

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ymous with renal disease when a low value is obtained.

MATERIAL AND METHODS

Study Population

Young Healthy Subjects. Thirty-seven healthy subjects under the age of 50 were studied. Their renal function was normal as determined by the absence of a history of renal disease, the presence of a normal urinalysis, urinary protein excretion less than 100 mg/24 h, and a normal blood pressure. A wide range of protein intake was studied in these subjects. Eighteen subjects called themselves "vegetarians" (including lacto-ova vegetarians); 8 subjects were on a voluntary low-protein diet (0.6 to 0.8 g/kg/day); 11 subjects were on an *ad libitum* diet. All individuals were on their diets for at least 6 months before the onset of the study (Table 1).

Elderly Healthy Subjects. Twenty-eight elderly subjects with a mean age of 70.2 (55 to 88) yr of age were studied. In these subjects, the absence of renal disease was determined by the same criteria as outlined above (Table 2).

Patients with Renal Disease. Thirty-three subjects with known renal disease were studied. The mean age of these subjects was 45.6 (22 to 66) yr of age. Renal disease was from a variety of causes (Table 3).

Methods

A standard 24-h urine collection was obtained and assayed for volume and creatinine, protein, and urea nitrogen concentrations. A blood sample was obtained at the completion of the urine collection, and the serum was assayed for urea nitrogen and creatinine concentrations. The patients' weight and height were also recorded. Creatinine concentration was determined by an alkaline picrate method and was measured by a Technicon RA-1000. Urea nitrogen concentration was measured with a Kodak Ektachem 700. Urine protein concentration was determined by a modified trichloroacetic acid method by using a turbimeter. Microalbuminuria was measured by an ELISA method. In some patients (Table 2) protein excretion was determined with a Dipstick®.

Protein intake was calculated from urea nitrogen appearance rate by the following equation (24,25).

$$\text{Estimated protein intake (g/kg/day)} = 6.25 \times (\text{urinary urea nitrogen excretion [g/kg24 hr]} + 0.031)$$

Urea Loading Studies:

Eighteen of the young healthy subjects repeated the 24-h urine collection on a day in which 5 g of urea was ingested between 8 a.m. and noon in addition to their usual diet.

Acute Protein Loading Studies with Inulin Clearance

Twelve subjects (five young healthy subjects and seven patients with renal disease) had simultaneous measurements of inulin and creatinine clearances and urinary urea excretion during 30-min intervals before and after an acute oral protein load of 70 to 80 g of cooked red meat. The priming injection of inulin was calculated as 60 mg/kg body wt. A third of this dose was infused rapidly, and the remainder was infused over 20 min. The sustaining infusion was started shortly after the priming infusion and delivered at a rate of 33 mg/min by using an infusion pump. Sterile pyrogen-free inulin was used (American Critical Care, Decatur, Illinois). Plasma and urine insulin concentrations were measured by the method described by Wesson (26).

Iothalamate Clearance Studies

GFR in 33 patients with renal disease was assessed both by a standard 24-h creatinine clearance and by a timed [^{125}I]iothalamate clearance (27). In the latter, after the subjects received a water load and a saturated solution of potassium iodine, they were given a sc injection of 0.035 mCi of Glofil®. After 60 to 90-min, timed collections of urine and serum were obtained. GFR was equal to the urinary clearance of the marker.

Data are reported as mean ± SD. Statistical analysis, correlation coefficient, and paired and unpaired *t* test were performed by using a computerized program (Stat View 512 +; Brain Power, Calabasas, CA). Significance was assumed when $P < 0.05$.

RESULTS

Figure 1 (left panel) depicts the relationship between urea nitrogen excretion and creatinine clearance in the 37 young healthy subjects. A significant correlation between these two parameters was demonstrated ($r = 0.8$; $P < 0.0001$). The wide range of urea nitrogen excretion observed (from 2.0 to 17.0 g/day) was the result of diet variation in the study population. Figure 1 (right panel) shows the same data as the left panel of Figure 1 with the calculated protein intake on the *x* axis ($r = 0.8$; $P < 0.0001$). A significant number of these subjects was ingesting less than the daily recommended amount of protein without apparent nutritional deficits. The current recommended daily allowance of protein is 0.8 g/kg/day (28). It is of interest that a protein intake of 1.3 g/kg/day corresponds to a creatinine clearance of 120 mL/min/1.73 m^2 (Figure 1, right panel). Probably 1.2 to 1.4 g/kg/day of dietary protein represents the average protein intake in developed countries, thereby the accepted "normal value" for creatinine

TABLE 1. Young healthy subjects[a]

