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Long-Term Follow-Up of the Tubular Secretion of Creatinine in Renal Graft Recipients

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Summary

The differences in glomerular filtration rate (GFR) based on creatinine clearance (C_{cr}) or obtained by the more exact methods are caused mainly by tubular creatinine secretion. In this study, we monitored creatinine clearance (C_{cr}), GFR on the basis of polyfructosan renal clearance (C_{PF}) and parameters characterizing tubular creatinine secretion (C_{cr}/C_{PF}, $C_{cr} - C_{PF}$, $T_{cr}/C_{PF} \times 100$) in 12 individuals with renal grafts (Group A), 12 kidney graft donors for related transplantation (Group B), and in 27 individuals undergoing nephrectomy for a pathological process in one kidney (Group C). In the monitored groups, C_{PF} and C_{cr} values were within the limits consistent with the normal function of a single kidney in a healthy individual. The values characterizing tubular creatinine secretion in Group A did not differ significantly from those obtained in Groups B and C. However, the parameters showed a wide range in all groups. In seven individuals with a renal graft, all the above functional parameters were monitored at three-month intervals for a period of 24 months. Significant differences in the time courses of C_{cr} and C_{PF} due to marked intra-individual fluctuations were found in tubular creatinine secretion. The findings suggest that the rate of tubular creatinine secretion in the renal graft does not differ significantly from that in individuals with a single native (normally functioning) kidney. However, there are large inter-individual differences. The large intra-individual fluctuations in tubular creatinine secretion in the kidney graft result in significant differences in the time courses of C_{cr} and C_{PF} and a possibility of erroneous evaluation of graft function if based exclusively on C_{cr}.

Key words
Tubular creatinine secretion – Renal transplant – Glomerular filtration rate

Introduction

It has been known for some time that, creatinine in man is eliminated primarily by glomerular filtration; however, a part of this is also excreted by tubular secretion (Shannon 1935). The ratio between renal creatinine clearance (C_{cr}) and the glomerular filtration rate (GFR) in individuals with normal renal function is in the range of 1.10–1.20; however, it is 1.50 to 2.00 in individuals with a decreased GFR (Shemesh *et al.* 1985). These findings are important in terms of the functional examination of kidneys since evaluation of the GFR based on C_{cr} becomes less accurate as renal function declines.

In everyday practice, the GFR of renal graft recipients is evaluated on the basis of serum creatinine and C_{cr}, although it is a well-known fact that, even in these individuals, C_{cr} also exceeds GFR to a varying extent (Kasiske 1989, Mobb *et al.* 1990, Ross *et al.* 1987, Slomowitz *et al.* 1990). The long-term follow-up of GFR based on C_{cr} determination assumes that, although C_{cr} is not an exact indicator of GFR,

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the changes in C_{cr} would occur more or less in parallel with changes in GFR. This assumption, however, is not accepted by some clinicians when more accurate assessment of GFR changes of the renal graft is required to evaluate the effect of novel immunosuppressive agents (Nankivell *et al.* 1996).

When evaluating the relationship between C_{cr} and GFR in individuals with a renal graft, it should also be taken into account that some drugs such as trimethoprim (Berg *et al.* 1989) or cimetidine (Pachon *et al.* 1989) markedly decrease tubular creatinine secretion. From the practical point of view, it is important to note that cyclosporin A does not affect the tubular transport of creatinine (Schück *et al.* 1992, Hilbrands *et al.* 1996).

In this paper, we sought to determine whether the rate of tubular creatinine secretion (in individuals with a renal graft whose GFR corresponds to that of the intact kidney and who are treated by a standard combination of immunosuppressive agents) is quantitatively the same as in individuals with one normally functioning kidney (who have had unilateral nephrectomy performed for related donation or a unilateral pathological process). We also tried to get an answer if, and to what extent, tubular secretion varies in one and the same individual with a renal graft over long-term (two-year) follow-up.

The aim of this research is to identify appropriate procedures in examining renal graft function.

