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URINARY CONNECTIVE TISSUE GROWTH FACTOR LEVEL AS AN EARLY NON-INVASIVE BIOMARKER OF CHRONIC ALLOGRAFT NEPHROPATHY

By

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ABSTRACT

Background: Chronic allograft nephropathy (CAN) is a major cause of renal graft loss. Connective tissue growth factor (CTGF) expression is increased in fibrotic renal diseases including diabetic nephropathy and CAN.

Objective: Assessing urinary CTGF as a non-invasive marker of CAN.

Patients and method: Urinary CTGF was measured in samples collected from all the study candidates which included transplanted patients with normal kidney functions tests and estimated glomerular filtration rate(e GFR) more than 60 ml/minute as a control, transplanted patients with biopsy-proven diagnosis of IF/TA indicating presence of CAN, and e GFR between 30 -59 ml/minute and transplanted patients with biopsy-proven diagnosis of interstitial fibrosis (IF/TA), indicating presence of CAN, and e GFR less than 30 ml/minute. To assess the effect of the native kidneys, hemodialysis patients were recruited and their urine samples were collected and to measure CTGF. To adjust for decreasing GFR and urine output, urinary creatinine was measured in all samples, and CTGF/creatinine ratio was calculated.

Results: The mean urinary CTGFin patients with CAN was significantly higher than the mean level in transplant candidates with normal kidney function.The mean urinary CTGF in patients with CAN and marked graft dysfunction was significantly higher than the mean level in those with milder graft dysfunction. The mean urinary CTGF was found to be significantly higher in patients with history of acute rejection than in those without history of acute rejection. There was a significant positive correlation between urinary CTGF level and both of serum creatinine and duration of transplantation, and a negative correlation between urinary CTGF level and e GFR. The CTGF/creatinine ratio showed similar results.

Conclusion: Urinary CTGF level and CTGF/creatinine ratio could be used as an early non-invasive marker of chronic allograft nephropathy.

Key words: Kidney transplantation, chronic allograft nephropathy, connective tissue growth factor.

INTRODUCTION

The long term survival of the renal allografts has shown little progress over the past 2 decades despite the great improvement of the short-term outcome of kidney transplantation. The two major causes of graft loss are death and chronic allograft nephropathy "CAN" (Nankivell and Chapman, 2006). The term "chronic allograft nephropathy" is a non-specific term that does not carry any information regarding the cause. In Banff classification working group (2009), it was replaced by the term interstitial fibrosis

and tubular atrophy "IFTA" which was used for description of the histological changes in the biopsy (Siset al., 2010).

Both antigen-dependent (immunological) and antigen independent (non-immunological) factors are implicated in the etiology of CAN and, not uncommonly, difficult to pinpoint a single etiological factor as more than one factor is usually implicated in the pathogenesis of CAN (Shrestha and Haylor, 2014).The gold standard of diagnosis and follow up of CAN is histo-pathological evaluation of tissue from renal biopsies. Studies have identified various biomarkers from blood and urine for monitoring graft function after kidney transplantation. (Li and Zhuang, 2014).

Connective tissue growth factor "CTGF", also known as CCN2, is a member of the CCN family of modular matricellular proteins (Lau, 2011). CTGF/CCN2 contains an N-terminal secretory peptide, followed by four multi-functional domains that potentially impact multiple signaling mechanisms. Interactions between CTGFand its binding partners mediate its effects on cell proliferation, survival, differentiation, adhesion, migration, and extracellular matrix "ECM" production (Leask, 2006).

CTGF is expressed in a wide variety of structures at later stages of development during normal wound healing and in various fibrotic diseases. Elevated CTGF expressionis a hallmark of fibrosis (Tyler et al., 2006). CTGF is an immediate early response gene product that is induced by of TGF-β. CTGF mediates many of the fibrogenic activities of TGF-β (Lee et al., 2015).

