Renal impairment after hip or knee arthroplasty

Urinary excretion of protein markers studied in 59 patients

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We studied renal function during and after surgery in 38 patients undergoing total hip replacement (THR) and 21 patients undergoing total knee replacement (TKR). Serum creatinine and renal excretion of albumin, IgG , protein HC and creatinine were recorded preoperatively and on days 1, 2, 4, and 8. THR patients were randomized to treatment with (n 17) or without (n 21) prophylactic isoxazolyl penicillins, which all TKR patients had. In all 3 groups, the urinary concentration of proteins increased postoperatively with a peak in the glomerular markers (albumin, IgG) on days 1 and 2, and in the tubular marker (protein HC) on days 2 and 4. There were no statistically significant differences between the groups. On day 8, all urinary protein concentrations had essentially returned to their preoperative levels. Serum creatinine decreased by 10% in THR patients on day 1 and then returned to baseline levels, but there was a gradual increase up to 13% in TKR patients.

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Several studies (Gelman et al. 1979, Isacson and Collert 1984, Nordbring 1984, Hedström and Hybbinette 1988, Wahlström et al. 1992a, b) have indicated a transient renal impairment in connection with total hip replacement (THR). Morand and Littlejohn (1990) considered reduced renal function to be the commonest postoperative medical problem after THR and in some cases acute renal failure was fatal (Isacson and Collert 1984, Morand and Littlejohn 1990). Prophylactic systemic antibiotic treatment, with isoxazolyl penicillins, can contribute to renal dysfunction (Isacson and Collert 1984, Nordbring 1984, Hedström and Hybbinette 1988, Wahlström et al. 1992a, b). Other reasons could be preexisting renal dysfunction in these often elderly patients, an effect of the stress and hemodynamic instability during anesthesia and surgery, or an adverse effect of drugs given per- or postoperatively.

We have previously found that THR patients differ from total knee replacement (TKR) patients as regards lower clearance of cloxacillin and lower preoperative creatinine clearance (Vinge et al., unpublished data). They also have lower cloxacillin clearance than healthy subjects over 60 years of age (Nergelius et al., unpublished data).

Analyses of serum creatinine or creatinine clearance assess only glomerular filtration rate. More comprehensive monitoring requires measurement of urinary excretion of specific marker proteins as markers for impaired glomerular (albumin, IgG) or tubular (protein HC) function (Grubb 1992a, b, Hofmann et al. 1992).

We studied the effect of systemic cloxacillin on renal function, following hip arthroplasty, and compared the renal function after THR and TKR.

Methods

Patients

Patients with coxarthrosis or gonarthrosis, 55 years of age or older, and scheduled for primary, elective hip or knee arthroplasty at the Department of Orthopedics, Lund University Hospital, were included. Exclusion criteria comprised renal disease or a serum creatinine above the reference range preoperatively, diabetes, rheumatoid arthritis, immune deficiencies, or a reported allergy to penicillin. 38 patients underwent hip arthroplasty and 21 had knee arthroplasty (Table).

The study was approved by the Ethics Committee of Lund University and informed consent was obtained from all patients.

Procedures

For THR, cemented Scan-hip® or Optima® (both Mitab, Sweden) prostheses were used and for TKR, cemented Duracon®, PCA® (both Howmedica, USA)

Demographic data. Measurements are given as mean (SD)

	Knee patients	All hip patients	Hip patients with cloxacillin	Hip patients without cloxacillin
Sex (F / M)	16 / 5	25 / 13	12 / 5	13 / 8
Age (mean and range)	73 (59–87)	71 (55–85)	70 (55–82)	72 (56–85)
Weight, kg	74 (11)	75 (13)	75 (12)	75 (15)
Height, cm	162 (7) [a]	169 (8) [a]	169 (8)	169 (8)
Body surface, m²	1.79 (0.16)	1.85 (0.19)	1.84 (0.16)	1.86 (0.21)
BMI, kg/m²	28 (3.3)	26 (3.7)	26 (4.3)	27 (3.3)
S-creatinine, µmol/L	61 (9) [b]	74 (13) [b]	73 (14)	75 (14)
Cl-creatinine, ml/min/1.73m²	89 (27) [c]	72 (15) [c]	76 (16)	70 (14)

[a] p = 0.002, [b] p = 0.0003, [c] p = 0.005.

or Osteonic® (Stryker Corp., USA) prostheses were used. Gentamicin-impregnated bone cement (Palacos®, Merck, Germany) was used.

