ORIGINAL ARTICLE

Urinary hepatocyte growth factor indicates ischemia/reperfusion injury after kidney transplantation

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KEY WORDS

hepatocyte growth factor, ischemia/reperfusion insult, kidney transplantation, xanthine oxidase

ABSTRACT

INTRODUCTION Despite the development of immunosuppressive regimens in kidney transplantation, long-term graft survival rates have not increased significantly. One of the causes of long-term graft loss is ischemia-reperfusion insult. Hepatocyte growth factor (HGF) is a regenerative factor produced in response to injury.

OBJECTIVES Our aim was to assess the effect of HGF and xanthine oxidase (indicators of ischemia/reperfusion insult) on early and late kidney function.

PATIENTS AND METHODS In 17 patients, HGF levels in urine and xanthine oxidase activity in blood were examined 1, 7, 14, 30 days, 3 and 6 months after kidney transplantation. We also measured 24-hour diuresis and serum creatinine levels after transplantation.

RESULTS Urinary HGF levels were highest 1 day after transplantation. During the following week, it rapidly decreased and was maintained at similar levels in the later period. Creatinine at 1 day showed a positive correlation with urinary HGF levels at 1 day and at 3 months ($R = 0.54$, $P < 0.05$ and $R = 0.82$, $P < 0.01$, respectively). Creatinine at 7 days positively correlated with HGF levels at 6 months ($R = 0.82$, $P < 0.05$). HGF levels at 1 day and at 6 months positively correlated with xanthine oxidase activity at 1 day ($R = 0.73$, $P < 0.001$ and $R = 0.77$, $P < 0.02$, respectively). A negative correlation was observed between HGF levels at 6 months and diuresis 1 and 7 days after transplantation ($R = -0.99$, $P < 0.00001$ and $R = -0.77$, $P < 0.05$, respectively).

CONCLUSIONS Urinary HGF is a good marker of perioperative kidney damage and may affect long-term graft function.

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INTRODUCTION The last decades have brought major development in organ transplantation. The introduction of new, more effective immunosuppressants has decreased the number of acute graft rejections. However, it has not improved the long-term function of a transplanted kidney. The pathogenesis of this phenomenon has not yet been fully explained.[1] Increasing attention is being paid to perioperative period and its influence on early and long-term graft function. The pathophysiology of ischemia and reperfusion stress, generation of reactive oxygen species, and activation of antioxidative defense mechanisms are significant, nonimmunological factors affecting kidney survival.[2,3]

Ischemia/reperfusion insult results from restoration of interrupted blood circulation in the kidney. It not only causes perioperative kidney damage but also starts the development of chronic allograft nephropathy (CAN). It is assumed that the imbalance between the production of the extracellular matrix and its degradation

TABLE 1 Characteristics of the study group

	Mean	SD	Median	Min.	Max.	Lower quartile	Upper quartile
age at transplantation, y	45	15.05	49	19	73	29	54
BMI at transplantation, kg/m^2	25.61	5.67	25.74	18.88	38.05	20.97	27.66
systolic BP, mmHg	138.3	18.35	130	120	170	130	150
diastolic BP, mmHg	83.3	5.16	80	80	90	80	90
time on HD, mo	30.4	22.2	24	9	79	15	36
residual diuresis, ml	421	472	250	0	1500	0	600
cold ischemia time, h	18.9	4.8	18.3	7	26	16.3	23
donor age, y	46.6	13.5	52	16	60	33	53
number of mismatches							
A	1.25	0.89	1.50	0	2	0.5	2
B	1.63	0.52	2	1	2	1	2
DR	0.5	0.53	0.5	0	1	0	1

Abbreviations: A, B, DR – HLA antigens, BMI – body mass index, BP – blood pressure, HD – hemodialysis, SD – standard deviation

plays the most important role in the development of CAN.[4]

The kidney has its own ability to regenerate in response to injury. HGF, a cytokine of multiple activity, has been suggested to support this ability. Its antifibrotic activity has been widely described in the literature. It reduces the production of type IV collagen, the main component of the extracellular matrix. On the other hand, HGF enhances collagen degradation through activation of metaloproteinases-2 and -9. HGF antagonizes the transforming growth factor β, which is responsible for the activation of mesangial myofibroblasts and transformation of tubular epithelial cells into mesenchymal cells. HGF also shows antiapoptotic activities in tubular epithelial cells exposed to ischemia and thus protects against acute graft failure.[5,6]

In the present study, we determined urinary HGF in kidney transplant recipients. Our aim was to assess the effect of HGF levels on early and late kidney function and its correlation with the extent of ischemia/reperfusion insult indicated by plasma activity of xanthine oxidase.