CTGF is not expressed in normal kidneys but it is upregulated in various human and animal models of kidney fibrosis including diabetic nephropathy(Wang et al., 2015) and chronic allograft nephropathy (Cheng et al., 2006).Uurinary CTGF was positively correlated with serum creatinine, histologic changes of CAN, and CTGF in the kidney tissue after transplantation (Bao et al., 2008).

The aim of the present study was to assess urinary connective tissue growth factor (CTGF) as a non-invasive marker of chronic allograft nephropathy in living donor transplantation.

PATIENTS AND METHODS

Forty five transplanted patients were recruited from different centers in Egypt (Maadi's Armed Forces Hospital, Mokattam Health Insurance Hospital, National Institute of Urology and Nephrology, Al-Safa Kidney Center and Wadi Al-Nil Hospital) during the period between January to August 2015. The study protocol was approved by the Ethics committee of Al-Azhar Faculty of Medicine. Oral consents were taken from the all included candidates. The transplanted patients of the study were assigned to three equal groups; group I: Transplanted patients with normal kidney function tests and e GFR more than 60 ml/minute as a control, group II: Transplanted patients with biopsy-proven diagnosis of IF/TA, indicating presence of CAN, and e GFR between 30 -59 ml/minute, and group III: Transplanted patients with biopsy-proven diagnosis of IF/TA, indicating presence of CAN, and e GFR less than 30 ml/minute.

All the included candidates were transplanted for more than 1 month from living donors, with age ranged between 18 - 60 years, and both genders.

Patients with urinary tract infection, sepsis, vascular or surgical complication within the graft, e.g. lymphocele and urine leak,uncontrolled blood pressure, poor glycemic control,ongoing acute kidney injury, acute rejection, and patients not fitting the target therapeutic drug level of immunosuppression drugs were excluded.

All patients were subjected tofull history and clinical examination, kidney function tests (creatinine was measured and glomerular filtration rate "GFR" was estimated using Modification of Diet in Renal Disease study equation "MDRD" (Levey et al., 2003), liver function tests (AST, ALT), immunosuppression drugs level, electrolytes' level (sodium and potassium), random blood sugar and glycosylated hemoglobin for diabetic patients and abdominal and pelvic ultrasound.

Urinary CTGF was measured in samples collected from all the study candidates using ELISA based kit obtained from *DRG International Inc.*, USA (code: EIA-5295). Urine samples were aseptically collected and stored at – 20 C°. Repeated freezing and thawing was avoided. Creatinine was measured in all samples, and CTGF/creatinine ratio was calculated (to adjust for decreasing GFR and urine output).

Urine samples from 15 hemodialysis patients (with residual urine output; defined by passing more than 250 ml/day of urine) were collected for urinary CTGF, creatinine and CTGF/creatini-neratio measurement.

The aim of this group was to evaluate CTGF excretion attributable to the native kidneys and to compare their values with samples of transplanted patients groups.

Statistical Method: Data were coded and entered using the statistical package SPSS version 15.0.Data were summarized using number and percent for qualitative variable mean and standard deviation for quantitative variable. Comparison between groups were done using Chi Square test for qualitative data, independent sample t test and analysis of variance (ANOVA) for qualitative data which are normally distributed, while non-parametrical Kruskal-Wallis and Mann-Whiteny tests were used for qualitative data which were not normally distributed. Correlations were done to test for linear relations between variables. P values less than or equal to 0.05 were considered to be statistically significant.

RESULTS

There was no significant difference between the three transplant candidate groups regarding the age, gender distribution, type of donor distribution (related versus unrelated), immuno-suppression protocol, and the duration of transplantation (Table 1).

There was a significant difference between the transplant candidates (groups I, II, III) in one hand, and hemodialysis patients, on the other hand regarding the age and gender distribution (Table 2).

