Plasma connective tissue growth factor is an independent predictor of end-stage renal disease and mortality in type 1 diabetic nephropathy

Tri Q. Nguyen, MD1, Lise Tarnow, MD, DMSC2, Anders Jorsal2, Noelynn Oliver, PHD3, Peggy Roestenberg, PHD1,7, Yasuhiko Ito, MD4, Hans-Henrik Parving, MD, DMSC5,6, Peter Rossing, MD, DMSC2, Frans A. van Nieuwenhoven, PHD1,8, and Roel Goldschmeding, MD, PHD1

1Pathology, University Medical Center Utrecht, Utrecht, Netherlands, 2Steno Diabetes Center, Gentofte, Denmark, 3FibroGen, Inc, South San Francisco, CA, USA, 4Nephrology, Nagoya University School of Medicine, Nagoya, Japan, 5Endocrinology, Rigshospitalet, Copenhagen, Denmark, and 6Faculty of Health Science, Aarhus University, Aarhus, Denmark.
Current address: 7Biochemistry, Radboud University Nijmegen Medical Center, Netherlands, and 8Physiology, CARIM, Maastricht University, Netherlands.

Corresponding Author:
R. Goldschmeding MD, PhD
UMC Utrecht, Department of Pathology
Heidelberglaan 100
3584 CX, Utrecht, Netherlands
R.Goldschmeding@umcutrecht.nl

Received for publication 31 December 2007 and accepted in revised form 07 March 2008
Objective: We evaluated the predictive value of baseline plasma connective tissue growth factor (CTGF; CCN-2) in a prospective study of patients with type 1 diabetes.

Research Design and Methods: Subjects were 198 type 1 diabetic patients with established diabetic nephropathy and 188 type 1 diabetic patients with persistent normoalbuminuria. Follow-up time was 12.8 years. Prediction of end-stage renal disease (ESRD) and mortality by plasma CTGF was analyzed in conjunction with conventional risk factors.

Results: Plasma CTGF was higher in patients with nephropathy than in patients with normoalbuminurina (median 381 pmol/l [interquartile range 270-630] vs. 235 [168-353]). In patients with nephropathy, elevated plasma CTGF was an independent predictor of ESRD (covariate-adjusted hazard ratio 1.6 [95% CI 1.1-2.5]), and correlated with the rate of decline in GFR (cumulative R=0.46). Area under the ROC curve for prediction of ESRD was 0.72. Plasma CTGF above a cutoff level of 413 pmol/l predicted ESRD with a sensitivity of 73% and a specificity of 63%, and was associated with a higher rate of decline in GFR (5.4±4.9 ml/min/1.73 m²/year vs. 3.3±3.5). Moreover, in patients with nephrotic range albuminuria (>3 g/day), plasma CTGF was the only predictor of ESRD (covariate-adjusted hazard ratio 4.5 [2.0-10.4]). Plasma CTGF was an independent predictor also of overall mortality (covariate-adjusted hazard ratio 1.4 [1.1-1.7]). In contrast, in normoalbuminuric patients, plasma CTGF did not correlate with clinical parameters and did not predict outcome.

Conclusions: Plasma CTGF contributes significantly to prediction of ESRD and mortality in patients with type 1 diabetic nephropathy.
Diabetic nephropathy is the most important cause of end-stage renal disease (ESRD) and contributes importantly to mortality, mainly through increase of cardiovascular disease (1). However, the course of diabetic nephropathy remains unpredictable and the pathogenesis of progression is not completely understood.

Connective tissue growth factor (CTGF; CCN-2) was first identified in conditioned media of endothelial cells as a 36-38 kDa polypeptide containing chemotactic activity towards fibroblasts (2). CTGF has been acknowledged as a key factor in extracellular matrix production and other profibrotic activity mediated by transforming growth factor-β (3). Other biological functions of CTGF include angiogenesis, chondrogenesis, osteogenesis, and cell adhesion, migration, proliferation and differentiation (4).

Recently, CTGF has emerged as an important factor in diabetic nephropathy. In renal cells, CTGF is induced by high glucose, and it is critically involved in diabetes-associated changes like extracellular matrix synthesis, cell migration, and epithelial-to-mesenchymal transition (5-8). Furthermore, upregulation of CTGF has been observed in human and experimental diabetic nephropathy (6,9-12), while structure and function of the kidney is largely preserved in diabetic mice with hemizygous CTGF deletion, and in diabetic mice treated with CTGF antibody, or CTGF antisense oligonucleotides (13-15).