Patient No.	Sex	Age (yr)	Weight (kg)	Height (cm)	Volume (mL)	P(Cr) (mg/dL)	P(BUN) (mg/dL)	Cr Excr mg/day)	Pr Intake (g/kg/day)	Cr Cl (mL/min/1.73 m^2)
Effect of Protein Intake										
Low Intake										
1	M	31	89.0	193.0	1,035	0.93	13.4	1,718	0.76	100.4
2	F	33	68.0	163.0	1,325	0.64	17.3	798	0.64	84.1
3	F	45	59.0	168.0	2,200	0.80	8.5	409	0.40	38.4
6	F	41	64.5	160.0	2,305	1.03	9.4	1,277	0.68	86.1
9	F	30	68.0	152.0	640	0.77	9.1	1,100	0.78	100.4
11	M	49	95.0	185.0	870	1.12	6.6	1,651	0.75	79.4
12	M	28	60.0	150.0	1,505	0.98	9.0	391	0.39	29.6
13	F	27	76.5	160.0	475	1.17	8.0	1,216	0.61	66.8
14	M	30	46.3	190.0	1,900	1.02	9.0	443	0.46	29.5
15	M	22	52.0	155.0	910	0.96	8.0	764	0.74	65.5
17	F	27	82.0	160.0	3,365	0.50	8.0	774	0.65	95.9
18	M	22	70.0	150.0	1,490	1.00	18.0	1,192	0.77	82.8
19	M	36	86.0	193.0	2,780	1.00	8.00	1,807	0.70	101.9
20	F	32	62.7	172.0	660	0.90	8.00	924	0.49	71.3
21	F	37	57.7	161.0	570	0.70	12.0	690	0.71	73.1
23	F	28	60.0	183.0	2,380	0.70	5.0	714	0.66	72.9
Mean		32.4	68.5	168.4	1,526	0.89	9.8	992	0.64	73.6
SD		7.6	13.8	15.5	877	0.19	3.6	456	0.13	23.6
High Intake										
4	F	20	48.0	155.0	2,000	0.71	10.6	978	0.98	111.8
5	F	32	88.6	164.0	1,420	0.94	11.5	1,741	0.87	109.1
7	F	33	80.9	175.0	1,490	0.86	12.6	1,608	0.86	112.3
8	F	46	56.8	163.0	1,516	0.81	24.3	1,128	1.25	105.8
10	F	50	69.0	163.0	780	0.86	12.3	1,106	0.82	85.4
16	F	28	72.0	144.0	890	1.40	18.0	2,545	1.32	126.3
22	M	41	66.0	168.0	1,180	1.00	12.0	1,676	1.21	113.7
24	F	25	65.9	180.0	2,110	0.80	20.0	1,372	1.74	113.2
25	F	23	57.0	160.0	980	0.70	9.0	911	0.92	96.6
26	M	40	64.0	179.0	1,945	1.00	16.0	1,595	0.99	108.9
27	F	42	52.3	157.0	940	0.64	18.1	1,019	1.13	124.2
28	F	36	54.5	169.0	2,120	0.70	14.0	1,336	1.71	143.3
29	M	28	68.2	173.0	1,580	0.90	14.0	1,691	1.44	125.4
30	M	22	77.3	180.0	580	1.10	11.0	1,926	0.92	106.2
31	M	24	77.3	183.0	960	0.80	13.0	2,285	1.27	173.3
32	M	28	70.5	178.0	1,090	0.90	14.0	2,071	1.70	147.0
33	M	26	54.5	168.0	520	1.00	26.0	1,321	1.19	99.2
34	M	30	75.0	180.0	1,180	1.00	14.0	2,077	1.25	129.3
35	M	31	72.7	180.0	2,260	1.00	16.0	1,718	1.59	106.9
36	M	26	88.6	188.0	1,360	1.30	13.0	2,203	1.11	94.3
37	M	28	80.8	155.0	867	0.90	12.6	1,604	0.86	112.7
Mean		31.4	68.6	169.6	1,322	0.92	14.9	1,615	1.20	116.4
SD		8.2	11.7	11.4	524	0.21	4.3	458	0.30	19.9
P[b]		NS	NS	NS	NS	NS	<0.0006	<0.0002		<0.0001

[a] P(Cr), plasma creatinine concentration; P(BUN), plasma BUN concentration; Cr Excr, urinary creatinine excretion; Pr Intake, protein intake; Cr Cl, creatinine clearance.
[b] Low versus high by unpaired *t* test. NS, not significant.

clearance. If 90 mL /min/1.73 m^2 is considered the lower limit of normal for creatinine clearance, at least 13 (35%) of the subjects studied would have been assumed to have renal impairment. Gender does not appear to be important in the relationship between urea nitrogen excretion and creatinine clearance (Table 1; Figure 1). The mean protein intake and creatinine clearance in females and males averaged 0.90 and 1.00 g/kg/day and 95.6 and 100.3 mL/min/1.73 m^2, respectively. These findings suggest

TABLE 2. Elderly healthy subjects[a]

