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Postprandial increase in serum creatinine in renal transplant recipients

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Abstract. Daily variation in serum creatinine and the effect of a protein load was studied in 18 patients with renal transplants and in 10 healthy controls. Serum creatinine was analyzed both with a standard Jaffé method and with a specific HPLC technique. Following a protein meal, a 30% increase in serum creatinine levels was noted in both groups, but the rise in absolute terms was more prominent among the transplanted patients. Urinary excretion of creatinine did not increase in the transplanted group, indicating a reduced ability to deal with the surplus creatinine in the protein meal. It is concluded that serum creatinine levels are diet-dependent and that this variation is more pronounced when renal function is reduced. Standardized blood sampling is important when following serum creatinine in renal transplant recipients from one day to the next.

Key words: Creatinine, postprandial variation – Kidney transplantation, variation in serum creatinine

Determination of serum creatinine is the most frequently used method for estimating renal function after kidney transplantation. Even minor changes in the creatinine level may influence diagnostics and lead to therapeutic changes. Serum creatinine gives an unreliable reflection of the glomerular filtration rate (GFR) but is so far unrivalled when it comes to following renal function from one day to the next. There is, however, an analytical variation and a day-to-day variation, and the critical difference between results has been estimated to be 14% [2].

Reports in the literature concerning the circadian variation have shown different figures [5, 7, 8, 10, 12]. Factors that can affect serum creatinine levels during the day (aside from changes in renal function) include dietary intake and physical activity. Intake of cooked meat can temporarily raise the serum creatinine level [3, 6]. Despite creatinine's dependence on muscle mass, physical activity seems to influence serum levels relatively little [11].

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Administration of a protein meal to healthy subjects results in an increased excretion of creatinine through glomerular filtration and tubular secretion. It is possible that patients with reduced renal function are less capable of eliminating the additional creatinine that a meal with cooked meat contains, leading to greater fluctuations in serum levels in this group. Data are, however, insufficient concerning renal transplant recipients.

The aim of this study was to estimate the daily variation in serum creatinine in renal transplant recipients and to study the serum levels after a protein load. In addition, attention was focused on whether variations in serum levels were caused by a genuine change in creatinine concentration or whether other substances may have influenced the method used to analyze creatinine.

Materials and methods

Eighteen patients who had received a renal transplant at least 9 months earlier and whose renal function was stable constituted the study group. Serum creatinine ranged from 86 to 495 μmol/l (median 168 μmol/l) and the patients' ages from 27 to 71 years (median 60 years). Conventional immunosuppression was used, consisting of either prednisolone, azathioprine, and cyclosporin A or an older protocol with only prednisolone and azathioprine. Ten healthy hospital personnel, without any history of renal disease or ongoing pharmacological treatment, were used as controls.

Experimental protocol

Laboratory tests were followed during two 24-h periods in both the patients and the controls. On day 1, a 5-ml blood sample was taken at 8 a.m. after an overnight fast. Further samples were collected at 2 p.m. and 7 p.m. Dietary intake was free but was registered during this day. On day 2, blood samples were taken at 8 a.m., 2 p.m., and 7 p.m. with the test persons fasting in the morning until 11 a.m. At that time a meat meal, consisting of 0.75 g protein per kg body weight, was given. The amount of meat was chosen to correspond to a plausible meal and consisted of veal that had been boiled for 45 min. A final blood test was taken in a fasted state in the morning of day 3. During both these days urine was collected between 8 a.m. and 12 noon, 12 noon and 4 p.m., 4 p.m. and 8 p.m., and 8 p.m. and 8 a.m. and the volume measured. Both serum and urine were stored at −20°C for later analyses.

Laboratory analyses

Serum creatinine was measured using a routine Jaffé method on a Greiner G-450 automatic multichannel analyzer and an HPLC method using a weak cation exchange column [4].

Reagents. Creatinine standard, 265 μ*M* in 20 m*M* hydrochloric acid, was obtained from Sigma (St. Louis, Mo.). Bovine creatinine standard, Autonorm batch nr 2416, was obtained from Nycomed (Oslo, Norway).

HPLC apparatus and chromatographic conditions. The HPLC instrumentation consisted of a JASCO 880 – PU pump and a JASCO 875 – UV variable wavelength detector (Japan Spectroscopic, Tokyo, Japan). The samples were injected by a Waters 710B autoinjector (Waters, Millipore, Milford, Mass., USA). A Shimadzu C-R5A integrator (Shimadzu, Tokyo, Japan) was used for the analysis of the data collected.

The flow rate was 1.0 ml/min. Creatinine was detected at 234 nm.