CTGF is a secreted protein and can be detected in biological fluids. Previous small studies have reported that both urinary CTGF excretion and plasma CTGF levels are elevated in patients with diabetic nephropathy (16-19). Recently, we have shown in a large cross-sectional study of patients with type 1 diabetes that urinary CTGF excretion is associated with urinary albumin excretion (UAE) and inversely with glomerular filtration rate (GFR), both important clinical markers for severity of renal disease (20). In aggregate, these data suggest that CTGF might be a useful marker of renal deterioration in patients with diabetic nephropathy.

Since all previous clinical studies addressing CTGF as a biomarker were performed in cross-sectional designs, the possible prognostic value of CTGF levels in diabetic nephropathy still has remained elusive. Therefore, we set out to evaluate whether plasma CTGF might predict loss of GFR, ESRD, and mortality in a prospective study of 386 type 1 diabetic patients with and without diabetic nephropathy, during a follow-up period of 12.8 years.

**RESEARCH DESIGN AND METHODS**

**Subjects:** Patients with type 1 diabetic nephropathy attending the outpatient clinic of Steno Diabetes Center in 1993 were invited to participate in a case-control study (21,22). Type 1 diabetes was considered present if the age at onset of diabetes was ≤35 years and time to definite insulin therapy ≤1 year. Patients were categorized as having diabetic nephropathy if they had persistent albuminuria (>300 mg/day) in at least two of three consecutive 24-h urine collections, diabetic retinopathy, and no other kidney or renal tract disease (23). Patients with equally long-lasting type 1 diabetes (>15 years) and persistent normoalbuminuria (<30 mg/day), who were matched for sex, age, and duration of diabetes, served as controls. Thus, 198 patients with nephropathy and 188 patients with normoalbuminuria were included in the study. The study was approved by the local ethics committee, in accordance with the Helsinki Declaration, and all patients gave their informed written consent.

Investigations were performed in the morning after an overnight fast. Blood pressure was measured twice following at least 10 min rest in the supine position. UAE was measured by an enzyme immunoassay from 24-h urine collections. Plasma creatinine was assessed by a kinetic Jaffé method. GFR was measured after a
single intravenous injection of $^{51}$Cr-EDTA (3.7 MBq) by following the plasma clearance of the tracer for 4 hrs (24). Linear regression of yearly GFR measurements in each individual was used to estimate rate of decline in GFR. In normoalbuminuric patients, GFR was estimated by the Modification of Diet in Renal Disease equation (25).

Diabetic retinopathy was assessed by fundus photography and graded as nil, simplex or proliferative retinopathy. Patients were interviewed using the WHO cardiovascular questionnaire. Major cardiovascular events were diagnosed as a history of stroke and/or myocardial infarction. Smoking was defined as smoking one or more cigarettes/cigars/ pipes a day. In a prospective observational study design, patients were followed up until 1 November 2006 or until death (n=99) or emigration (n=3). If a patient had died, the date of death was recorded and the cause of death was obtained from the death certificate. Additional available information from necropsy reports was included. All deaths were classified as cardiovascular deaths unless an unequivocal non-cardiovascular cause was established. Information about the date of ESRD was obtained from patient records or discharge letters from other hospitals. ESRD was defined as the need for dialysis or renal transplantation.

**ELISA for plasma CTGF:** CTGF was measured in plasma samples drawn at study entry that had been stored at -80°C at the Steno Diabetes Center. Storage time and freeze-thaw cycles of all samples were identical. CTGF was determined by a sandwich ELISA using monoclonal antibodies against two distinct epitopes on the N-terminal part of human CTGF (FibroGen, South San Francisco, CA), as described previously (18,20).

**Statistical Analysis:** Normally distributed variables are expressed as means±SD. UAE, plasma creatinine, and plasma CTGF were logarithmically transformed before analysis and are expressed as medians (interquartile range).