Material and Methods

Three groups of individuals with a single kidney were examined in our study. Group A comprised 12 individuals with a renal graft obtained from a cadaveric donor. In one of these individuals, the examination was performed after a second and, in another one, after a third transplantation. In the other subjects, the examination was carried out after their first kidney transplantation. The interval after the transplantation (in the case of a repeated procedure, after the last transplantation) ranged from one to 64 months (mean 20.2 months). In seven patients, graft function was followed at three-month intervals, for a period of 24 months. All transplantations were performed at the Institute for Clinical and Experimental Medicine in Prague. The group included 8 female and 4 male patients aged 35 to 71 years (mean age 51 years). At the time of the examination, there were no sudden changes in graft function. Immunosuppressive therapy comprised the administration of cyclosporin A (Consupren, Galena, Czech Republic) in a dose maintaining blood levels in the range of 300–500 ng/ml. Blood cyclosporin A levels were measured using RIA with a non-specific monoclonal antibody. Furthermore, these patients were also given prednisone in a dose of 10–15 mg/kg/day and azathioprine in a dose of 1–1.5 mg/kg/day. Whenever needed, antihypertensives (ACE inhibitors, calcium channel blockers, beta-blockers) were provided. At the time of examination, none of the subjects were treated with cimetidine or trimethoprim.

Group B included 12 individuals who were related donors of kidneys for transplantation. Before elective nephrectomy, these individuals were thoroughly examined by an internist and a nephrologist. The group was made up of 7 women and 5 men aged 49–72 years (mean age 57.5 years). The examination was carried out 0.17–17 years (mean 8.2 years) after nephrectomy.

A third group (Group C) consisted of 27 individuals after unilateral nephrectomy for a pathological process in one kidney. This group included 11 men and 16 women aged 14–62 years (mean age 41.5 years). The time after nephrectomy was 1–34 years (mean 11.5 years). The indications for nephrectomy were as follows: renal artery graft or arterio-venous bypass occlusion were involved in 14 cases; pyelonephritis or pyonephros were present in 9 cases, severe post-traumatic changes were diagnosed in three cases, and a tumour in one case. Twelve individuals in this group were being treated with antihypertensive drugs and their diet was not modified in any way; there were no restrictions on protein and liquid intake.

Renal functions were examined in a separate quiet room in the morning. A light breakfast (a cup of weak tea, one roll or a slice of bread) was served before the examination. Half an hour before the examination 10 ml/kg of water were provided. A loading dose of polyfructosan S (Inutest, Levosan) was injected into a peripheral vein (50 mg/kg); immediately after the injection, a cannula was connected to a microinfusion pump operating at a rate of 0.36 ml/min which maintained the plasma levels of polyfructosan within the range of 200–300 mg/l. After an equilibration phase (30–45 min), the examined subject urinated spontaneously and a collecting urine period was started which lasted 60–90 min and was terminated by spontaneous micturition. None of the examined individuals showed any signs of impaired bladder emptying. Diuresis amounted to a minimum of 3 ml/min.

During the urine collecting period, blood samples were withdrawn from a peripheral vein artery (at the beginning, in the middle, and before the end of the collecting period); plasma and urine samples were used for determining the concentrations of polyfructosan (White and Samson 1954). The variation coefficient of this method is 2.1 %. Creatinine concentrations were determined using Hitachi 704 and 717 autoanalyzers. The variation coefficient of this method is 2.2 %.

The values of renal clearance were calculated by standard methods. GFR was assessed on the basis of renal PF clearance (C_{PF}). The tubular secretion of creatinine was assessed using the C_{cr}/C_{PF} ratio, tubular creatinine clearance as the difference $C_{cr} - C_{PF}$, and the calculated effective creatinine secretion (T_{cr}) using the equation:

$$T_{cr} = U_{cr}V - C_{PF} \times S_{cr}$$

where $U_{Cr}V$ is the urinary excretion of creatinine and S_{cr} denotes serum creatinine level. This value was related to 100 ml of C_{PF}.