PATIENTS AND METHODS

Study group The study involved 17 recipients of a kidney from deceased donors (7 women, 10 men; median age, 49 years; range, 19–73 years). These transplants were performed in the years 2006–2008. Cold ischemia time varied between 7 and 26 hours (mean, 18.8 h; median, 18.25 h). Residual diuresis range was 0.00 to 1500.00 ml (mean, 420.71 ml; median, 250.00 ml). None of the examined patients required hemodialysis 6 months after transplantation. None of the patients experienced acute rejection within 6 months after transplantation. All patients used triple immunosuppressive regimen: glucocorticosteroids, tacrolimus, mycophenolate mofetil. Characteristics of the study group are presented in TABLE 1.

Methods Urine was collected at 1 day (HGF1), 7 days (HGF2), 14 days (HGF3), 30 days (HGF4), and then at 3 months (HGF5) and 6 months (HGF6) after transplantation.

Immediately after collection, urine was centrifuged, and supernatant was frozen at –80°C. Urinary HGF levels were evaluated by an enzyme-linked immunosorbent assay using the immunoassay human HGF kit (R&D Systems, United States). Blood was drawn at 1 day (O1), 7 days (O2), 14 days (O3), 30 days (O4), and then at 3 months (O5) and 6 months (O6) after transplantation. Blood was aliquoted into tubes containing 109 mM trisodium citrate (9:1; v/v) and centrifuged. The resulting platelet-poor plasma was deconted into fresh tubes and stored at 80°C until assayed. Xanthine oxidase activity was measured using a spectrophotometric method. The extinction of the samples (50 mM Tris/HCl buffer [pH 8.0], 100 mM xanthine, plasma) was measured at 302 nm, against a reference sample (50 mM Tris/HCl buffer [pH 8.0], 100 mM xanthine). Plasma creatinine levels were assessed using the Jaffe method with the Aqua-Med kit (Łódź, Poland). Creatinine clearance (CCr) was assessed using the Modification of Diet in Renal Disease calculator (by Stephen Z. Fadem, M.D., FACP, FASN and Brian Rosenthal) 1 year and 2 years after transplantation.

Statistical analysis Results are presented as: sample number, arithmetic mean, standard deviation, median, and upper and lower quartile. The nonparametric Wilcoxon signed-rank test was used. Correlations between the examined parameters were analyzed using the Spearman's rank correlation coefficient. Statistical analysis was performed using the STATISTICA PL v 7.1 program (Statsoft, Kraków, Poland). Statistical significance was set at a P level <0.05.

RESULTS

The highest urinary HGF levels were observed at 1 day after kidney transplantation. HGF levels decreased over time (TABLE 2).

Comparing urinary HGF levels at 1 day with subsequent collections (2–6), a statistically

TABLE 2 Urinary HGF levels at various time points after transplantation

Urinary HGF concentration, ng/ml							
time	mean	SD	median	min.	max.	lower quartile	upper quartile
day 1	1.87	0.91	1.65	0.81	4.12	1.33	2.33
day 7	1.01	0.33	0.95	0.56	1.74	0.86	1.02
day 14	1.02	0.51	0.77	0.54	2.34	0.65	1.31
month 1	0.87	0.33	0.78	0.45	1.43	0.59	1.26
month 3	0.81	0.36	0.68	0.48	1.43	0.53	1.30
month 6	0.90	0.29	0.74	0.61	1.55	0.73	1.00

Abbreviations: HGF – hepatocyte growth factor, others – see TABLE 1

significant difference was observed (Wilcoxon test). No significant differences in HGF levels were observed between collections 2 and 3, 3 and 4, and 4 and 5 (FIGURE 1). The activity of xanthine oxidase increased over time (TABLE 3). The activity of xanthine oxidase at 1 day positively correlated with HGF levels at 1day. Such relationship was also observed between plasma xanthine oxidase activity at 1 day and urinary HGF levels at 3 and 6 months. The higher the xanthine oxidase activity at 1 day, the larger the difference between HGF levels at 1 day and 7 days and 1 day and 30 days. Xanthine oxidase activity at 7 days did not affect HGF levels (Spearman's rank correlation test) (FIGURE 2).