The weak cation exchange column was a 150 × 4.6 mm ID column from Bio-Rad (Richmond, Calif., USA). The analytical column was protected by a 40 × 4.6 mm ID precolumn (Bio-Rad) packed with the same material as the analytical column. The elution buffer consisted of 20 m*M* lithium acetate (pH 4.8) – methanol (95:5 v/v).

Procedure. A total of to 200 μl of 0.6 *M* trichloroacetic acid was added to 200 μl of standard or serum specimen. The mixture was agitated and then centrifuged at 2000 *g* for 10 min. The supernatants were removed and 5 μl was injected into the liquid chromatograph.

The protocol was approved by the local ethics committee and every patient gave informed consent.

Statistical calculations

Statistical analyses were conducted with nonparametric methods and the material was described using median and first and third quartiles.

Results

There was a highly significant correlation between creatinine analyzed with HPLC and with the Jaffé reaction ($r = 0.996$, $n = 195$). A small intercept was noted with higher values for the method using the Jaffé reaction, which is interpreted as an effect of pseudocreatinines. Hyperglycemia and raised levels of ketone bodies are examples of substances that may influence the Jaffé reaction and give falsely elevated creatinine values. None of our patients was diabetic, however. The good agreement between the two methods was maintained at higher creatinine levels.

Figure 1 shows the median values for creatinine analyzed with the Greiner G450. During the first 24 h, there was no significant difference within any of the two groups. During the second 24 h, a significant rise was noted at 2 p.m. and 7 p.m. in the transplant group. For the controls an elevation was registered only at 2 p.m., 3 h after the protein meal. A comparison of the groups shows a 30% rise in serum creatinine after the protein load, both for the transplant patients and the healthy controls. The absolute rise in μmol/l differed, however, significantly.

Figure 2 presents the values for individual patients. During the 1st day, when the group as a whole did not show any difference, four patients exhibited prominent increases at 7 p.m. Three of the four patients had ingested meals containing meat. During the 2nd day, prominent rises were noted for all patients. The corresponding individual results among the controls are given in Fig. 3.

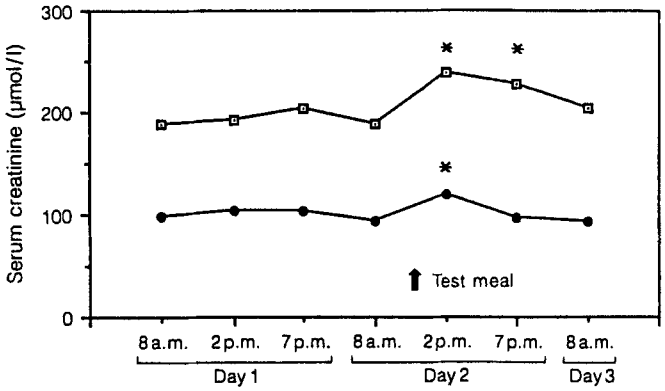

Fig. 1. Fluctuations of serum creatinine (median values) during the 2-day study period. □ Transplanted patients; ● controls. * $P < 0.05$ compared with the value at 8 a.m.