Table (1): Comparison of basic characteristics of candidates in different transplant groups of the study**.**

Variables \ Groups		Group I	Group II	Group III	p
Age (years)	Mean	38.67	37	36	> 0.05
	SD	11.19	10.54	15.13	
Gender	Males	14(93.3 %)	10(66.7%)	13(86.7%)	> 0.05
	Females	1(6.7%)	5(33.3%)	2(13.3%)	
Type of donor	R	5 (33%)	6 (40 %)	3 (20 %)	> 0.05
	U	10 (66.7 %)	9 (60 %)	12 (80 %)	
Immuno-suppression	CsA/MPA/St	7 (46.7 %)	5(33.3 %)	8 (53.3 %)	> 0.05
	Ever/MPA/St	1 (6.7)	3 (20 %)	1 (6.7%)	
	Tac/Aza/St	0 (0 %)	1 (6.7 %)	0 (0 %)	
	Tac/MPA/St	7 (46.7 %)	6 (40 %)	6 (40 %)	
Duration of Tx (months)	Mean	45	81	75.73	> 0.05
	SD	46.17	86.5	60.98	

Abbriviations: SD: Standard deviation; CsA: Cyclosporin A; MPA: Mycophenolic acid derivatives; Tac: Tacrolimus; Aza: Azathioprine; Ever.:Everolimus; R: related; U: unrelated donor. Tx: transplantation; St: steroids.

Table (2): Comparison of basic characteristics between transplant candidates and hemodialysis patients in the study.

Variables \ Groups		Transplantion (Groups I, II, III)	Hemodialysis	p
Age (years)	Mean	37.56	50.67	< 0.0015
	SD	12.2	15.97	
Gender	Males	37 (82.2%)	4 (26.7 %)	< 0.0001
	Females	8 (17.8%)	11 (73.3 %)	

Original diseases of transplant candidates were diabetes mellitus (2- 4.4%), hypertension (8 -17.8%), focal segmental glomerulosclerosis (2 - 4.4%),

chronic pyelonephritis (1- 2.2 %), Alport syndrome (1-2.2 %), vesico-ureteric reflux (2 - 4.4 %) and undefined cause in the rest of cases were(29 - 64.4 %).

Urinary CTGF level and CTGF /creatinine ratio weresignificantly higher in CAN patients (groups II and III collectively) than in transplant candidates with normal graft functions (group I). They werealso significantly higher in CAN patients with GFR ≤ 30ml/min (group III) than in those with GFR 31 - 60ml/min (group II).They were alsohigher in hemodialysis patients than in transplant candidates (group I, II, III collectively) (Table 3).

Table (3): Urinary CTGF and CTGF /creatinine ratioamong different study groups.

Values / Groups	CTGF		CTGF /creatinine		*p*
	Mean	SD	Mean	SD	
Group I	20.88	22.52	11.41	15.34	<0.05
Group II	34.04	32.34	21.67	25.78	
Group III	66.72	21.92	42.45	25.55	
Hemodialysis	72.87	11.65	148.2	83.12	
Transplant candidates (groups I,II,III)	40.55	32.05	25.18	25.78	
CAN patients (groups II,III)	50	31.83	32	27.34	

N.B. Comparison between groups were done using non-parametrical Kruskal-Wallis and Mann-Whitenytests.

The mean urinary CTGF and CTGF/ creatinine ratios were significantly higher in candidates with history of acute rejection compared to those without. Otherwise, there was no association between either of them and any of the other variables tested i.e. gender, presence of diabetes, hypertension, any of the used immunosuppression protocols or the type of donor (Table 4).

Table (4): Urinary CTGF levels and CTGF/ creatinine ratios against different candidates' variables.

Variables / Levels		Gender		Diabetes		HTN		History of AR		Type of donor	
		M	F	+	-	+	-	+	-	R	U
CTGF	**Mean**	40.88	38.96	58.9	37.16	41.29	36.47	61.24	27.98	36.6	42.31
	SD	31.75	35.59	26	32.19	31.67	36.37	24.17	29.9	31.12	32.81
CTGF/cr	**Mean**	23.6	32.43	32.11	23.89	24.98	26.24	37.49	17.69	19.98	27.51
	SD	25.69	26.63	27.47	25.63	25.38	29.79	22.22	25.23	22.05	27.30
P		> 0.05		> 0.05		> 0.05		< 0.05		> 0.05	

Abbreviations: M: male, F: female, R: related donor, LU: unrelated donor, AR: acute rejection, (+): present, (-): absent. Values of CTGF were expressed in ng/ml, and of CTGF/creatinine level in ng/mg creatinine.