Plasma creatinine levels at 1 day positively correlated with HGF levels at 1 day and at 3 months. Creatinine levels at 7 days positively correlated with HGF levels at 6 months (FIGURE 3).

Diuresis inversely correlated with HGF levels. We found a statistically significant negative correlation between diuresis at 1 day and 7 days and HGF levels at 1 day and 6 months, respectively. A correlation between diuresis at 1 day and HGF levels in urine at 1 day was of borderline statistical significance (R = –0.52, P = 0.068) (FIGURE 4).

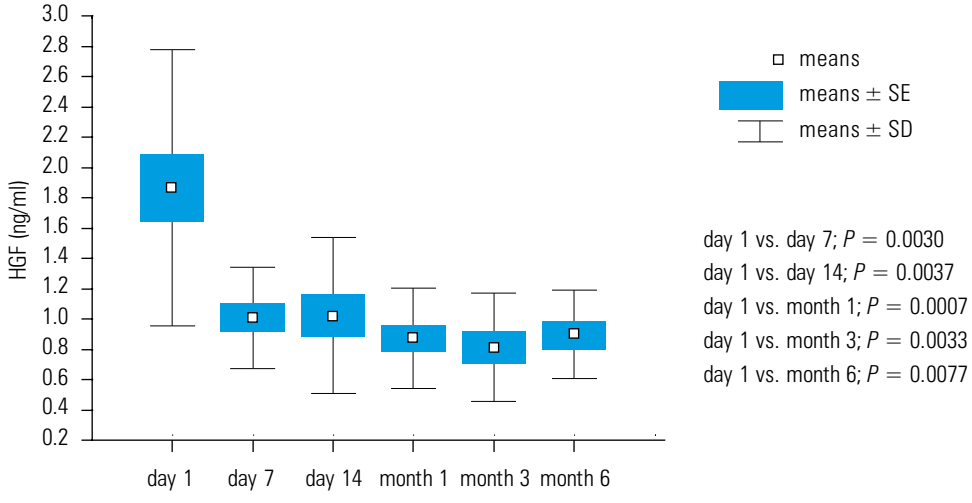

FIGURE 1 Changes in urinary HGF levels in time (Wilcoxon test) Abbreviations: SE – standard error, others – see TABLES 1 and 2

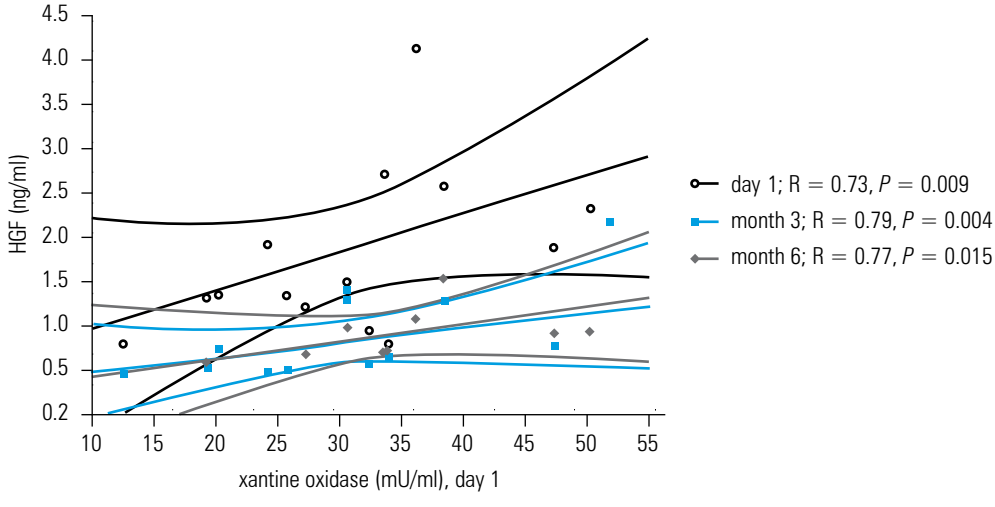

FIGURE 2 Correlation between xanthine oxidase activity at 1 day and HGF concentration at 1 day and at 3 and 6 months Abbreviations: see FIGURE 1