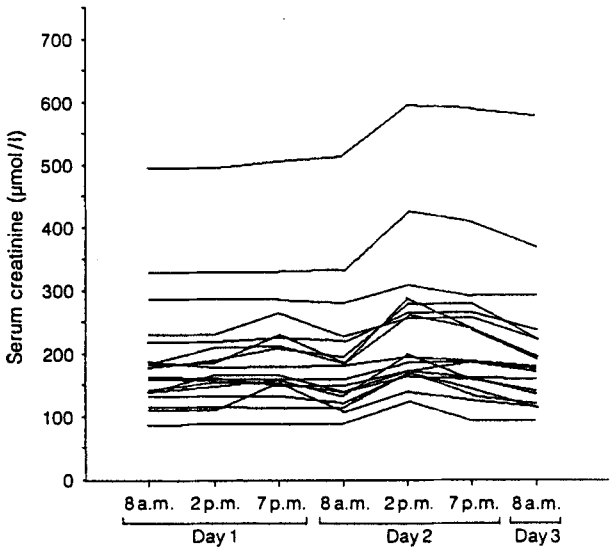

Fig. 2. Individual serum creatinine values in renal transplant recipients

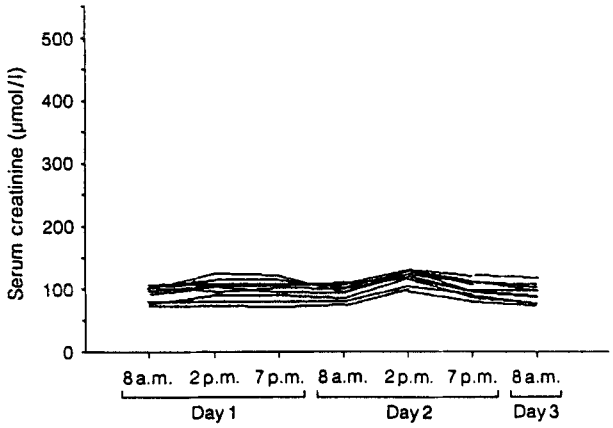

Fig. 3. Individual serum creatinine values in controls

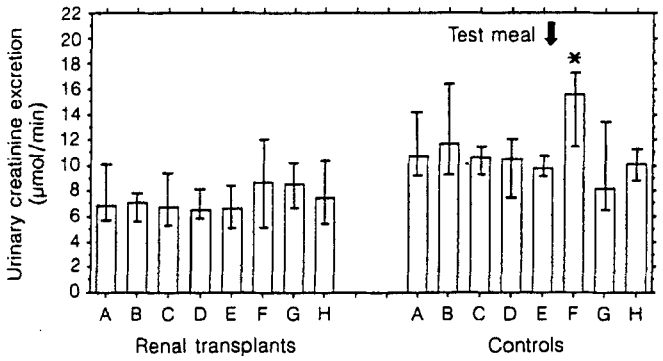

Fig. 4. Urinary creatinine excretion in the population studied (median, first, and third quartiles). First day: *A* 8 a.m.–12 noon; *B* 12 noon–4 p.m.; *C* 4 p.m.–8 p.m.; *D* 8 p.m.–8 a.m. Second day: *E* 8 a.m.–12 noon; *F* 12 noon–4 p.m.; *G* 4 p.m.–8 p.m.; *H* 8 p.m.–8 a.m.

Figure 4 presents the urinary creatinine excretion for each of the eight periods expressed as μmol/min. In controls a significant increase in creatinine excretion was found in the urine sampled after the protein meal. In the renal transplant patients, this increase was lacking.

Discussion

Serum creatinine is the most important parameter for following renal function in kidney transplant recipients. Early detection of renal impairment is mandatory for the discovery of graft rejection or cyclosporin nephrotoxicity.

Creatinine is usually determined using methods based on the so-called Jaffé reaction. This is a more than 100-year-old method that utilizes the reaction between creatinine and picric acid under alkaline conditions to produce a color that can be read spectrophotometrically. Several substances can interfere (e.g., ketone bodies, glucose, bilirubin, and certain drugs) and give a similar reaction with picric acid. These pseudocreatinines can produce falsely elevated creatinine values. These sources of error can, however, be reduced in different ways with varying degrees of success. It is important to remember that analytical errors may influence day-to-day serum creatinine determination. Recently, several specific enzymatic tests have appeared that use enzymatic degradation of creatinine. These tests are less influenced by interfering substances, although high bilirubin levels affect the result. In the present study, analyses of serum creatinine using the Greiner G450 instrument show excellent agreement with an HPLC method.

The results presented here further stress the importance of standardized blood sampling. Although no significant changes were recorded during the day, some patients had a rise in their afternoon serum creatinine after intake of a meal containing meat. When a protein load was given during the 2nd day, there was a universal rise in serum creatinine concentration.

A high protein load has been shown to increase the glomerular filtration rate (GFR), a phenomenon called "the functional reserve" [9]. Bosch et al. [1] found the rise in GFR, measured as creatinine clearance, after a protein meal to be reduced or absent in patients with reduced renal function. Our study is the first to show in renal transplant patients that loss in renal function reduces the ability to deal with an increased load of creatinine. The high and lengthy rise in serum creatinine levels in the patients is explained by their incapacity to excrete creatinine that has been absorbed from the cooked meat administered orally. Only cooked meat contains sufficient amounts of creatine and creatinine to influence serum levels [3]. Calculating the actual creatinine clearances, it was found that 7 of the 18 patients had a decrease after protein loading, as creatinine rose more rapidly in serum than it was excreted. Thus, it is obvious that other methods of following GFR or other ways of inducing hyperfiltration, e.g., i.v. amino acid load, should be used when it comes to measuring the functional reserve in chronic renal failure.

In conclusion, we have demonstrated a 30% increase in serum creatinine in renal transplant patients following a protein-rich meal. The more prominent rise in the patients than in the controls may indicate a loss in functional reserve in the transplanted kidneys. The results presented emphasize the importance of determining serum creatinine in the morning on an empty stomach and judging values during the rest of the day with precaution.

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