Patient No.	Sex	Age (yr)	Weight (kg)	Height (cm)	Volume (mL)	P(Cr) (mg/dL)	P(BUN)	Cr Excr (mg/day)	Pr Intake (g/kg/day)	Cr Cl (mL/min/1.73 m^2)	Albuminuria (mg/day)
38	F	88	56.0	165	1,466	0.60	19.0	562	0.83	73.6	0[b]
39	F	64	50.0	165	1,260	1.60	14.0	1,068	0.59	53.8	0[b]
40	F	60	41.0	150	550	0.50	9.0	282	0.44	50.8	0[b]
41	M	83	80.0	176	704	0.80	14.0	785	0.48	56.5	0[b]
42	F	83	54.0	155	1,400	0.70	12.0	730	0.73	79.1	0[b]
43	F	82	42.0	157	594	1.20	27.0	359	0.51	26.5	0[b]
44	F	55	55.0	155	1,620	0.70	14.0	598	0.81	69.3	0[b]
45	F	65	82.0	155	1,125	1.20	22.0	1,181	0.79	60.6	0[b]
46	F	67	56.0	156	1,014	0.60	19.0	785	1.33	108.2	0[b]
47	F	77	63.6	156	1,015	0.90	20.0	518	0.70	41.1	0[b]
48	F	82	51.3	155	1,416	1.00	16.0	637	0.83	51.7	42.0
49	F	82	68.0	157	1,202	0.90	20.0	562	0.90	46.7	33.0
50	F	60	52.0	159	2,155	0.80	17.0	1,142	1.14	86.6	22.0
51	F	67	58.0	160	1,414	1.10	23.0	754	1.43	74.0	42.0
52	F	68	88.6	155	644	0.70	8.0	650	0.85	43.9	13.0
53	F	66	53.6	157	1,574	0.70	20.0	869	0.60	74.6	0[b]
54	F	73	44.5	152	2,074	0.70	18.0	834	0.94	92.4	83.0
55	F	81	83.2	191	1,007	1.30	19.0	1,591	1.13	83.9	2.6
56	M	63	63.0	165	3,890	0.80	15.0	1,284	0.92	69.7	78.0
57	F	70	84.0	175	2,962	1.10	27.0	1,718	1.18	111.4	51.7
58	F	68	52.0	165	3,936	0.70	15.0	1,181	1.20	92.0	39.0
59	F	66	67.3	157	858	0.80	15.0	755	1.68	128.3	19.0
60	F	63	59.1	163	2,220	0.90	12.0	1,066	0.78	65.5	22.0
61	F	74	50.9	163	1,782	0.70	17.0	1,034	0.87	86.7	56.0
62	F	62	82.0	173	1,854	1.00	12.0	1,920	1.58	116.7	38.2
63	M	72	75.0	163	1,750	0.90	14.0	893	1.14	114.7	75.6
64	F	57	68.0	154	550	0.60	16.0	809	1.02	93.0	11.0
65	F	69	61.4	165	2,247	0.90	14.0	1,124	0.98	88.2	45.0
Mean		70	62.2	161	1,557	0.87	16.8	910	0.94	76.4	39.59
SD		8.8	13.4	9	892	0.24	4.7	393	0.31	25.0	23.84

[a] Abbreviations are as defined in footnote to Table 1.
[b] Dipstick determination.

that the gender differences in creatinine clearance noted previously (16) are determined by differences in intake rather than in the gender *per se*. Table 1 depicts the mean values of these 37 subjects divided in two groups according to their diet: low protein intake (<0.8 g/kg/day), 16 subjects (7 males, 9 females); and high protein intake (>0.8 g/kg/day), 21 subjects (11 males, 10 females). Between groups, no significant differences were demonstrated in age, body weight, height, plasma creatinine, and urinary volume. Creatinine clearance averaged 73.6 ± 23.6 and 116.4 ± 19.9 mL/min/1.73 m^2 in low- and high-protein-intake groups ($P < 0.0001$), respectively. Significant differences in plasma urea nitrogen was demonstrated between the two groups ($P < 0.0006$). Creatinine excretion was significantly different between the groups. In the low-protein-intake group, creatinine excretion averaged 992 ± 456 mg/day or 14.5 ± 4.9 mg/kg/day, and, in the high-protein-intake group averaged 1,615 ± 458 mg/day or 23.5 ± 4.7 mg/kg/day ($P < 0.0002$). The decreased creatinine excretion in the low-protein-intake group in the presence of a reduced creatinine clearance accounts for comparable plasma creatinine values observed in both groups.