All except 2 patients had an epidural block with mepivacaine and morphine or intrathecally administered bupivacaine and morphine. The patients were sedated with midazolam or propofol. Due to lower back problems, 2 patients were given general anesthesia (thiopental, fentanyl, succinylcholine and isoflurane). To prevent anaphylactoid reactions, all patients were given 100 mg hydrocortisone 5 minutes before the cementation (Gammer et al. 1988). Low molecular weight heparin enoxaparin 40 mg subcutaneously o.d. was given as prophylaxis against deep venous thrombosis.

The patients were monitored with continuous ECG and S_aO_2; noninvasive blood pressure was measured every 1–2 minutes for the first 15 minutes after induction of anesthesia and thereafter every 5 minutes. Fluid administration included 0.5–1.0 L Ringer-acetate in connection with the regional anesthesia and 1–2 L of glucose infusion in the first 24 hours. Ringer-acetate, dextran (Macrodex 6%®, Pharmacia, Sweden), albumin (Albumin 4%®, Pharmacia, Sweden) and/or SAG (saline-adenine-glucose) suspension (packed red blood cells) was given, when needed, for volume substitution.

The patients undergoing THR were randomized into 2 groups. One group received systemic antibiotic prophylaxis (see below). The other group, which was not given systemic antibiotics, was operated on in a sterile enclosure, using a Hepafilter® (Crossworth, UK) where the airway exchange was approximately 600 times/hour. All patients undergoing TKR received systemic antibiotics, as below.

Systemic antibiotic prophylaxis followed the established routine procedure: an intravenous bolus dose injection of 1 g (= 2294 mmoles) of cloxacillin (Ekvacillin®, Astra, Sweden) dissolved in 20 mL of saline was given as a bolus dose over 3 minutes, at induction of anesthesia, i.e., 45 minutes before surgery, and then at 6-hour intervals up to a total of 4 doses. According to the local protocol, flucloxacillin (Heracillin®, Astra, Sweden) was thereafter given as tablets, 1.5 g b.i.d., for 3 days.

All patients were routinely instructed to avoid NSAIDs (nonsteroid antiinflammatory drugs) 1 week preoperatively and they took no NSAIDs during the study period.

Blood samples and morning urine samples for determinations of creatinine, albumin, IgG, and protein HC were collected preoperatively and on days 1, 2, 4, and 8, postoperatively. Serum and urine creatinine levels were determined by the Kodak Ektachem 700 XR-C system which uses the enzyme creatine amidinohydrolase. Urine levels of creatinine, albumin, IgG, and protein HC were determined within 24 h after collection and without prior freezing of the samples. The concentrations of albumin, IgG, and protein HC were determined by automated immunoturbidimetric techniques (Tencer et al. 1994). The limit of determination was 5 mg/L for these proteins. Reference values (albumin <25 mg/L, IgG <5 mg/L, protein HC <10 mg/L) were obtained from a healthy population of 97 adults (A. Grubb, unpublished data).

Calculations

Body surface area was calculated according to Dubois and Dubois (1916). Creatinine clearance was estimated from a modified version of the Cockcroft-Gault formula, taking into account serum creatinine, sex, age, and body weight (Rowland and Tozer 1989). Body Mass Index, BMI, was calculated as height/weight^2.

Urinary protein concentration is usually expressed as mg protein per mmol creatinine to adjust for individual and temporal differences in diuresis. This assumes that the urinary excretion of creatinine remains relatively constant. Since such is not the case in a surgical situation, we chose to express the excretion as mg protein per liter urine. This procedure facilitated statistical calculations.