Intransplant candidate groups (I, I, III), there was a statistically significant positive correlation between urinary CTGF levels and urinary CTGF/creatinine ratios (correlation coefficient 0.806) (Figure 1).

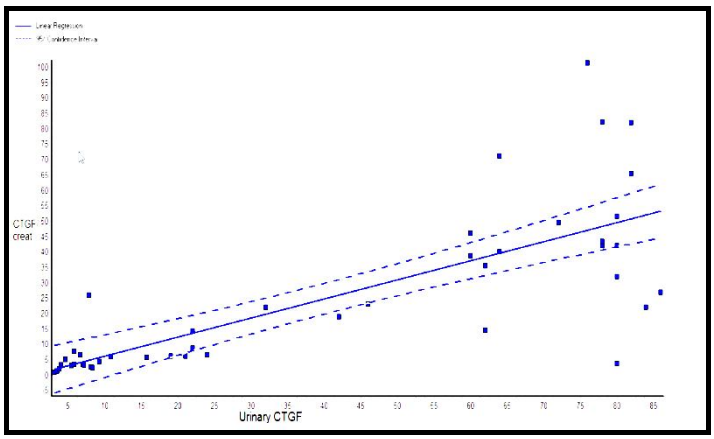

Figure (1): Linear regression curve represents the correlation between urinary CTGF (in ng/ml) to urinary CTGF/ creatinine ratio.

There was a statistically significant positive correlation between both of urinary CTGF levels and urinary CTGF/creatinine ratios, in one hand, and serum creatinine on the other hand (correlation coefficient 0.591 and 0.490 respectively) (Figure 2).

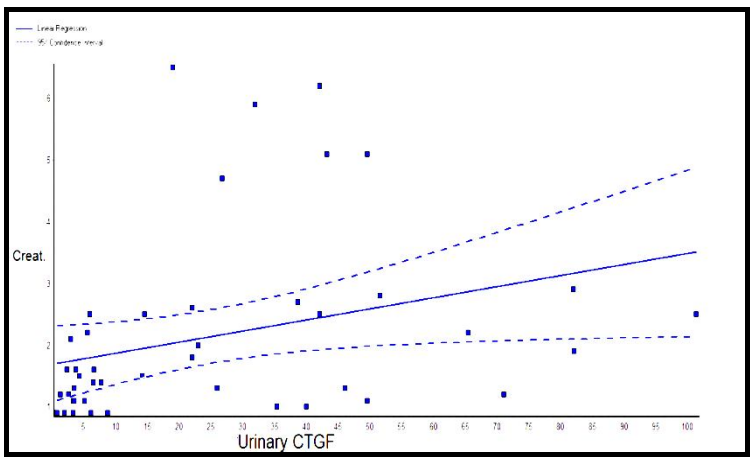

Figure (2): Linear regression curve represents the correlation between urinary CTGF (in ng/ml) to serum creatinine (in mg/dl).

There was a statistically significant negative correlation between both of urinary CTGF levels and urinary CTGF/creatinine ratios in one hand, and e GFR on the other hand (correlation coefficient -0.596 and -0.546 respectively) (Figure 3).

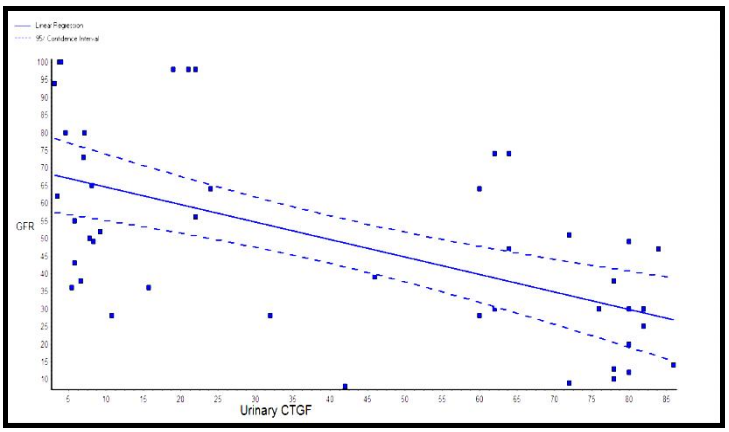

Figure (3): Linear regression curve represents the correlation between urinary CTGF (in ng/ml) to estimated GFR (in ml/min).