Statistical analysis was performed using the unpaired and paired t-tests and linear regression analysis.

Table 1. Serum creatinine levels (S_{cr}), renal clearance of creatinine (C_{cr}), polyfructosan clearance (C_{PF}), ratio and difference of these clearance values ($C_{cr} - C_{PF}$) and the calculated tubular secretion of creatinine (T_{cr}) in individuals with kidney transplant (Group A), in kidney donors for related transplantation (Group B), and in individuals after nephrectomy for a pathological process in one kidney (Group C).

Group	A	B	C
S_{cr} (μmol/l)	113.2±8.7 (95.0 - 124.0)	105.0±19.7 (65.0 - 130.0)	82.3±20.8 (61.0 - 115.0)
C_{cr} (ml/min/1.73 m^2)	88.6±13.8 (70.2 - 127.0)	89.0±21.4 (57.6 - 120.0)	88.4±24.3 (61.0 - 123.6)
C_{PF} (ml/min/1.73 m^2)	70.6±6.2 (61.0 - 79.4)	71.0±10.3 (61.2 - 93.0)	75.4±12.7 (60.0 - 106.8)
C_{cr}/C_{PF}	1.25±0.15 (0.95 - 1.68)	1.26±0.27 (0.84 - 1.73)	1.17±0.26 (0.95 - 1.46)
$C_{cr} - C_{PF}$ (ml/min/1.73 m^2)	18.0±11.7 (−3.0 - 51.6)	18.0±19.6 (−12.0 - 49.8)	13.0±19.6 (−64.6 - 37.9)
T_{cr}/C_{PF} x 100 (μmol/min/100C_{PF})	27.9±17.0 (−6.1 - 68.0)	28.1±33.1 (14.5 - 94.9)	18.6±13.1 (−9.2 - 42.5)

Data are means ± S.D. Range of values is given in parentheses.

Results

The mean values ± S.D. and the range of the monitored parameters of glomerular function and tubular secretion of creatinine in individuals with a renal graft (A), kidney donors (B), and in individuals after unilateral nephrectomy for a pathological process (C) are summarized in Table 1. It is evident that the mean values of C_{PF} of the monitored groups did not differ and are consistent with the function of a single kidney with a normal GFR. The values of C_{cr} were significantly higher than C_{PF} ($p<0.001$) in all groups and did not differ from each other. The mean serum level of creatinine (S_{cr}) in Group A was significantly higher that of Group C ($p<0.01$). The S_{cr} of Group B was also significantly higher compared with Group C ($p<0.01$). The mean values of the parameters characterizing tubular creatinine secretion (C_{cr}/C_{PF}, $C_{cr} - C_{PF}$ and T_{cr}/C_{PF} x 100) of the monitored groups did not differ from each other. The values characterizing tubular secretion clearly indicate a broad range of values. The ranges of C_{cr}/C_{PF} were 0.95−1.68 in Group A, 0.84−1.73 in Group B and 0.95−1.46 in Group C. A similarly wide range was found in all groups in terms of tubular creatinine clearance and calculated tubular secretion. The ranges of the monitored parameters made it clear that, in some individuals, tubular creatinine secretion was not expressed since the minimal values for C_{cr}/C_{PF} were below 1.0, the values of tubular creatinine clearance and calculated tubular secretion were negative.

Table 2. The same parameters as indicated in Table 1 which were monitored in individuals with a renal graft at three-month intervals for 2 years.