TABLE 3 Serum xanthine oxidase activity at various time points after transplantation

Serum xanthine oxidase activity, mU/ml							
time	mean	SD	median	min.	max.	lower quartile	upper quartile
day 1	30.23	9.19	30.37	12.60	49.10	24.23	33.67
day 7	32.50	13.69	29.82	4.52	58.42	28.10	38.46
day 14	34.29	17.17	31.66	15.18	79.94	22.29	37.47
month 1	43.42	25.10	32.63	6.46	96.88	26.49	58.79
month 3	98.06	41.98	99.49	35.50	181.19	73.01	116.94
month 6	76.98	46.35	63.77	11.63	157.60	47.49	107.84

Abbreviations: see TABLE 1

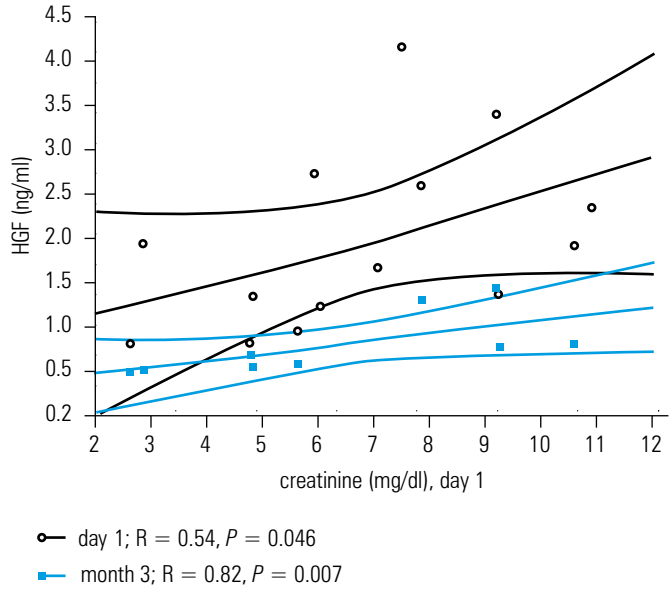

FIGURE 3 Correlation between plasma creatinine levels at 1 day and urinary HGF levels at 1 day and at 3 months
Abbreviations: see TABLE 2

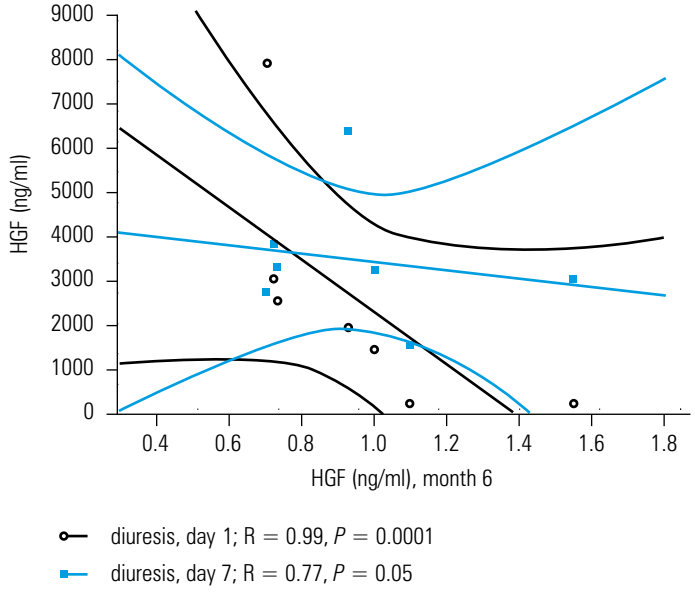

FIGURE 4 Correlation between diuresis at 1 day and urinary HGF levels at 6 months
Abbreviations: see TABLE 2

We did not find a relationship between residual diuresis and HGF levels during the posttransplant period.