The creatinine clearance in elderly healthy subjects (Table 2) was below 120 mL/min/1.73 m^2 in 27 of the 28 subjects. Protein intake in these subjects averaged 0.94 ± 0.31 g/kg/day. The relationship between urea nitrogen excretion and creatinine clearance in this group is depicted in Figure 2. The slope of this line was the same as the one described in healthy young subjects (Figure 1). The y intercept (creatinine clearance) was significantly different. In the normal younger subjects, $y = 43$ mL/min/1.73 m^2, and, in the elderly subjects, $y = 31$ mL/min/1.73 m^2. It is possible to speculate that the difference between these two values represents aging of the kidney in the absence of hypertension and/or renal disease.

In subjects with renal disease (Figure 3), a significant relationship between urea nitrogen excretion and creatinine clearance was also observed ($r = 0.5$; $P < 0.007$). A r value of 0.5, albeit significant, was

TABLE 3. Renal disease patients[a]

Patient No.	Sex	Age (yr)	Weight (kg)	Height (cm)	Volume (mL)	P(Cr) (mg/dL)	P(BUN) (mg/dL)	Cr Excr (mg/day)	Pr Intake (g/kg/day)	Cr Cl (mL/min/1.73 m²)	Iothalamate Cl (mL/min/1.73 m²)
66	F	58	114.1	176	1,980	1.70	30.0	1,426	0.66	44.0	46.0
67	F	45	95.5	172	2,400	1.50	18.0	2,016	0.76	76.9	51.0
68	F	25	60.6	171	2,690	2.60	29.0	1,049	0.86	28.7	21.0
69	F	45	102.6	193	3,480	5.30	74.0	2,227	1.01	25.0	14.0
70	F	39	67.8	179	2,750	2.20	24.0	1,210	0.80	35.7	32.0
71	M	39	80.6	182	2,780	1.40	29.0	1,807	1.29	76.8	62.0
72	F	65	81.0	155	1,880	1.60	27.0	771	0.70	32.0	48.0
73	M	66	78.3	164	1,370	1.30	29.0	1,151	0.69	49.9	52.0
74	F	39	105.7	170	2,190	1.50	24.0	1,511	0.83	56.0	52.0
75	M	41	112.7	186	2,590	1.60	23.0	1,813	0.72	57.4	57.4
76	M	64	107.5	172	3,700	2.80	31.0	1,887	0.86	37.0	37.0
77	F	27	54.8	168	1,960	1.70	30.0	980	1.08	43.0	43.0
78	M	29	91.2	187	1,600	2.00	27.0	1,760	0.86	48.7	48.7
79	M	33	72.9	175	2,050	5.10	79.0	1,640	0.98	20.6	20.6
80	M	52	83.5	165	3,270	1.90	37.0	1,635	1.08	54.1	54.1
81	F	53	67.0	155	3,150	4.00	45.0	1,386	0.94	25.1	25.1
82	M	38	81.6	170	3,100	1.50	19.0	1,799	0.75	74.6	74.6
83	F	51	57.8	167	1,580	1.50	40.0	743	1.26	36.8	36.8
84	M	46	101.9	185	1,460	5.60	42.0	1,694	0.54	16.2	16.2
85	F	23	60.4	161	3,555	3.90	54.0	1,315	1.17	24.9	24.9
86	M	54	71.2	175	2,540	2.00	25.0	2,667	1.55	86.1	86.1
87	M	35	78.9	182	2,620	3.00	38.0	1,860	1.11	37.2	37.2
88	M	43	58.4	154	3,120	4.20	35.0	905	0.81	16.5	16.5
89	M	49	88.4	180	3,240	1.40	15.0	2,203	1.04	82.8	82.8
90	M	62	110.1	186	2,790	3.90	62.0	1,339	0.78	17.6	17.6
91	M	39	97.0	179	2,880	2.00	32.0	2,045	1.12	56.9	56.9
92	F	40	90.8	152	1,910	3.40	53.0	1,012	0.72	19.2	19.2
93	M	36	77.0	175	1,710	2.60	38.0	1,573	0.89	37.9	37.9
94	F	54	71.8	169	2,930	2.50	35.0	1,113	0.98	29.9	29.9
95	F	51	66.3	168	2,170	5.20	65.0	1,237	0.87	16.3	16.3
96	M	22	50.5	157	1,970	3.60	51.0	1,478	1.41	33.1	33.1
97	F	52	51.0	160	1,850	1.60	27.0	851	1.27	42.3	42.3
98	M	65	75.8	169	3,370	4.00	64.0	1,584	1.20	25.4	25.4
Mean		45	80.75	171	2,504	2.73	37.9	1,506	0.96	41.4	39.9
SD		12	18.41	11	657	1.31	16.1	453	0.23	20.1	19.0

[a] Abbreviations are as defined in footnote to Table 1. Iothalamate Cl, iothalamate clearance.

less than the correlation coefficient observed in the young ($r = 0.8$) and elderly ($r = 0.8$) healthy subjects. This suggests that, in the presence of renal disease, factors other than diet are also important in the relationship between creatinine clearance and urea nitrogen excretion. The relationship between creatinine and iothalamate clearances in these subjects is shown in Table 3 ($r = 0.95$; $P < 0.0001$).