Subject	Sex	Age (years)	S_{cr} (μmol/l)	C_{cr} (ml/min/1.73 m^2)	C_{PF} (ml/min/1.73 m^2)	C_{cr}/C_{PF}	$C_{cr}-C_{PF}$ (ml/min/1.73 m^2)	T_{cr}/C_{PF} x 100 (μmol/min/100C_{PF})
P.J.	M	62	102.7±5.3 (95.0 - 112.0)	98.8±15.1 (76.9 - 127.0)	73.4±14.1 (50.5 - 94.3)	1.40±0.40 (1.02 - 2.06)	25.3±21.8 (1.7 - 55.1)	40.7±42.8 (2.1 - 116.6)
P.O	M	71	119.0±8.3 (103.0 - 130.0)	83.9±13.1 (70.0 - 104.1)	65.4±98 (45.0 - 78.6)	1.28±0.11 (1.14 - 1.53)	18.4±6.2 (8.8 - 25.5)	33.5±13.9 (16.5 - 66.7)
P.G.	M	32	115.9±4.9 (110.0 - 123.0)	91.9±14.3 (70.2 - 120.4)	75.2±11.6 (61.0 - 98.3)	1.23±0.18 (0.87 - 1.41)	16.7±14.3 (−12.3 - 31.4)	25.8±23.6 (−16.1 - 47.9)
F.B.	F	38	172.8±22.2 (139.0 - 199.0)	62.4±13.7 (40.2 - 82.2)	36.8±78 (19.2 - 43.8)	1.71±0.29 (1.31 - 2.13)	25.6±9.6 (10.2 - 39.6)	124.5±56.0 (43.0 - 224.8)
V.V.	F	61	158.8±14.2 (143.0 - 185.0)	52.0±12.6 (30.5 - 70.8)	37.9±4.3 (31.8 - 45.3)	1.37±0.29 (0.84 - 1.80)	14.1±11.3 (−5.5 - 31.5)	59.1±46.9 (−24.8 - 118.4)
Š.E.	F	40	80.8±5.9 (74.0 - 89.0)	70.9±5.9 (59.3 - 77.7)	55.0±8.0 (43.3 - 71.1)	1.30±0.17 (1.08 - 1.66)	15.8±7.4 (5.9 - 30.9)	24.0±13.3 (6.3 - 48.8)
P.O.	M	39	172.8±22.4 (139.0 - 199.0)	62.4±13.8 (40.4 - 82.2)	41.0±8.9 (20.8 - 50.6)	1.54±0.22 (1.21 - 1.94)	21.4±7.7 (7.5 - 32.5)	93.8±40.2 (29.1 - 148.5)

Data are means ± S.D. Range of values is given in parentheses.

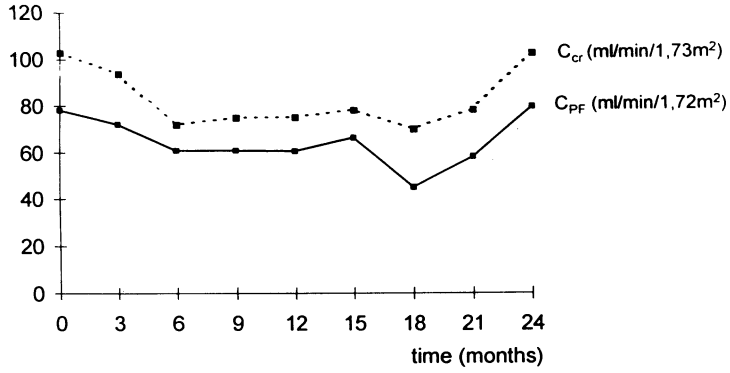

Fig. 1. *An example of a parallel course of polyfructosan and creatinine clearance during the follow-up period.*