Statistics

Since such urinary proteins had not been much studied in surgical situations, we had no knowledge of their variability. This made it impossible to make a proper a priori power analysis before designing the study. Earlier studies had reported clinically relevant renal impairment in 10–15% of the patients undergoing hip arthroplasty. Hence, the subclinical incidence would be even higher and we assumed that a statistically significant renal involvement could be detected in a group of 20 patients.

Demographic data were compared statistically with an unpaired t-test. Changes in serum creatinine were compared with a paired t-test. Regarding changes in urinary protein levels, 3 main analyses were made: (I) hip (with antibiotics) vs. hip (without antibiotics), (II) hip (with antibiotics) vs. knee (with antibiotics) and (III) hip (both with or without antibiotics) vs. knee (with antibiotics). The statistical comparisons between the methods of surgery (endpoint-baseline) were done with one-way analysis of variance and with 95% confidence intervals (CI). Missing data were handled with the last observation carried forward (LOCF). The statistical analyses were also made by ANOVA with repeated measurements. Changes in urinary protein levels within each of the 3 groups were compared with the Wilcoxon signed-rank sum test. A p-value less than 0.05 was regarded as statistically significant.

Results

3 patients withdrew after 2–4 days of the study for personal reasons and 6 hip patients were discharged from the hospital before day 8. 2 patients, although randomized to the non-cloxacillin group, were given cloxacillin and sampling was stopped. On one occasion blood sampling was forgotten. 7 urine creatinine samples were never analyzed. All these patients are included in the calculations covering the period when they were still in the study.

Subjects

Hip patients (as 1 group) were taller than knee patients, had a higher preoperative serum creatinine and lower values for creatinine clearance, normalized for body surface area (Table 1). There were 12 hip and 7 knee patients on antihypertensive treatment with ß-blockers, calcium antagonists, ACE-inhibitors or diuretics and 10 hip and 7 knee patients on medication with NSAIDs.

Blood loss and fluid substitution

All patients were circulatory and respiratory stable throughout the procedure. The mean amounts of bleeding during the first 24 hours were 894 (SD 432) mL among hip patients and 482 (SD 434) mL among knee patients ($p = 0.002$). In all, only 6 hip patients and no knee patients received blood, 2 or 3 units of SAG. Hip patients received 3.8 (SD 0.7) L, and knee patients 3.6 (SD 0.7) L of fluids during the first 24 hours ($p = 0.4$).

Creatinine

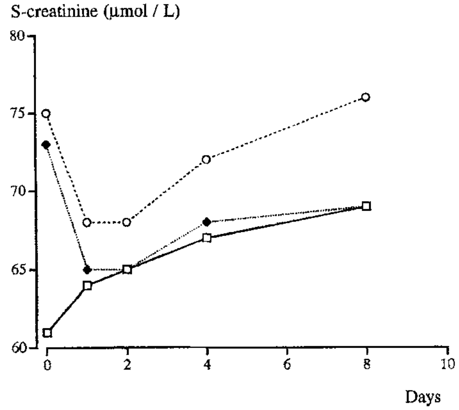
Serum creatinine was within the normal range in all patients before surgery. Postoperatively, serum creatinine levels were lower on days 1 and 2 in both groups of hip patients ($p = 0.02$ in the patients with cloxacillin, and $p = 0.0002$ in the patients without). In contrast, serum creatinine in knee patients increased gradually—on day 8 by 13% ($p = 0.0006$). Urine creatinine levels increased transiently, but significantly, in all 3 groups during the same period (Figure 1).

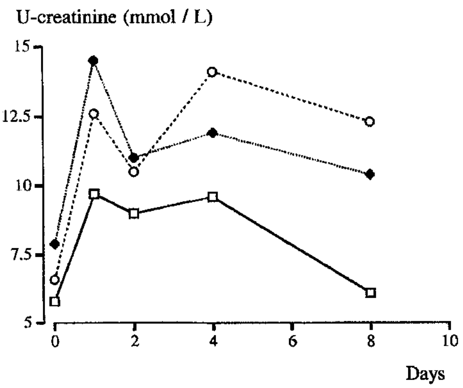
Urinary protein excretion

Preoperatively, there were no statistically significant differences between hip and knee patients in urine levels of albumin or of IgG or protein HC. However, 12 hip patients had at least one protein level above the reference range, while there were no elevated levels in any of the knee patients.