Figure 4 depicts the relationship between creatinine excretion (milligrams per kilogram per day) and protein intake (grams per kilogram per day) in all 98 subjects studied. No difference was demonstrated between young healthy subjects and patients with renal disease. The elderly subjects, on the other hand, had lower levels of creatinine excretion per level of protein intake, a finding compatible with a diminished muscle mass observed in this group. When subjects ingested a high protein intake, the wide range of creatinine excretion may be due to the effects of muscle mass, exogenous chromogen, or changes in creatinine secretion.

The results of the urea loading experiments are shown in Table 4. The mean urea nitrogen excretion in the 18 subjects at baseline average 9.8 ± 4.0 g/day. After 5 g of urea (2.5 g of urea nitrogen), urea nitrogen excretion averaged 11.8 ± 4.0 g/day. Creatinine excretion averaged 1,518 ± 499 mg/day at baseline and 1,573 ± 564 mg/day after urea supplementation ($P < 0.0001$). Plasma creatinine did not change. These changes are all compatible with a primary increase in GFR induced by urea supplementation. Seven of the 18 subjects had a decrease in urea nitrogen excretion, presumably because they altered their diet. Of the 11 subjects that had an increase in urea nitrogen excretion, the increment averaged 3.9 g/day. The relationship between the

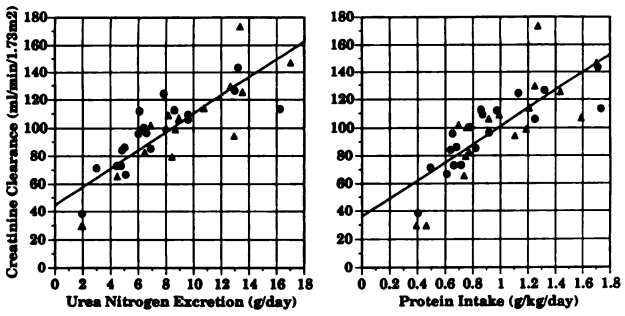

Figure 1. Creatinine clearance versus urea nitrogen excretion and protein intake in young healthy subjects. Closed triangles represent males, and closed circles represent females.

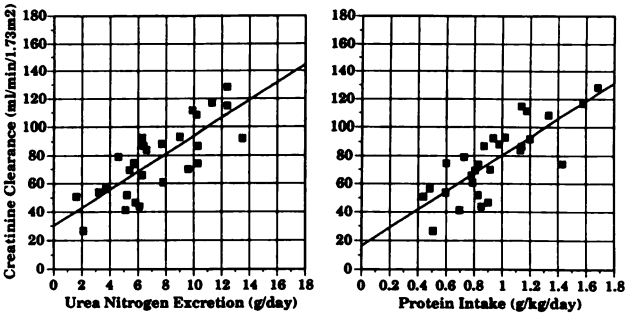

Figure 2. Creatinine clearance versus urea nitrogen excretion and protein intake in elderly healthy subjects. Closed squares represent all elderly subjects of both sexes over the age of 50 yr.

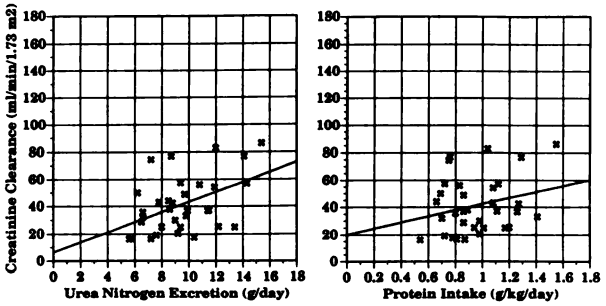

Figure 3. Creatinine clearance versus urea nitrogen excretion and protein intake in subjects with renal disease. Clover leaves represent patients with renal disease; $r = 0.5$.

changes in urea nitrogen excretion versus the changes in creatinine clearance was also significant (Figure 5; $r = 0.7$; $P < 0.002$).

The relationship between simultaneous creatinine and inulin clearances is depicted in Figures 6 and 7. Each subject was studied under two different urea nitrogen loads, before and after an acute oral protein load. Renal function measured by creatinine and inulin clearances in five healthy subjects is shown in Figure 6, whereas renal function in seven subjects with renal disease is shown in Figure 7. These results

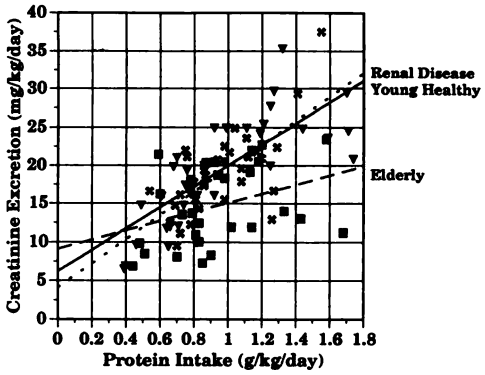

Figure 4. Creatinine excretion and protein intake in all subjects. Closed triangles and the solid line represent young healthy subjects, squares and the dashed line represent elderly healthy subjects, and clover leaves and the dotted line represent subjects with renal disease.

indicate that, for clinical purposes and under the present experimental conditions, the creatinine clearance is an adequate assessment of GFR.