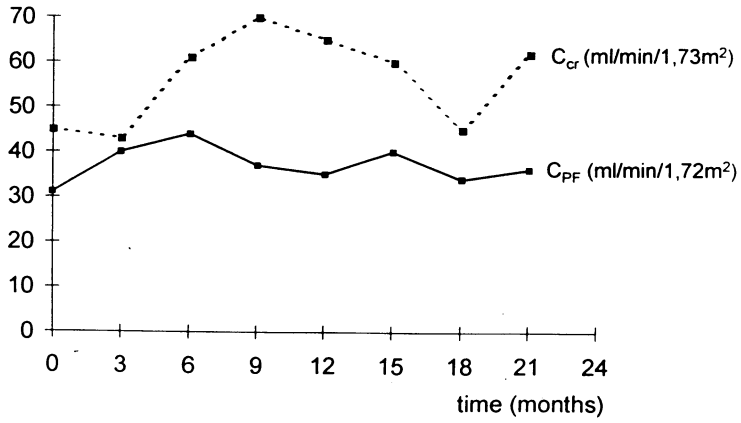

Fig. 2. *An example of discrepancy between the time courses of polyfructosan and creatinine clearance during the follow-up period.*

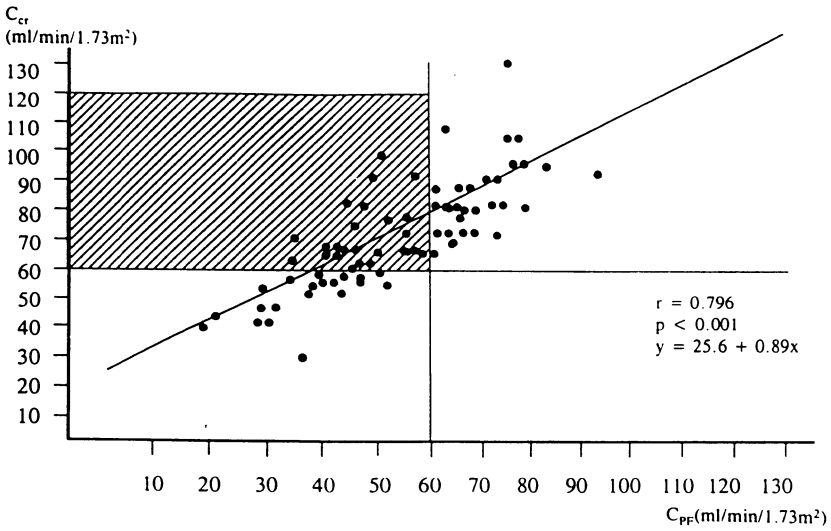

Fig. 3. *The relationship of the renal clearance of polyfructosan and creatinine clearance in individuals with a renal graft. Hatched field indicates values where C_{PF} was lower than 60 ml/min/1.73 m^2 while C_{cr} exceeded the value corresponding to the function of one normal kidney.*

Table 2 summarizes the results of repeated measurements (at three-month intervals) for a period of 24 months in seven individuals with varying renal graft function. When monitoring the time course of C_{cr} and C_{PF} over the follow-up period, we found a more or less parallel course of these parameters although their differences varied during the follow-up in some cases. An example of such a course of changes in C_{cr} and C_{PF} is shown in Figure 1. By contrast, the time course of changes in C_{cr} and C_{PF} was very different in other cases. Figure 2 gives an example whereby C_{PF} was almost stabilized during the follow-up period while C_{cr} exhibited very marked fluctuations and the changes in C_{cr} were not consistent with the time course of C_{PF}.

The discrepancy in the time courses of C_{cr} and C_{PF} in individual cases is obvious from the large range of values of C_{cr}/C_{PF}, $C_{cr} - C_{PF}$ and T_{cr}/C_{PF} x 100, as is evident from the values indicated for each monitored individual in Table 2. Although the differences in C_{cr} and C_{PF} in time in the examined cases showed a broad range, a significant correlation could still be demonstrated between the C_{cr} and C_{PF} established in these cases (Fig. 3). It is evident from Figure 3 that there is a hatched area of values whereby C_{PF} is already appreciably decreased yet the values of C_{cr} are still in the range over 60 ml/min/1.73 m^2. The slope of the regression line does not differ significantly from 1.0, but the intercept is significantly greater than zero ($p<0.001$).