Comparisons between groups were performed by unpaired Student’s t test or Mann-Whitney test. Multiple logistic regression analysis was used to identify the contribution of parameters to risk of diabetic nephropathy. Pearson and Spearman correlations and forward stepwise regression analysis were used to identify parameters that correlated with rate of decline in GFR. All time-to-event variables were analyzed using log rank test and displayed on Kaplan-Meier plots according to levels being above or below cutoff value, as determined by receiver operating characteristic (ROC) curve. The cutoff value with the most discriminative value was defined as the point of the ROC curve closest to the left upper corner ($d = \sqrt{[(1\text{-spec})^2 + (1\text{-sens})^2]}$).

Cox proportional hazard regression models with forward selection were used to evaluate the contribution of baseline covariates to ESRD and overall mortality. For this, continuous variables were standardized for one standard deviation (1-SD) difference. In the Cox regression model for ESRD, baseline covariates that were associated with rate of decline in GFR (P<0.1) were entered into the model. These covariates were plasma CTGF, sex, duration of diabetes, UAE, GFR, and systolic blood pressure. In the Cox regression models for cardiovascular and overall mortality, the following pre-specified baseline covariates were entered into the model: plasma CTGF, sex, age, smoking, UAE, GFR, HbA1c, history of cardiovascular event, and systolic blood pressure. Results are given as hazard ratios with 95% confidence intervals.

In all cases, P<0.05 was considered significant (two-tailed). All calculations were performed using SPSS (version 12.0).

**RESULTS**

**Plasma CTGF is increased in patients with diabetic nephropathy:** General characteristics and baseline parameters of patients are summarized in Table 1. Plasma CTGF was higher in patients with diabetic nephropathy than in patients with normoalbuminuria (381 [270-630] pmol/l
Plasma CTGF predicts ESRD and mortality

vs. 235 [168-353], P<0.001). In patients with nephropathy, plasma CTGF correlated with UAE (R=0.16, P=0.02), and inversely with GFR (R=-0.58, P<0.001) (Figure 1A and B). In these patients, plasma CTGF was higher in those receiving antihypertensive medication (n=151), as compared to those without antihypertensive medication (n=47) (588 [289-697] pmol/l vs. 333 [197-422], P=0.01), but this difference disappeared after adjustment for GFR. In patients with normoalbuminuria, plasma CTGF did not correlate with any of the clinical parameters.

**Plasma CTGF contributes to risk of diabetic nephropathy:** After adjustment for duration of diabetes, BMI, systolic blood pressure, HbA1c, and GFR, a standardized increase of plasma CTGF resulted in 2.0-fold increased chance of diabetic nephropathy (odds ratio 2.0, [95% CI 1.5-2.8]). This was comparable with the odds ratios for diabetic nephropathy of increased HbA1c (2.2 [1.6-2.9]) and systolic blood pressure (1.7 [1.5-2.9]) after adjustment for duration of diabetes, GFR, plasma CTGF, and systolic blood pressure or HbA1c, respectively.

**Baseline plasma CTGF correlates with rate of decline in GFR:** In patients with nephropathy, the mean rate of decline in GFR was 4.3 ml/min/1.73 m^2 per year. With rate of decline in GFR as a dependent variable, UAE was identified as the regression parameter with the strongest correlation (R=0.43, P<0.001). Applying significance cutoff at P<0.05, baseline plasma CTGF was the next and only parameter significantly contributing to increase of this correlation, resulting in a cumulative R of 0.46 (P=0.001). Addition of other parameters did not significantly increase correlation with rate of decline in GFR. In particular, the effect of plasma CTGF concentration on this regression was independent of baseline GFR.

Similarly, in separate analysis of KDOQI subgroups for chronic kidney disease, patients with plasma CTGF above median of their particular subgroup tended to have higher rate of decline in GFR, but this trend did not reach statistical significance (Figure 1C). Also within subgroups stratified for UAE, a similar trend was observed of higher rate of decline in GFR in patients with higher plasma CTGF levels (Figure 1D).

**Baseline plasma CTGF predicts ESRD in diabetic nephropathy:** At baseline, 6 of 198 patients with diabetic nephropathy had already developed ESRD. These patients were excluded from further prospective analyses. Area under the ROC curve for prediction of ESRD by plasma CTGF was 0.72, for UAE 0.73, and for systolic blood pressure 0.68. The optimal cutoff value for plasma CTGF (413 pmol/l) predicted ESRD with a sensitivity of 73% and a specificity of 63% (Figure 1E).