In all patients who completed the study, the absolute levels of glomerular and/or tubular markers in the urine rose above the normal range on at least one occasion. The temporal changes in the urinary excretion of albumin and IgG differed markedly from those of protein HC, the rise in the glomerular markers being most pronounced on days 1 and 2, whereas the tubular marker had its peak on day 2. On day 8, all 3 protein markers had essentially returned to their preoperative levels (Figure 2). The ratios of urine proteins versus urine creatinine are presented in Figure 3. There was a great interindividual variation in the total changes in urine protein levels. In 1 patient U-albumin increased from a preoperative 40 mg/L to a maximum of 34,520 mg/L, U-IgG from 330 mg/L to 1,130 mg/L, and U-protein HC from 20 mg/L to 64 mg/L, whereas U-creatinine increased only from 87 preoperatively to a maximum of 98 mmol/L. During the same period, serum creatinine varied between 75 and 98 (preoperatively 87) µmol/L.

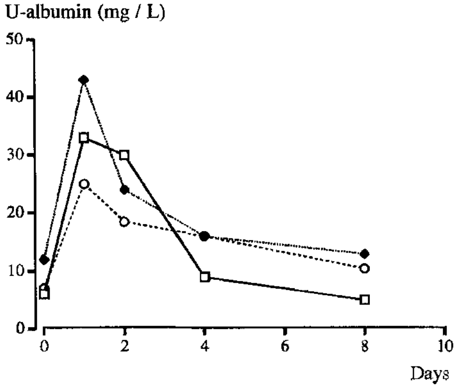
Compared to the preoperative values, the 17 hip patients who received cloxacillin had elevations in the



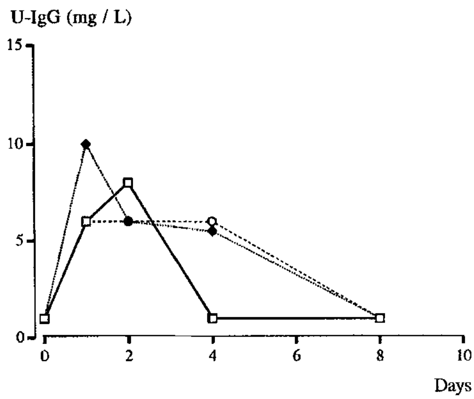


Q_1-Q_3	0	1	2	4	8
K+C	3.7-9.4	7.1-13.0	5.8-11.0	7.0-12.6	4.0-8.6
H+C	3.3-11.6	10.3-22.1	5.6-14.8	8.0-14.5	7.0-14.8
H	3.8-11.0	9.1-18.5	7.0-11.5	7.0-20.2	9.1-14.7

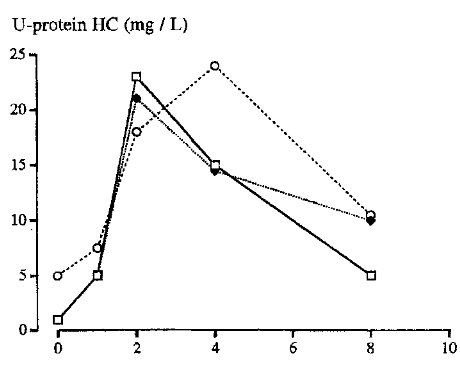
Figure 1. Serum creatinine levels (means) in patients undergoing arthroplasty (top). Urine creatinine levels (medians) in patients undergoing arthroplasty (bottom).Interquartile ranges in table.
❑ knee arthroplasty with cloxacillin (n 21)
◆ hip arthroplasty with cloxacillin (n 17)
○ hip arthroplasty without cloxacillin (n 21)