Figure 8 depicts the relationship between creatinine clearance (milliliters per minute) and urea nitrogen excretion (milligrams per minute) during 30-min periods before and after an acute oral protein load ($r = 0.5$; $P < 0.02$).

DISCUSSION

These studies demonstrate that creatinine clearance in healthy subjects is influenced by urea nitrogen excretion. Urea nitrogen generation is related to protein intake and, in steady state, is equivalent to urea nitrogen excretion. In normal subjects, creatinine clearance is dependent on diet. Creatinine clearance is highly variable from individual to individual or even in one subject when dietary habits are not constant. The effect of urea excretion on creatinine clearance is quantitatively important. In Figure 1, a linear curve was used to illustrate the correlation between creatinine clearance and urea nitrogen excretion or protein intake. A closer examination of the points reveal that creatinine clearance does not continue to increase with increasing protein intake but tends to level off. Because none of the subjects' estimated protein intake was greater than 1.7 gm/kg, it is difficult to know exactly where this plateau will occur. As shown in Figure 1, when urea nitrogen excretion is changed by 5 g/day, creatinine clearance increased by 30 mL/min/1.73 m^2. In this context, it is apparent that urea nitrogen excretion is a major determinant of creatinine clearance in normal humans. The urea loading experiments (Figure 5; Table 4) further support the view that urea nitrogen excretion is an important determinant of creatinine clearance in humans. In these experiments, an increase in 5 g/day in urea nitrogen excretion resulted in a

TABLE 4. Urea supplementation in healthy subjects[a]

Patient No.	Control					Urea Supplementation				
	P(Cr) (mg/dL)	P(BUN) (mg/dL)	UN Excretion	Cr Excretion (mg/day)	Cr Cl (mL/min/1.73 m²)	P(Cr) (mg/dL)	P(BUN) (mg/dL)	UN Excretion (mg/day)	Cr Excretion (mg/day)	Cr Cl (mL/min/1.73 m²)
1	0.93	13	7,990	1,718	100.0	1.10	13	8,888	1,868	92.0
2	0.64	17	4,850	798	84.0	0.60	14	8,936	901	101.0
5	0.94	12	9,599	1,741	109.0	0.82	4	8,461	1,627	117.0
9	0.77	9	6,400	1,100	100.0	0.69	8	11,482	1,350	137.0
10	0.86	12	6,911	1,106	85.0	0.70	9	11,049	1,195	112.0
20	0.90	8	2,996	924	71.0	0.80	8	5,105	828	72.0
21	0.70	12	4,794	690	73.0	0.60	8	6,095	621	77.0
27	0.64	18	7,837	1,019	124.0	0.73	18	7,282	856	91.0
28	0.70	14	13,229	1,336	143.0	0.80	16	13,207	1,041	97.0
29	0.90	14	13,541	1,691	125.0	0.90	19	21,583	2,230	165.0
30	1.10	11	8,932	1,926	106.0	1.00	12	12,827	2,207	134.0
31	0.80	13	13,354	2,285	173.0	0.80	15	12,171	1,776	135.0
32	0.90	14	17,015	2,071	147.0	1.00	15	15,936	1,884	121.0
33	1.00	26	8,668	1,321	99.0	1.10	20	11,873	1,438	98.0
34	1.00	14	12,673	2,077	129.0	1.00	18	16,629	2,295	143.0
35	1.00	16	16,227	1,718	107.0	1.10	25	14,918	1,880	107.0
36	1.00	13	12,934	2,203	94.0	1.30	12	12,754	2,397	103.0
37	0.90	13	8,612	1,607	113.0	0.79	15	12,914	1,923	148.0
Mean	0.87	13	9,809	1,518	110.1	0.88	14	11,784	1,573	113.9
SD	0.14	5	4,031	499	26.6	0.19	5	4,040	564	25.5

[a] Abbreviations are as defined in footnote to Table 1. UN, urea nitrogen.