During follow-up, 40 of 192 patients with nephropathy and none of the patients without nephropathy developed ESRD. Within the nephropathy group, development of ESRD occurred in a larger proportion of patients with plasma CTGF above 413 pmol/l (P<0.001, Figure 1F). The rate of decline in GFR was higher in these patients than in those with plasma CTGF below 413 pmol/l (5.4±4.9 ml/min/1.73 m^2/year vs. 3.3±3.5, P<0.001, Figure 1G).

In all patients with diabetic nephropathy, the covariate-adjusted hazard ratio of plasma CTGF for ESRD was 1.6 (1.1-2.5, P=0.03). In patients with nephrotic range albuminuria (>3 g/day), 17 of 32 patients developed ESRD, consistent with previous studies in type 1 and type 2 diabetes (26,27). In this subgroup, plasma CTGF was the only independent predictor of ESRD, with a covariate-adjusted hazard ratio of 4.5 (2.0-10.4, P<0.001) (Table 2). In patients with non-nephrotic range albuminuria, the only independent predictor of ESRD was GFR (data not shown).

**Baseline plasma CTGF predicts mortality in diabetic nephropathy:** Mortality in patients with nephropathy was 40%, of which 54% was due to cardiovascular mortality. In patients with diabetic nephropathy, area under the ROC curve for prediction of both overall mortality and
cardiovascular mortality by plasma CTGF was 0.66. A cutoff value for plasma CTGF of 413 pmol/l predicted overall mortality with optimal sensitivity and specificity (59% and 63%, respectively). A cutoff value for plasma CTGF of 419 pmol/l predicted cardiovascular mortality with optimal sensitivity and specificity (67% and 61%, respectively). Both cardiovascular mortality and overall mortality were higher in patients with plasma CTGF above either of these cutoff values (P<0.001, overall mortality shown in Figure 1H).

Significant independent baseline predictors of overall mortality in patients with nephropathy were sex, plasma CTGF, HbA1c, systolic blood pressure, and age. The covariate-adjusted hazard ratio of plasma CTGF for prediction of overall mortality was 1.4 (1.1-1.7, P=0.005) (Table 3). In the subpopulation of nephrotic range albuminuric patients, this hazard ratio was 2.3 (1.2-4.4, P=0.01). As for cardiovascular mortality, this was predicted independently by history of major cardiovascular event, systolic blood pressure, and GFR, but not by plasma CTGF.

In normoalbuminuric patients, overall mortality was 11%, of which 42% was due to cardiovascular mortality. Although plasma CTGF at baseline was higher in normoalbuminuric patients who died during follow-up as compared to those who were still in study (274 [202-392] pmol/l vs. 230 [164-343], P=0.034), plasma CTGF was an independent predictor of neither overall mortality, nor cardiovascular mortality in patients with normoalbuminuria.

CONCLUSIONS
The major findings in this study are that plasma CTGF level correlates with rate of decline in GFR, and that it is an independent predictor of both ESRD and mortality in patients with type 1 diabetic nephropathy.

Baseline plasma CTGF was higher in patients with diabetic nephropathy than in patients with normoalbuminuria. This is in accordance with our previous observations in a smaller study, in which plasma CTGF levels were increased in 10 patients with diabetic nephropathy (18). Although the correlations between plasma CTGF and UAE (R=0.16) and between plasma CTGF and GFR (R=-0.58) are relatively weak, the association of diabetic nephropathy with plasma CTGF is of similar strength as its association with the established risk factors HbA1c and systolic blood pressure. Of interest, the odds ratio for diabetic nephropathy of elevated plasma CTGF is of comparable magnitude as that of increased urinary CTGF excretion observed in a previous study (OR=2.0 and 2.3, respectively) (20). However, because urine and plasma samples have not been available from the same patients thus far, the relation between CTGF levels in plasma and urine remains to be determined in future studies.

In normoalbuminuric patients, renal function remained well preserved, and progression to ESRD was not observed during the follow-up period. However, in patients with diabetic nephropathy, renal function deteriorated progressively, and 21% developed ESRD. Consistent with previous reports, rate of decline in patients with overt diabetic nephropathy was most strongly associated with UAE (R=0.43) (28,29). Of interest, addition of plasma CTGF increased this correlation to a cumulative R of 0.46, while no such increase was observed with addition of any other baseline parameter, including baseline GFR. Accordingly, patients with high plasma CTGF levels had a steeper slope of decline in GFR than those with low plasma CTGF (cutoff 413 pmol/l).