Patients were divided into 2 subgroups; median HGF in the studied period was set as the criterion. There was a statistically significant difference in CCr between the subgroup with HGF values lower than median (<Me) and the subgroup with HGF values higher than median (>Me) at 1 year and 2 years (P = –0.027 and P = 0.027, respectively) (U Mann-Whitney's test). The subgroup <Me had significantly higher CCr than the subgroup >Me both at 1 year and 2 years (FIGURES 5 and 6).

DISCUSSION We observed the highest urinary HGF levels at 1 day after kidney transplantation. These values gradually decreased up to 6 months. The largest and the only significant decrease in HGF levels was between day 1 and day 7. After day 7, HGF levels remained stable (TABLES 1, 2, and 3). High HGF levels at 1 day reflect the exposure of the kidney to ischemia/reperfusion insult in the perioperative phase. Consequent "oxygen burst" starts a series of biochemical changes that begin the process of chronic kidney damage, i.e., lipid peroxidation, microvascular dysfunction, and neutrophil activation.[7-9] Herrero-Fresneda et al.[10] in their studies on rats found the highest plasma HGF levels in the early phase of kidney transplantation and then its rapid decrease. The authors emphasize that high HGF levels immediately after kidney transplantation were associated with inflammatory response to ischemia/reperfusion injury. Similarly, Ohnishi et al.[11] observed a rapid increase in HGF levels in response to ischemia/reperfusion injury, which was associated with regenerative processes in the tubules.[11]

In experimental in-vivo and in-vitro studies on rats with increasing HGF levels in the transplanted kidney (gene therapy, administration of exogenous HGF, or gene electrotransfer), HGF reduced the occurrence of such changes as inflammatory infiltration or acute tubular necrosis caused by ischemia and reperfusion. Long-term observations in these groups did not show the presence of chronic allograft nephropathy. Apoptosis of tubular cells exposed to ischemia was not observed either. In control groups, without administration of exogenous HGF, inflammatory changes were

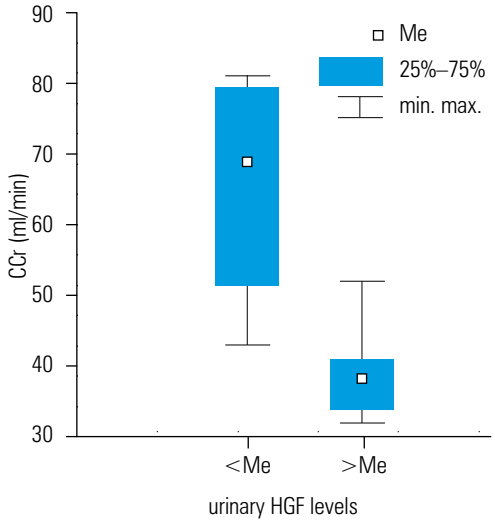

FIGURE 5 Correlation between HGF levels at 6 months (<Me and >Me) and CCr 1 year after kidney transplantation
Abbreviations: CCr – creatinine clearance, Me – median, others – see **TABLE 2**

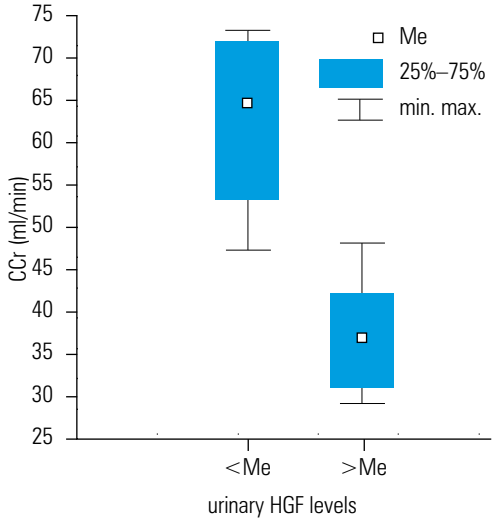

FIGURE 6 Correlation between HGF levels at 6 months (<Me and >Me) and CCr 2 years after kidney transplantation
Abbreviations: see **TABLE 2** and **FIGURE 5**

more intense, acute renal failure or chronic graft damage was more frequently observed.[10,12] Similar effects were observed in rats with induced ischemia/reperfusion injury.[13,14]