There was a statistically significant positive correlation between both of urinary CTGF levels and urinary CTGF/creatinine ratios in one hand, and duration of transplantation on the other hand (correlation coefficient 0.312 and 0.392 respectively) (Figure 4).

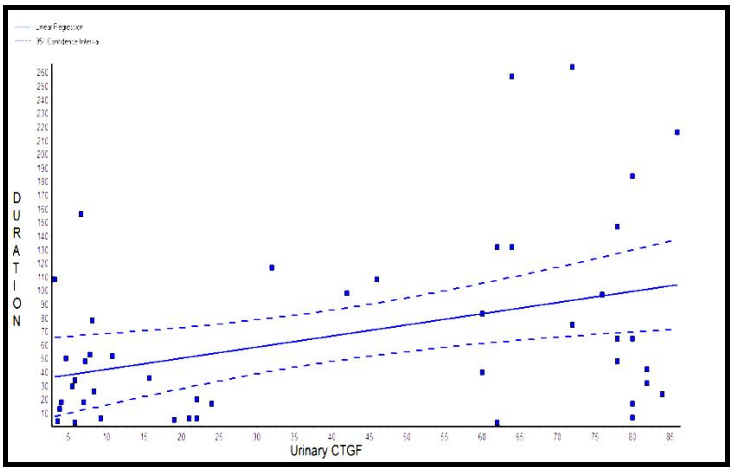

Figure (4): Linear regression curve represents the correlation between urinary CTGF (in ng/ml) to duration of transplantation (in months).

There was a statistically significant negative correlation between both of urinary CTGF levels and urinary CTGF/creatinine ratios in one hand, and hemoglobin level on the other hand (correlation coefficient -0.392 and -0.416 respectively) (Figure 5).

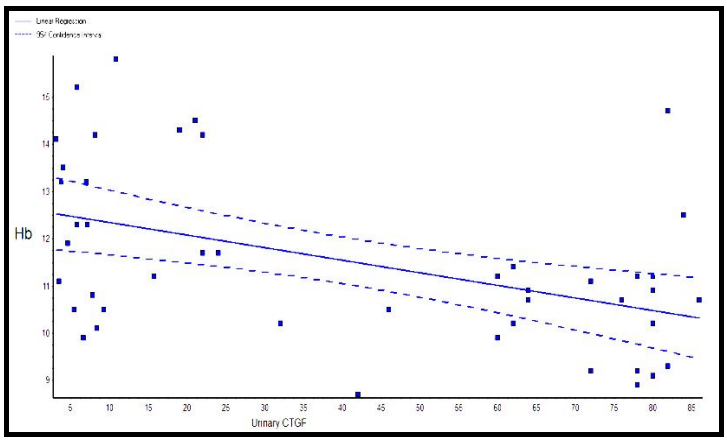

Figure (5): Linear regression curve represents the correlation between urinary CTGF (in ng/ml) to hemoglobin level (in g/dl).

There was no statistically significant correlation between any of urinary CTGF levels and urinary CTGF/creatinine ratios in one hand, and any other variable on the other hand (i.e. age, weight, Na, K, ALT). Also, there is no significant correlation between urinary CTGF and urinary creatinine levels.

In hemodialysis group, there was a statistically significant positive correlation between urinary CTGF levels and urinary CTGF/creatinine ratios (correlation coefficient 0.607) (Figure 6).