Baseline plasma CTGF was identified as an independent parameter, but its association with decline in renal function was much stronger in patients with severe, than in those with mild proteinuria. Separate analysis of patients with nephrotic range albuminuria revealed that plasma CTGF was the only independent predictor of ESRD, while difference even in GFR or UAE no longer predicted outcome in this subgroup. On the other hand, despite
Plasma CTGF predicts ESRD and mortality

overlapping plasma CTGF levels, no such correlation or predictive value was found in patients with normoalbuminuria. It thus appears that plasma CTGF has unique potential as a prognostic biomarker of renal function decline, especially in diabetic patients with severe proteinuria.

Previously, we have observed that urinary CTGF excretion is elevated only in macroalbuminuric, and not in microalbuminuric and normoalbuminuric patients (20). Together with the well established profibrotic effects of CTGF on tubular epithelial cells (8,30), these observations suggest that progressive loss of renal function might relate to excess plasma CTGF leaking into the urine in patients with severe proteinuria. It would be interesting to study if levels of CTGF in unselected normoalbuminuric or microalbuminuric patients could identify subjects at high risk for progression of albuminuria, but this could not be investigated in the present study as the normoalbuminuric control group was selected for having long diabetes duration, and thus low risk of progression of albuminuria. A microalbuminuric group was not available for this study.

In summary, addition of plasma CTGF to conventional risk factor assessment significantly improves prediction of ESRD and mortality in patients with overt type 1 diabetic nephropathy. Its unique predictive value for disease progression in patients with diabetic nephropathy, in particular those with heavy proteinuria, suggests that plasma CTGF might find clinical application as a biomarker. In addition, our findings lend further support to the notion that CTGF is an important pathogenic factor in progression of human diabetic nephropathy, consistent with previous observations in preclinical models.

ACKNOWLEDGMENTS
This study was supported by the Dutch Kidney Foundation (C05.2144) and the Netherlands Organization for Scientific Research (017.003.037). We thank Lotte Wieten for technical assistance and Jack Wetzels for helpful discussions. Part of this work was presented at Renal Week 2007 in San Francisco.
REFERENCES


Table 1. Baseline parameters of 386 type 1 diabetic patients with and without diabetic nephropathy

<table>
<thead>
<tr>
<th></th>
<th>Nephropathy</th>
<th>Normoalbuminuria</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General patient characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (% men)</td>
<td>198 (62%)</td>
<td>188 (61%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Age (years)</td>
<td>41.0 ± 9.5</td>
<td>42.5 ± 9.9</td>
<td>0.14</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>27.7 ± 8.0</td>
<td>26.8 ± 8.5</td>
<td>0.26</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.0 ± 3.3</td>
<td>23.7 ± 2.5</td>
<td>0.20</td>
</tr>
<tr>
<td>Retinopathy (nil/simplex/proliferative)</td>
<td>0/61/137</td>
<td>66/103/19</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.6 ± 1.5</td>
<td>8.5 ± 1.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Renal function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary albumin excretion (mg/24h)</td>
<td>794 (342-2050)</td>
<td>8 (5-13)</td>
<td>-</td>
</tr>
<tr>
<td>Plasma creatinine (µmol/l)</td>
<td>103 (82-134)</td>
<td>76 (69-83)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>GFR (ml/min per 1.73 m²)</td>
<td>74 ± 33</td>
<td>94 ± 16</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Cardiovascular characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>151 ± 23</td>
<td>132 ± 18</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>86 ± 13</td>
<td>76 ± 10</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Smokers</td>
<td>99 (50%)</td>
<td>81 (43%)</td>
<td>0.17</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>10 (5.1%)</td>
<td>2 (1.1%)</td>
<td>0.036</td>
</tr>
<tr>
<td>History of stroke</td>
<td>14 (7.1%)</td>
<td>1 (0.5%)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>CTGF levels</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma CTGF (pmol/l)</td>
<td>381 (270-630)</td>
<td>235 (168-353)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Data are means ± SD or median (interquartile range).
**Table 2.** Cox proportional hazard model for ESRD of baseline risk factors associated with rate of decline in GFR in patients with diabetic nephropathy.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with diabetic nephropathy (n=198)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR (per 1 SD decrease = 34 ml/min/1.73 m²)</td>
<td>3.13 (1.90-5.15)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sex (male vs. female)</td>
<td>2.52 (1.23-5.14)</td>
<td>0.01</td>
</tr>
<tr>
<td>UAE (per 1 SD increase = 3.6-fold)</td>
<td>2.08 (1.44-3.01)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Plasma CTGF (per 1 SD increase = 1.9-fold)</td>
<td>1.62 (1.05-2.50)</td>
<td>0.03</td>
</tr>
<tr>
<td>Patients with nephrotic range albuminuria (n=33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma CTGF (per 1 SD increase = 1.9-fold)</td>
<td>4.53 (1.96-10.44)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Adjusted for systolic blood pressure, duration of diabetes, and all other variables of this table.
**Table 3.** Cox proportional hazard model of baseline risk factors for overall mortality in patients with diabetic nephropathy.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male vs. female)</td>
<td>2.03 (1.18-3.48)</td>
<td>0.011</td>
</tr>
<tr>
<td>HbA1c (per 1 SD increase = 1.5%)</td>
<td>1.47 (1.16-1.86)</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (per 1 SD increase = 22 mm Hg)</td>
<td>1.41 (1.10-1.80)</td>
<td>0.007</td>
</tr>
<tr>
<td>Plasma CTGF (per 1 SD increase = 1.9-fold)</td>
<td>1.39 (1.11-1.74)</td>
<td>0.005</td>
</tr>
<tr>
<td>Age (per 1 SD increase = 9.5 years)</td>
<td>1.37 (1.10-1.69)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Adjusted for smoking, history of major cardiovascular event, UAE, GFR, and all variables of this table.
FIGURE LEGEND