The storage of kidney in preservation solution leads to energetic deficiencies in cells resulting from reduced production of adenosine-5'triphosphate (ATP). This is accompanied by dephosphorylation of high-energy nucleotides to nucleosides and their subsequent degradation to purine base (guanine) or oxypurine (hypoxanthine), which accumulate in the ischemic tissue.[15] During ischemia, the intracellular pH decreases, and this activates the sodium-proton exchanger (NHE). The exchanger is responsible for hydrogen ion efflux from the cell in exchange for sodium ion. NHE activation leads to intracellular sodium accumulation. The acidic environment and the lack of high-energy compounds (ATP) result in the inhibition of the sodium-potassium pump with the subsequent cellular sodium efflux. As a consequence, the sodium-calcium exchanger is activated and calcium accumulates in the cytosol. These calcium ions activate a calcium-dependent protease, calpain, which irreversibly transforms xanthine dehydrogenase to xanthine oxidase.[16]

In physiological conditions, xanthine dehydrogenase transforms hypoxanthine to xanthine and finally to uric acid.[17-19] In the presence of oxygen, xanthine oxidase transforms hypoxanthine to xanthine and uric acid with simultaneous production of superoxide anion radicals, which in the presence of ferrous ions form toxic hydroxyl radicals.[20-22] This triggers the so called oxygen burst.[7-9]

It can be assumed that purine oxidase levels in plasma on the first day after transplantation reflects the extent of damage caused by ischemia/reperfusion insult. We have confirmed that xanthine oxidase activity increases systematically after transplantation. We observed a strong positive correlation between xanthine oxidase activity on the first day after transplantation and urinary HGF levels. This could indicate that the greater the perioperative kidney damage, the higher the HGF levels. A perioperative increase in xanthine oxidase activity has been confirmed by other authors.[20-22] So far, an association between xanthine oxidase activity and HGF levels has not been proven. In this study we found that plasma xanthine oxidase levels at 1 day was associated with HGF levels in urine at 1 day and even 3 and 6 months after transplantation. Xanthine oxidase activity at 7 days did not influence HGF levels.

A continuous increase in xanthine oxidase activity from the first day to 6 months after transplantation is also difficult to explain. Probably, from the first week after transplantation onwards, xanthine oxidase levels is influenced by factors other than perioperative oxidative stress. It is possible that an increase in xanthine oxidase is associated with the use of immunosuppressants, particularly calcineurin inhibitors, which lead to perfusion disorders in the transplanted kidney. There have been reports on increased xanthine oxidase activity due to exposure to calcineurin inhibitors.[23,24] The described mechanism of a post-drug increase of xanthine oxidase activity does not influence urinary HGF levels. We observed a relationship between serum creatinine levels at 1 day and HGF levels at 1 day, 7 days, and 3 months after kidney transplantation.

Our results indicate that the worse the kidney function, the higher the HGF levels. Takada et al.[25] observed an increase in serum HGF levels obtained in patients with acute graft rejection. In their study, HGF levels positively correlated with creatinine levels. A similar strong correlation between creatinine and HGF levels in serum was observed by Randers et al.[26] in patients with chronic kidney disease. Diuresis after kidney transplantation is another marker of graft function. In our group we observed that the bigger the diuresis during the first 2 days after transplantation, the lower the urine HGF levels at 1 day and even 6 months. This also supports an association between HGF levels and the degree of

kidney damage. Immediate graft function confirms minimal perioperative injury and is associated with lower urinary HGF levels. Because there was a wide range of residual diuresis in our group (mean, 420.71; median, 250.00; min., 0.00; max., 1500.00), we did not observe any effect of residual diuresis on urinary HGF levels or any other parameter. There have been no reports in the literature about the relationship between urinary HGF levels and diuresis after transplantation.