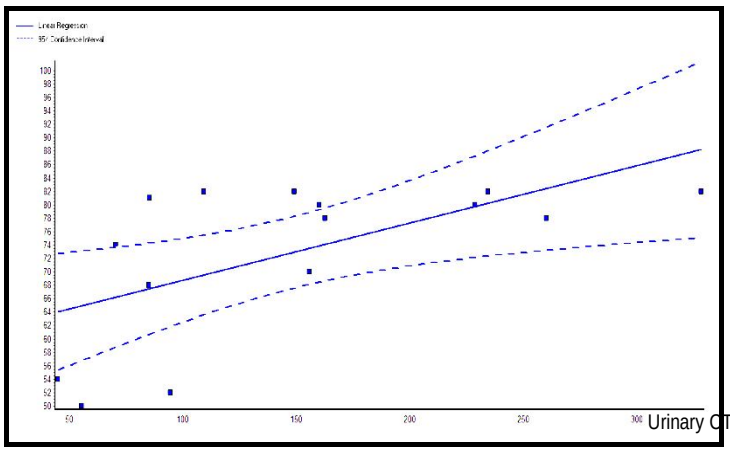

Figure (6): Linear regression curve represents the correlation between urinary CTGF and CTGF/ creatinine ratio in hemodialysis patients group.

There was a statistically significant negative correlation between urinary CTGF/creatinine ratio and urinary creatinine level (correlation coefficient -0.88) (Figure 7).

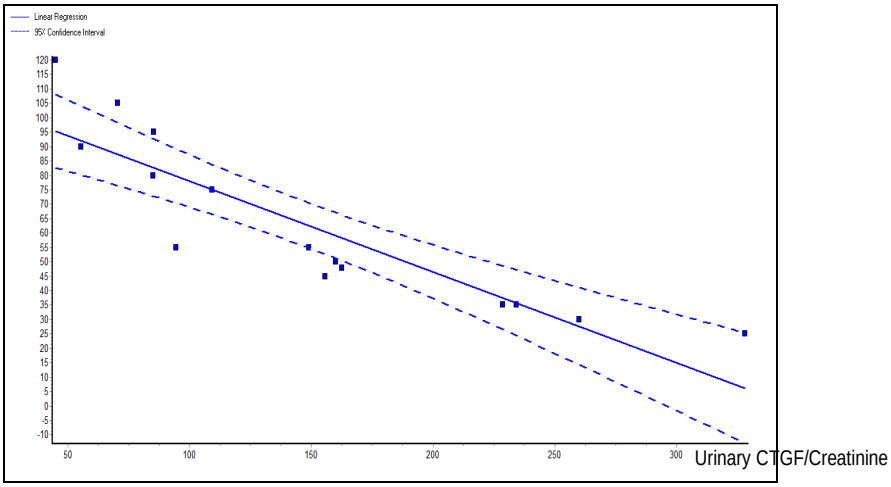

Figure (7): Linear regressioncurve represents the correlation between urinary CTGF/creatinine ratio (in ng/mg creatinine) and urinary creatinine (in mg/dl) in hemodialysis patients' group.

There was no statistically significant correlation between any of urinary CTGF levels and urinary CTGF/creatinine ratios in one hand, and any other variable on the other hand (i.e. age or duration of diaysis). Also, there was no significant correlation between urinary CTGF and urinary creatinine levels.

DISCUSSION

Chronic allograft nephropathy "CAN" is a major cause of graft loss beside death. CTGF is upregulated in the transplanted kidney with CAN and the level of expression correlates with the severity of histo-pathologic features of CAN.

In the current study,urinary CTGF was assessed as a non-invasive marker of CAN. It was found that the mean urinary CTGF and mean urinary CTGF/creatinine ratio in patient with CAN were significantly higher than the mean levels in transplant candidates with normal kidney function. These results were in concordance with the results obtained by Cheng et al. (2006) who found that urinary CTGF levels (represented as CTGF/creatinine ratio) were the highest in patients with biopsies demonstrating features of CAN compared to patients without rejection and patients with acute rejection. The difference between means of urinary CTGF in the two studies may be attributed to the fact that patients in the current study received grafts from living donors, while the study of Cheng et al. (2006) was conducted in deceased-donor transplant patients with more risk of ischemia-reperfusion injury.