Figure 1. Baseline plasma CTGF in patients with diabetic nephropathy. A: Log plasma CTGF correlates with log UAE (R=0.16, P=0.02). B: Log plasma CTGF correlates inversely with GFR (R= 0.58, P<0.001). C: Analysis per KDOQI subgroup for chronic kidney disease. Within each subgroup, patients with plasma CTGF above median tend to have higher rate of decline in GFR. D: Analysis per subgroup for UAE. Within each subgroup, patients with plasma CTGF above median tend to have higher rate of decline in GFR.*P<0.05 vs. group with plasma CTGF below median. E: Area under the ROC curve for prediction of ESRD by plasma CTGF is 0.74. With a cutoff value for plasma CTGF of 413 pmol/l, ESRD is predicted with a sensitivity of 73% and a specificity of 63%. F: Kaplan-Meier curve for prediction of ESRD. Cumulative hazard for ESRD is higher in patients with plasma CTGF above 413 pmol/l than in patients with plasma CTGF below 413 pmol/l. Log rank test, P<0.001. G: Graphic illustration of the relation between plasma CTGF and GFR at baseline, and rate of decline in GFR during 12.8 yr follow-up. Mean rate of decline in GFR is higher in patients with high plasma CTGF (>413 pmol/l, solid line, 5.4±4.9 ml/min/1.73 m2/year) than in patients with low plasma CTGF (<413 pmol/l, dashed line, 3.3±3.5 ml/min/1.73 m2/year). Regression lines were computed from all available data points. The X-intercept value of 10.2 years for the high plasma CTGF group indicates mean time to ESRD. H: Kaplan-Meier curve for prediction of overall mortality. Cumulative hazard for overall mortality is higher in patients with plasma CTGF above 413 pmol/l than in patients with plasma CTGF below 413 pmol/l. Log rank test, P<0.001.
Plasma CTGF predicts ESRD and mortality

A

Log UAE (mg/24h)

Log plasma CTGF (pmol/l)

B

GFR (ml/min/1.73 m²)

Log plasma CTGF (pmol/l)

C

Rate of decline in GFR (ml/min/1.73 m²)

Baseline GFR (ml/min/1.73 m²)

(% of patients in each group)

D

Rate of decline in GFR (ml/min/1.73 m²)

Baseline UAE (g/24h)

(% of patients in each group)

E

GFR (ml/min/1.73 m²)

1 - Specificity

F

Cumulative hazard for ESRD

Follow-up period (years)

G

GFR (ml/min/1.73 m²)

Follow-up (years)

CTGF < 413 pmol/l
mean slope = -3.3 ml per year

CTGF > 413 pmol/l
mean slope = -5.4 ml per year

H

Cumulative hazard for overall mortality

Follow-up period (years)