In the group of patients with urinary HGF <Me 6 months after kidney transplantation, the long-term graft function was better than in the group of patients with urinary HGF levels >Me. This observation confirms the results obtained in our study. We observed higher urinary HGF in patients with low diuresis and higher creatinine levels. Vaidya et al.[27] studied urinary HGF in patients with acute kidney injury. HGF levels positively correlated with the severity of the disease and need for renal replacement therapy.

Ischemia/reperfusion injury leads to a significant increase in urinary HGF levels in the perioperative period, which rapidly decreases in the days and months following transplantation. The degree of kidney damage expressed as xanthine oxidase activity influences HGF levels. High creatinine levels on the first day after transplantation is associated with high HGF levels in urine. Creatinine levels, on the other hand, are affected by many factors. Diuresis during the first 2 days after transplantation seems to be a better marker of posttransplant graft function and is negatively correlated with urinary HGF levels both on the first day and 6 months after transplantation. We conclude that urinary HGF levels are a good marker of perioperative kidney damage and is prognostic of long-term graft function.

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ARTYKUŁ ORYGINALNY

Czynnik wzrostu hepatocytów w moczu wskaźnikiem uszkodzenia nerki w procesie niedokrwienia i reperfuzji w przeszczepionej nerce

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SŁOWA KLUCZOWE

czynnik wzrostu hepatocytów, mechanizm ischemii/reperfuzji, oksydaza ksantynowa, przeszczep nerki

STRESZCZENIE

WPROWADZENIE Mimo olbrzymiego postępu, jaki nastąpił w leczeniu immunosupresyjnym w transplantologii, nie osiągnięto poprawy długoterminowego przeżycia przeszczepionej nerki. Jedną z przyczyn tego zjawiska jest uszkodzenie nerki w mechanizmie ischemii/reperfuzji. W odpowiedzi na uszkodzenie produkowany jest czynnik wzrostu hepatocytów (*hepatocyte growth factor* – HGF), umożliwiający regenerację nerki.

CELE Celem badania była ocena wpływu stężenia HGF i oksydazy ksantynowej (wskaźnika nasilenia zjawiska ischemii/reperfuzji) na wczesną i późną czynność przeszczepionej nerki.

PACJENCI I METODY U 17 pacjentów oznaczono stężenie HGF w moczu oraz aktywność oksydazy ksantynowej we krwi w 1., 7., 14. i 30. dniu oraz w 3. i 6. miesiącu po przeszczepieniu nerki. Oceniano również wielkość dobowej diurezy oraz stężenie kreatyniny po przeszczepieniu.

WYNIKI Stężenie HGF w moczu osiągnęło najwyższy poziom w 1. dobie po transplantacji nerki, a następnie uległo zmniejszeniu w ciągu 7 dni, pozostając na tym samym poziomie przez pozostały okres. Poziom kreatyniny w 1. dobie po transplantacji wykazywał dodatnią korelację ze stężeniem HGF w moczu w 1. dobie i w 3. miesiącu po transplantacji (odpowiednio $R = 0{,}54$; $P < 0{,}05$ i $R = 0{,}82$; $P < 0{,}01$). Stężenie kreatyniny w 7. dobie dodatnio korelowało ze stężeniem HGF w 6. miesiącu ($R = 0{,}82$; $P < 0{,}05$). Stężenie HGF w 1. dobie i 6. miesiącu wykazywało dodatnią korelację z aktywnością oksydazy ksantynowej w 1. dobie po transplantacji nerki (odpowiednio $R = 0{,}73$; $P < 0{,}001$ i $R = 0{,}77$; $P < 0{,}02$). Stwierdzono ujemną korelację pomiędzy stężeniem HGF w 6. miesiącu i wielkością diurezy w 1. i 7. dobie po przeszczepieniu nerki ($R = -0{,}99$; $P < 0{,}000\,01$ i $R = -0{,}77$; $P < 0{,}05$).

WNIOSKI HGF jest dobrym markerem okołooperacyjnego uszkodzenia przeszczepionej nerki i może wpływać na długoterminową czynność nerki.

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