In the present study, it was also found that mean urinary CTGF and urinary CTGF/creatinine ratio were significantly higher in patients with CAN and marked graft dysfunction than in those with milder graft dysfunction. It was also found that there was a significant positive correlation of urinary CTGF levels and urinary CTGF/creatinine ratios with serum creatinine. Also, there was a significant negative correlation of urinary CTGF levels and urinary CTGF/creatinine ratios

with e GFR. These findings agreed with results of Shiet al. (2009) who found that urinary CTGF concentration was positively correlated with serum creatinine and degree of interstitial fibrosis.

In the present study, the mean urinary CTGF and urinary CTGF/creatinine ratio were found to be significantly higher in patients with history of acute rejection than in those without history of acute rejection. These results went in agreement with the results of Cheng et al.(2006) who found that urinary CTGF levels were higher in patients with acute rejection compared to patients without rejection.

There was a significant positive correlation of urinary CTGF levels and urinary CTGF/creatinine ratios with the duration of transplantation. This may indicate that use of either of the markers as a predictor of CAN may need time adjustment.These results went in agreement with those of Bao et al. (2008)who had found a time-dependent elevation of concentration of urinary CTGF in the kidney tissue after transplantation.

In the present study, there was a significant negative correlation of urinary CTGF levels and urinary CTGF/creatinine ratios with hemoglobin level. There was also a significant negative correlation between urinary CTGF/creatinine ratio and urinary creatinine level. This could be explained by that CTGF excretion increased as the renal fibrosis and graft dysfunction progress which, in turn, associated with decreasing creatinine excretion and hemoglobin level.

The mean urinary CTGF and urinary CTGF/creatinine ratio in hemodialysis patients were significantly higher than in transplant candidates with normal graft function. This might nullify the effect of native kidneys on urinary CTGF excretion. These results agreed with those of Gerritsen et al.(2012) who observed that, in patients with end-stage kidney disease, plasma CTGF level correlated negatively and independently with residual kidney function. Successful kidney transplant resulted in a decrease in plasma CTGF level proportional to the increase in estimated GFR.They also found in pharmacokinetic studies in nonuremic rodents that renal clearance is the major elimination route of N-CTGF. This explains the marked elevation of urinary CTGF level in hemodialysis patients compared to transplant patients.

There wasa significant positive correlation between urinary CTGF levels and urinary CTGF/creatinine ratios in transplant candidates as well as in hemodialysis patients. This might indicate that urinary CTGF and urinary CTGF/creatinine ratio can be used inter-changeably.

CTGF is not expressed in normal kidneys but it is up-regulated in kidneys of human renal disease. Furthermore, the level of expression correlates with the severity of renal fibrosis (Yokoi et al., 2008). CTGF is an immediate early response gene product that is induced by of TGF-β. Once TGF-β1 has been activated (by a multiple immune and non-immune stimuli), an activation of multiple signaling pathways occurs leading to activation of molecules involved in matrix accumulation and fibrosis including CTGF. CTGF, in turn, mediates many of the fibrogenic activities of TGF-β (Tyler et al., 2006).

Yueet al. (2010) had found that the expression of CTGF in the graft, ofa rat model of CAN,markedly elevated compared with the control group.The urinarylevels correlated positively with the histological presence of CAN. They concluded that, urine CTGFconcentrations reflected the course of CAN.

The results of the current study supported the suggestion of use of CTGF as an early marker of CAN. This agreed with the suggestion of Bao et al. (2008) who suggested that urinary CTGF is apotential noninvasive strategy to predict the early onset of CAN.

Urinary CTGF measurement has the advantage of being simple, non-invasive, repeatable, non-coasty and non-operator dependent.This would offer an early, non-invasive trigger to modify immuno-suppression and enable monitoring of therapeutic intervention (i.e. drug minimization or withdrawal).