Q_1-Q_3	0	1	2	4	8
K+C	1.0-11.3	17.5-124.5	15.8-43.3	5.8-11.0	1.0-7.3
H+C	5.0-21.3	35.5-100.0	15.3-59.5	11.8-23.8	6.0-19.0
H	1.0-14.3	15.5-43.5	15.0-46.0	8.0-35.3	9.0-39.5



Q_1-Q_3	0	1	2	4	8
K+C	<5-<5	<5-20	5-12	<5-7	<5-<5
H+C	<5-<5	6-29	5-14	<5-7	<5-5
H	<5-<5	<5-9	5-9	<5-10	<5-9

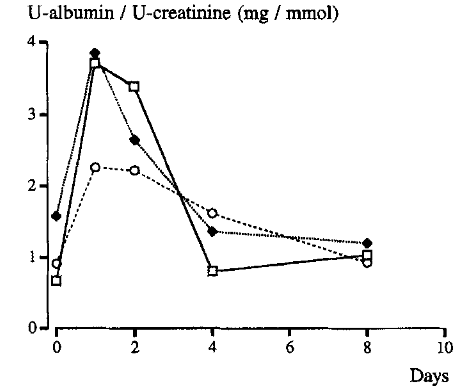


Q_1-Q_3	0	1	2	4	8
K+C	<5-6	<5-10	13-48	7-24	<5-11
H+C	<5-6	<5-9	9-31	10-20	<5-20
H	<5-9	6-14	5-42	8-31	7-22

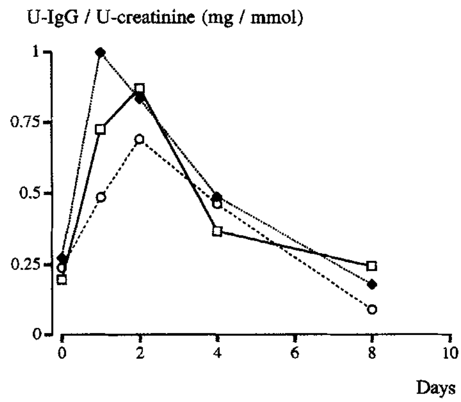
Figure 2. Urine protein levels (medians) in patients undergoing arthroplasty.
❑ knee arthroplasty with cloxacillin (n 21)
◆ hip arthroplasty with cloxacillin (n 17)
○ hip arthroplasty without cloxacillin (n 21)
Interquartile ranges in table.

levels of urine albumin and of urine IgG, with peaks on day 1 ($p = 0.0003$ and 0.0004, respectively), and of urine protein HC, which peaked on day 2 ($p = 0.002$). The 21 hip patients without cloxacillin treatment had elevations in the levels of urine albumin, with a peak on day 1 ($p = 0.001$), of urine IgG, which peaked on day 2 ($p = 0.003$), and of protein HC, which had its peak on day 4 ($p = 0.003$). The 21 knee patients had elevated levels of urine albumin, with a peak on day 1 ($p < 0.0001$), of urine IgG with its peak on day 2 ($p = 0.0002$), and of urine protein HC, which also peaked on day 2 ($p < 0.0001$). On day 8, all protein levels had essentially returned to preoperative levels.

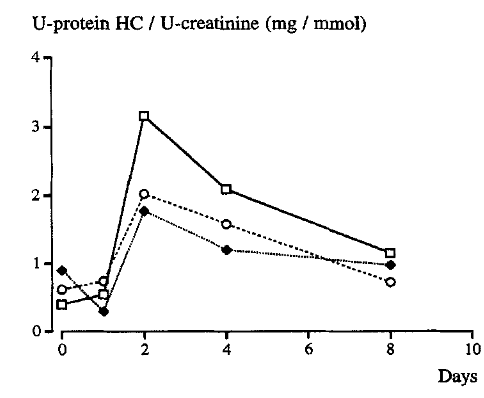
There were no statistically significant differences in urine protein levels between hip patients with or without systemic cloxacillin, or between hip patients, as one group, and knee patients (Figure 4).