Discussion

It is evident from the present results that in individuals with a renal graft whose GFR corresponds to normal values of a single kidney, the intensity of tubular creatinine secretion (assessed on the basis of C_{cr}/C_{PF}, $C_{cr} - C_{PF}$ and T_{cr}/C_{PF} x 100) is equal to that in individuals with one normally functioning kidney. This conclusion is based on the finding that, in all the groups monitored (A, B, C), the mean value of renal polyfructosan clearance did not differ significantly and, furthermore, no significant difference was observed in the monitored parameters characterizing tubular creatinine secretion. However, it is also evident that the parameters characterizing tubular creatinine secretion showed a broad range in all the groups monitored. In some individuals, the value of tubular secretion was not even demonstrable as the values of $C_{cr} - C_{PF}$ and T_{cr}/C_{PF} x 100 were negative in these cases. A possible explanation for this finding could be that tubular creatinine reabsorption was involved in these cases. The same finding was reported by other authors (Mandell *et al.* 1953, Chesley 1938, Ladd *et al.* 1956). However, this was usually under the conditions where urinary flow rate was low. In our measurements, however, this factor was apparently not involved since the measurements were performed under hydration (after a water load of 10 ml/kg). It is also evident from Table 1 that, in some cases, the parameters characterizing tubular creatinine secretion reached relatively high values. The maximum value of C_{cr}/C_{PF} was 1.46–1.73 in individual groups, tubular creatinine clearance was 37.9–51.6 ml/min/1.73 m^2 and the calculated tubular creatinine transport was 42.5–94.9 μmol/min/100 C_{PF}.

Our determinations do not make it possible to identify the cause of the large inter-individual differences in tubular creatinine secretion. The broad range of the values cannot be explained by the concomitant administration of drugs affecting tubular creatinine secretion. As the value of the C_{cr}/C_{PF} ratio does not show dependence on age (Rowe *et al.* 1976), the large inter-individual differences cannot be attributed to this factor. The male/female ratio was practically identical in groups A and B but was different in Group C (11 M, 16 F). Despite this, the groups did not differ in terms of the monitored parameters so that the extensive range of values of tubular creatinine secretion cannot be explained by sex differences. The effect of varied protein intake and body proportions was explored in more detail from the point of view of urinary elimination of creatinine (Bleiler and Schedl 1957), but not in terms of tubular creatinine secretion. In principle, however, an effect of these factors cannot be ruled out. The broad range of values characterizing tubular creatinine secretion cannot be explained by a methodological error. The differences in these values exceed errors inherent in the analytical methods employed. Moreover, when assessing tubular creatinine secretion on the basis of C_{cr}/C_{PF} and T_{cr}/C_{PF} x 100, the effect of a possible error in quantitative urine collection can be ruled out. Any mistake in urine collection would also have an effect on C_{cr} and C_{PF} values so that the effects of this error would cancel each other out.

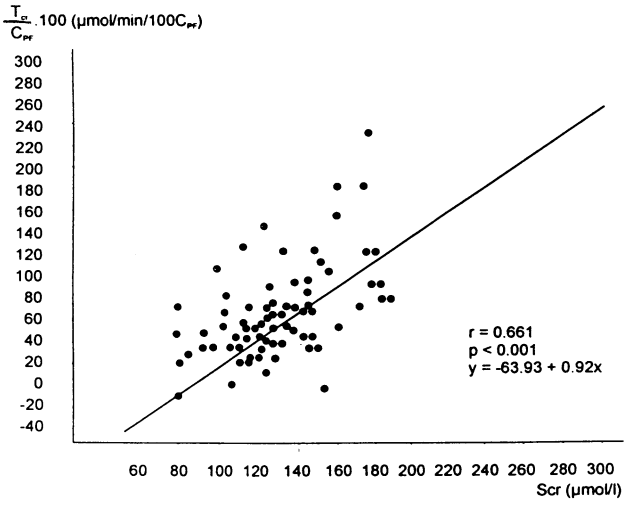

Fig. 4. *The relationship of the serum levels of creatinine (Scr) and tubular secretion of creatinine calculated per 100 ml C_{PF} in individuals with a renal graft.*