CONCLUSION

Urinary CTGF level and CTGF/ creatinine ratio could be used as early non-invasive markers of chronic allograft nephropathy.

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قياس عامل نمو النسيج الضام في البول كمؤشر مبكر لحدوث اعتلال الكلى المزروعة المزمن

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خلفية البحث : يعد الإعتلال المزمن للكلى المزروعة من أهم أسباب فقد الكلى المزروعة.

ولقد تم إكتشاف زيادة تمثيل عامل النمو للنسيج الضام في العديد من أمراض الكلى مثل مرض الكلى السكرية وإعتلال الكلى المزروعة المزمن.

الهدف من البحث : دراسة نسبة اخراج عامل النمو للنسيج الضام في البول للمرضى المصابين بإعتلال الكلى المزروعة المزمن مما يمكن من إستخدامه كمؤشر مبكر لحدوث إعتلال الكلى المزروعة المزمن.

المرضى و طرق البحث: تم قياس نسبة عامل النمو للنسيج الضام في البول في ثلاث مجموعات من مرضى زرع الكلى. المجموعة الأولى تضم مستقبلين لكلى مزروعة ذات وظائف سليمة ومعدل إستخلاص كبيبي طبيعي، والمجموعة الثانية تضم مستقبلي كلى مزروعة لديهم إعتلال مزمن بهذه الكلى ومعدل إستخلاص كبيبي يتراوح بين ٣٠ -٥٩ مللي لتر/دقيقة، والمجموعة الثالثة تضم مستقبلي كلى مزروعة لديهم إعتلال مزمن بتلك الكلى ومعدل إستخلاص كبيبي أقل من ٣٠ مللي لتر/دقيقة. وتم قياس نسبة عامل النمو للنسيج الضام في بول مرضى فشل كلوي مزمن يعالجون بالغسيل الدموي لإستبعاد تأثير الكلى الأصلية على النتائج، كما تم قياس نسبة كرياتنين في البول لجميع المرضى و حساب نسبة عامل النمو للنسيج الضام/كرياتنين لتفادي تأثير معدلات الإستخلاص الكبيبي المختلفة على النتائج.

النتائج: وجد أن متوسط نسبة عامل النمو للنسيج الضام وعامل النمو للنسيج الضام/كرياتنين في البول أعلى في مرضى الإعتلال المزمن في الكلى المزروعة عن مستقبلي زراعة الكلى ذوي الوظائف الطبيعية للكلى و أن متوسط نسبتيهما أعلى في مرضى الإعتلال المزمن في الكلى المزروعة ذوي القصور الكلوي الأشد مقارنة بذوي القصور الأقل شدة. كما وجد أن متوسط نسبة عامل النمو للنسيج

الضـام وعامل النمو للنسيج الضـام/كرياتنين فـي البـول أعلـى فـي مرضـى الغسيل الـدموي عنهمـا فـي مستقبلي زراعة الكلى، ووجد أيضا إنهما أعلى في مستقبلي زرع الكلى ذوي التاريخ المرضـي لحدوث لفظ حاد مقارنة بالذين ليس لديهم تاريخ لفظ حاد، وقد وجد إرتباطاً طردياً بين متوسط نسبة عامل النمو للنسيج الضام وعامل النمو للنسيج الضام/كرياتنين في البول من ناحية مع مستوى الكرياتنين من ناحية أخرى، وإرتباط عكسي بينهما وبين معدل الاستخلاص الكبيبي في مستقبلي زراعة الكلى بالدراسة، كـذلك وجـد إرتباطـاً طرديـاً بـين متوسـط نسـبة عامـل النمـو للنسـيج الضـام وعامـل النمـو للنسـيج الضام/كرياتنين في البول من ناحية ومدة زرع الكلى.

الاستنتاج: يمكن إستخدام نسبة عامل النمو للنسيج الضـام وعامل النمو للنسيج الضـام/كرياتنين فـي البول كمؤشر مبكر لحدوث الإعتلال المزمن للكلى المزروعة.