Q_1-Q_3	0	1	2	4	8
K+C	0.37-2.13	2.39-12.97	2.22-4.47	0.56-1.63	0.28-1.03
H+C	0.56-5.80	2.63-5.20	1.56-3.69	1.01-2.40	1.00-1.42
H	0.25-1.93	1.15-3.50	1.39-6.01	0.94-2.62	0.46-4.08



Q_1-Q_3	0	1	2	4	8
K+C	0.12-0.47	0.41-2.73	0.69-1.30	0.10-0.51	0.16-0.40
H+C	0.11-0.91	0.44-1.30	0.46-1.09	0.18-0.79	0.12-0.34
H	0.14-0.39	0.36-0.82	0.47-1.08	0.61-0.77	0.07-0.68



Q_1-Q_3	0	1	2	4	8
K+C	0.19-1.02	0.14-1.10	1.73-4.58	0.93-2.95	0.25-1.83
H+C	0.24-1.01	0.21-0.54	0.96-2.42	0.72-2.01	0.21-1.28
H	0.23-1.24	0.45-1.34	0.86-5.00	0.98-1.87	0.54-1.74

Figure 3. Urine protein / creatinine ratio (medians) in patients undergoing arthroplasty.
❑ knee arthroplasty with cloxacillin (n 21)
◆ hip arthroplasty with cloxacillin (n 17)
○ hip arthroplasty without cloxacillin (n 21)
Interquartile ranges in table.

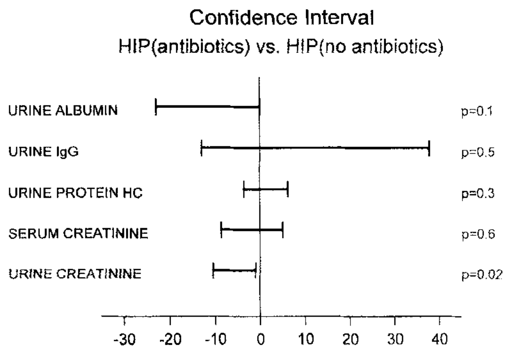


Figure 4. Confidence intervals for serum creatinine, urine creatinine, urine albumin, urine IgG and urine protein HC in patients undergoing hip arthroplasty with (n 17) or without (n 21) systemic cloxacillin.

Discussion

Previous studies have indicated postoperative renal impairment in about 10–15% of all patients undergoing hip arthroplasty (Gelman et al. 1979), mainly in patients on systemic antibiotic prophylaxis with isoxazolyl penicillins (Isacson and Collert 1984, Hedström and Hybbinette 1988, Ahnfelt and Steen 1992, Wahlström et al. 1992a, b). However, in patients receiving dicloxacillin and operated with gentamicin-free bone cement, only slight signs of tubular dysfunction were found one week after surgery (Stegmayr et al. 1992). There is a decline in renal excretion of ß-lactam antibiotics in elderly patients (Ljungberg and Nilsson-Ehle 1987); subsequently there could be a risk of accumulation of isoxazolyl penicillins and a greater impact on renal function .

Previous authors have studied glomerular function after THR by following serum creatinine levels (Isacson and Collert 1984, Hedström and Hybbinette 1988, Wahlström et al. 1992a, b). These could rise due to the large muscular trauma in hip surgery and it does not rise until the glomerular filtration rate is reduced by 40–50%. Tubular function has been followed by measuring the urinary level of $ß_2$-microglobulin (Wahlström et al. 1992a, b), but this protein could be degraded in urine and urinary concentrations are influenced by non-renal disorders.

Analysis of the excretion of selected urine proteins allows sensitive demonstration of nephrotoxicity of drugs and characterization of glomerular and/or tubular dysfunction (Grubb 1992a, b, Hofmann et al. 1992). Even a small increase in the urinary level of albumin signifies a glomerular dysfunction of clinical importance. IgG has a molecular mass more than twice that of albumin and elevated urinary levels indicate a more severe glomerular involvement. Protein HC should be almost completely reabsorbed by the proximal tubules. An elevated urinary concentration indicates tubular impairment of hypoxic or toxic origin.