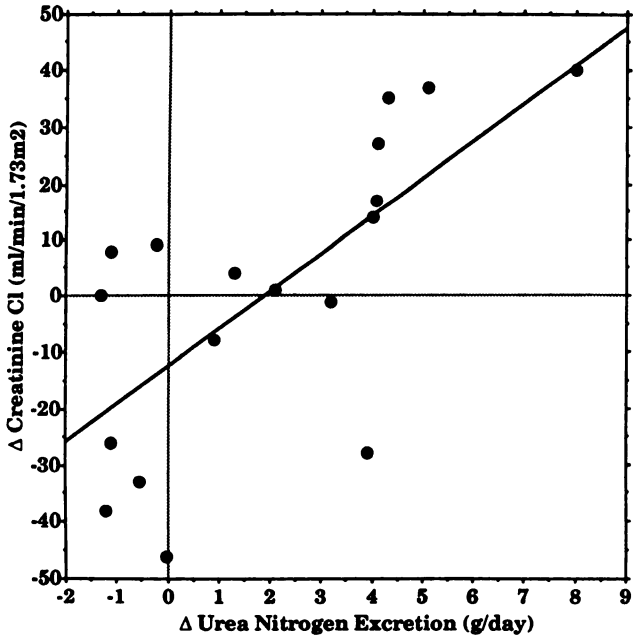

Figure 5. Changes in urea nitrogen excretion and changes in creatinine clearance (Cl) with oral urea supplementation to diet.

concomitant increase in creatinine clearance by 30 mL/min/1.73 m². During acute studies, such as during an acute oral protein load (Figure 8), an increase in 5 g of urea nitrogen corresponds to an increase in creatinine clearance by 11 mL/min. The recognition of this relationship between urea nitrogen excretion and creatinine clearance would suggest that the vasodilatory effect of protein on the kidney is not mediated by a specific amino acid but may be dependent on the metabolism of protein into urea. This finding may explain the clinical observation of elevated creatinine clearance and GFR in patients with high urea nitrogen excretion, such as patients with extensive body burns (29).

It is well known that creatinine clearance is not a direct measurement of GFR. Inulin or isotopic clearances are accepted methods by which to assess the volume of ultrafiltrate at the glomerulus. Nevertheless, numerous studies have demonstrated that there is a excellent correlation between creatinine and inulin clearances when GFR is above 40 and below 120 mL/min/1.73 m² (30–33). Our own observations (Figures 6 and 7; Table 3) confirm that there is a good correlation between creatinine and inulin, and iothalamate clearances under different dietary conditions.

The observation of a wide variability in creatinine clearances between 40 and 120 mL/min/1.73 m² in healthy subjects reported here (Figure 1) suggests that GFR in normal humans is not a fixed function. The view of a variable GFR is quite contrary to the traditional concept of GFR. Pitts defined GFR as a fixed function: "the rate of glomerular filtration in normal men averages 125 ml/min and in normal women 110 ml/min, both expressed per 1.73 m² surface area. In normal man, filtration rate is re-

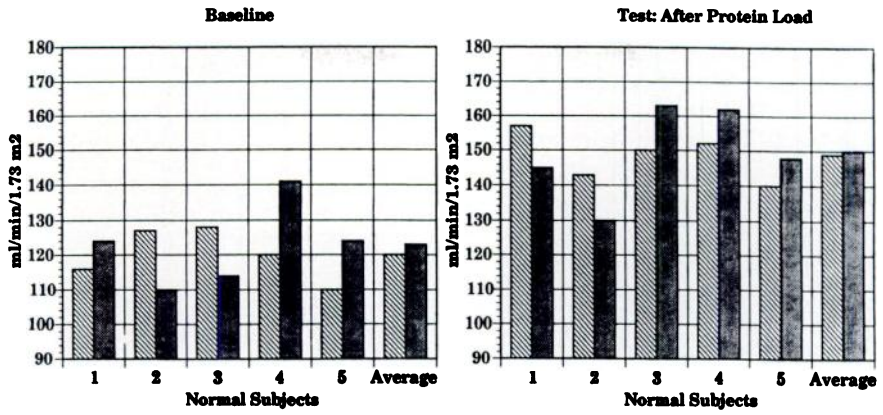

Figure 6. Simultaneous inulin and creatinine clearances in five healthy subjects before and after an acute oral protein load. The units are milliliters per minute per 1.73 square meters for creatinine clearance. Wide hatched bars represent creatinine clearance; narrow hatched bars represent inulin clearance.