It is evident from long-term follow-ups of individuals with a renal graft that the differences between C_{cr} and C_{PF} may largely vary in individual cases. The assumption that C_{cr} varies more or less in parallel with GFR need not be true in view of the finding that the intensity of tubular creatinine secretion undergoes great fluctuations in time in one and the same individual. The broad range of values of C_{cr}/C_{PF}, $C_{cr} - C_{PF}$ and T_{cr}/C_{PF} x 100 was found in all the individuals examined. When the changes in C_{cr} and C_{PF} are maintained in parallel, one would expect the differences in $C_{cr} - C_{PF}$ (tubular creatinine clearance)

to be more or less constant during the follow-up. However, it is evident from our data that the values of tubular creatinine clearance varied significantly in individual cases. These findings suggest that the time course of changes of C_{cr} in individuals with a renal graft does not allow to extrapolate, with a reasonable degree of accuracy, the changes in GFR due to the broad intra-individual fluctuations of tubular creatinine secretion. This fact is an important finding not only from the point of view of prognosis in individual cases but, especially when assessing the effect of different therapeutic approaches (e.g. new immunosuppressive agents) on the course of chronic transplant nephropathy. It is noteworthy that, although intra-individual tubular secretion varies markedly, significant correlation could be demonstrated for the values of C_{cr} and C_{PF} established in these cases. The positive correlation is apparently due to the fact that the decrease in GFR is associated with a decrease in C_{cr} although the decrease in C_{cr} does not follow closely the decrease in GFR. The existence of a correlation between C_{cr} and C_{PF} suggests that C_{cr} is markedly affected by GFR, however, this does not allow us to conclude that C_{cr} expresses, with a reasonable degree of accuracy, the level of GFR. When analyzing this correlation, one should also take into account the finding that the regression line characterizing this relation dependence does not cross zero. The value of the intercept is 25.6. This explains why the value of the C_{cr}/C_{PF} ratio must rise in an inverse relation to the decrease in C_{PF} (mathematically, this fact can be demonstrated by dividing either side of the equation of the regression line by C_{PF}). The finding that the intensity of tubular secretion in residual nephrons of the renal graft rises could be demonstrated in our investigation by the direct dependence between S_{cr} and $T_{cr}/C_{PF} \times 100$ (Fig. 4). This dependence makes us assume that a rise in S_{cr} due to a decrease in GFR apparently serves as a stimulus for creatinine secretion. Nevertheless, this finding does not explain the large intra-individual fluctuations in tubular creatinine transport completely, since the parameters characterizing tubular creatinine secretion markedly fluctuated periodically, whereas C_{PF} was stabilized. The factors responsible for the large intra-individual fluctuations of tubular creatinine secretion in the renal graft have not as yet been identified.

Finally, we should comment on the finding that the S_{cr} in individuals with a renal graft and normal GFR of one kidney (Group A) was slightly yet significantly higher than in Group C (individuals after nephrectomy for a pathological process). Similarly, a mildly higher mean value of S_{cr} was observed in Group B (donors of kidneys for transplantation) compared to Group C. As the compared groups did not differ significantly in GFR or in the parameters characterizing tubular creatinine secretion, it can be reasonably assumed that the differences in S_{cr} were due to extrarenal factors. In Group C, women prevailed over men more than in Groups A and B. As a result, one cannot rule out the possibility that the relatively low values of S_{cr} in Group C were affected by sexual differences. However, several other factors may explain this finding which had not been assessed in our study. These should not be disregarded and may include the volume of muscular mass and meat intake since, in cooked meat, creatine is transformed to creatinine which is absorbed readily in the gastrointestinal tract. Long-term administration of corticoids in transplant recipients should rather lead to a decrease in S_{cr} (Horber *et al.* 1985). The issue of S_{cr} and the effect of extrarenal factors on this value in individuals with a renal graft warrants a future study.

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