Hip and knee patients in this study were of the same age and would be expected to have similar renal function. The fact that THR patients, in this study as in an earlier one (Vinge et al., unpublished data), preoperatively had a higher serum creatinine and a lower creatinine clearance/m^2 than TKR patients indicates that these patients, although clinically judged as having a normal renal function, may preoperatively have a lower renal capacity than other patients of the same age. Some hip patients had augmented urinary protein levels preoperatively. Such patients reached the most extreme protein levels postoperatively, suggesting that some hip patients suffer from even an increased risk of renal impairment during and after THR.

One third of the patients in this study were on antihypertensive treatment which agrees with demographic studies in the Swedish population of this age (Åberg 1989). One third of the patients were on NSAID treatment. There was no indication that any of these treatments affected urinary protein excretion pre- or postoperatively.

Serum creatinine in our hip patients decreased during the first 24 hours. This differs from the results in previous studies (Isacson and Collert 1984, Hedström and Hybbinette 1988, Wahlström et al. 1992a, b), and is probably a dilutional effect. A similar decrease in serum urea was observed by Stegmayr et al. (1992) whose patients were similar to ours as regards bleeding (1 L) and transfusion (median 1 unit) . Compared to previous studies, the hip patients in our study had less bleeding (mean 0.9 L vs. 1.6 L (Hedström and Hybbinette 1988)) and received fewer blood transfusions (0.3–0.6 L of SAG compared to 6–13 units (Gelman et al. 1979) or 2.1 L blood (Isacson and Collert 1984)). In accordance with more recent principles in transfusion therapy (Miller 1994), they were given more cristalloids and dextran than blood products.

Urine creatinine levels increased in all groups of patients, reflecting a more concentrated urine or an increased renal excretion rate of creatinine. The fact that knee patients had lower levels of urine creatinine than hip patients throughout the study might reflect the smaller surgical trauma in knee surgery.

Hip and knee patients had raised levels of glomerular and tubular markers. Proteinuria is described after surgery (Gosling et al. 1988a) and after trauma and burns, without coexisting myoglobinuria or raised serum renin activity (Gosling and Sutcliffe 1986, Gosling et al. 1988b). This could reflect an impaired barrier function with a change in vascular permeability. The increased urinary excretion of albumin and IgG found in this study may reflect the kidneys' physiological reaction to surgical stress. Stegmayr et al. (1992) found no increased excretion of albumin after THR, but they collected urine only on the fourth postoperative day and may have missed the earlier peak.

All patients had increased urinary levels of protein HC, which has also been found after coronary by-pass surgery (Feindt et al. 1995). Stegmayr et al. (1992) and Wahlström et al. (1992a, b) also noted signs of tubular involvement after THR. These findings suggest that the kidneys have been exposed to a mild degree of medullary ischemia as shown in animal experiments (Mason et al. 1987) or to some other factor associated with the surgical procedure that has caused tubular dysfunction.

An interesting observation was that the glomerular markers had their peaks before the tubular marker. Previous studies also found indications of tubular dysfunction from the second postoperative day and onwards (Wahlström et al. 1992a, b, Feindt et al. 1995). Ischemic or hypoxic damage to the kidney mainly affects tubular function (Sladen 1994). The involvement noted in this study therefore seems to be, in part, of some other origin. One theory is that the gentamicin-impregnated bone cement (methyl-methacrylate) may induce toxic and/or inflammatory reactions in the kidneys. We are presently investigating patients operated with gentamicin-free bone cement as well as uncemented components.

In conclusion, elderly patients undergoing hip or knee arthroplasty suffer a transient renal impairment, as judged by the urinary excretion of proteins indicating glomerular or tubular involvement. The renal function returns essentially to the preoperative level within 8 days. Systemic antibiotic prophylaxis does not seem to be the main cause of this renal impairment.

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