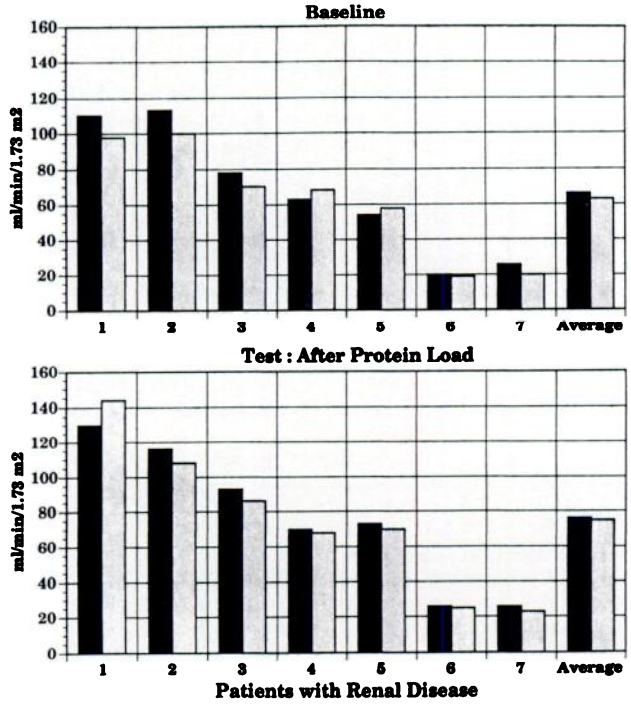

Figure 7. Simultaneous inulin and creatinine clearances in seven subjects with renal disease before and after an acute oral protein load. The units are milliliters per minute per 1.73 square meters for creatinine clearance. Solid bars represent creatinine clearance; dotted bars represent inulin clearance.

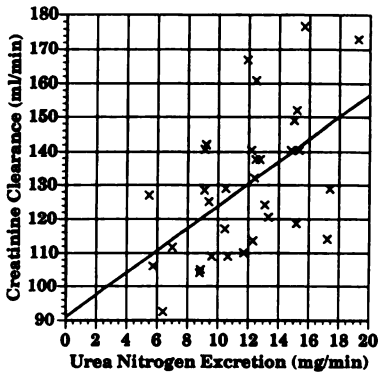

Figure 8. Creatinine clearance and urea nitrogen excretion during short timed intervals.

markably stable from day to day over a period of years. In patients with renal disease, filtration rate is reduced" (34). This view was based on a series of physiological experiments mostly carried out for a short period of time under controlled conditions. This traditional and "physiological" view of GFR as a fixed function was challenged in 1949 by Addis, who observed that urea and creatinine clearances were influenced by protein intake (35). We and others have been able to demonstrate that normal subjects eating a low-protein diet have creatinine clearances greatly below what is considered "normal" (5–7,9). An alternative explanation for the observed changes in creatinine clearance with diet could be because of changes in creatinine secretion induced by protein intake. It has been shown that at a high-protein diet (1.6 g/kg) creatinine clearance was significantly different from inulin clearance (36). In this same study, subjects who ingested a low-protein diet (0.5 g/kg) showed no significant differences between creatinine and inulin clearances. The majority of our patients ingested less than 1.6 g/kg of protein. Thus, the observed creatinine clearance is a reflection of glomerular filtration rather than changes in creatinine secretion. The studies presented here confirm the view that creatinine clearance is highly variable in healthy subjects. It goes further to establish a direct and quantitative relationship between dietary protein intake and creatinine clearance.

The studies of the elderly subjects illustrate the importance of considering diet when assessing kidney function. It has been accepted that aging is as-

sociated with a loss of kidney function (37–39). Nevertheless, an important longitudinal study (37) has demonstrated that aging is not necessarily accompanied by a loss in GFR. In fact, in that study, 35% of the elderly subjects had a stable creatinine clearance over 20 yr of observation. In our elderly subjects without evidence of renal disease, those who had protein intake of 1 g/kg/day or more had creatinine clearances in the high 90s to above 100, whereas those who ate less had a lower creatinine clearance (Figure 2).

The strength of the relationship between urea nitrogen excretion and creatinine clearance was also demonstrated in patients with renal disease (Figure 3). In these patients, there was a significant relationship between urea nitrogen excretion and creatinine or iothalamate clearances (Figure 3; Table 3). These data suggest that, as renal disease progresses, patients tend to eat less, probably an indication of the systemic nature of renal insufficiency.

Our studies also suggest a significant relationship between diet and creatinine excretion. It has been known for some time that daily creatinine excretion is influenced by diet (40–44). The acute effect of exogenous intake of creatinine has been previously shown (45). The studies presented here demonstrate that the daily amount of creatinine excreted in the urine is also influenced by protein intake and is not solely dependent on muscle mass or body weight. Therefore, 24-h urine collections need not be judged incomplete because of low values of creatinine excretion (Figure 4). Different protein intakes result in significant differences in creatinine clearance, whereas plasma creatinine concentration does not change. The alteration of creatinine generation by diet casts a doubt on the validity of the use of plasma creatinine concentration or its reciprocal value (1/Pcr) in the assessment of progression of renal disease when changes in diet are prescribed.

Protein intake is an important determinant of creatinine clearance in normal humans. Creatinine clearance is neither a fixed function nor a reliable index of renal parenchymal damage. When creatinine clearance is corrected for urea nitrogen excretion, it becomes a more sensitive parameter of renal function.

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