Transforming growth factor-β in diabetic nephropathy

Karima Y. Ahmed[a], Walaa F. El-Bazz[a], Hend A. Mohamed[c] and Maha M. Elkeshky[b]

Departments of [a]Internal Medicine, [b]Clinical Pathology, Faculty of Medicine, Al-Azhar University for Girls and [c]Department of Internal Medicine, Al-Mataria Hospital, Cairo, Egypt

Correspondence to Karima Y. Ahmed, Department of Internal Medicine, Faculty of Medicine, Al-Azhar University for Girls, Cairo, Egypt
Fax: +02 22722686;
e-mail: drkarimayoussef@yahoo.com

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Background
Renal failure is a common and serious complication of long-standing diabetes mellitus. Diabetes is the most common cause of end-stage renal failure. Transforming growth factor-β (TGF-β) is one of the major growth factors involved in extracellular matrix accumulation in fibrotic disorders including diabetic nephropathy.

Aim of the work
The aim of the present study was to evaluate the serum level of TGF-β as a marker for the development and progression of diabetic nephropathy.

Patients and methods
This work included 40 patients with diabetes and 40 healthy controls with matched age and sex. Individuals with diabetes included 25 patients with type 2 diabetes and 15 with type 1 diabetes. We considered the presence of hypertension, use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, and the degree of proteinuria. All patients were subjected to careful history taking, thorough physical examinations, and fundus examination. Routine laboratory tests such as analysis of complete blood count and determination of erythrocyte sedimentation rate were carried out to rule out patients with malignancy or autoimmune disease. Kidney function tests (blood urea and serum creatinine), complete urine analysis, and estimation of 24-h urinary protein or albumin, creatinine clearance, blood glucose measurement (fasting and 2 h postprandial), serum TGF-β level, and microalbuminuria were also carried out.

Results
The serum levels of TGF-β were statistically significantly higher in patients with diabetes compared with normal healthy people. The serum TGF-β level was statistically significantly higher in patients with diabetes with overt nephropathy compared with those without it. There was a statistically significant decrease in TGF-β levels in patients with diabetes who were taking angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers compared with those who were not taking such medications.

Conclusion
Serum TGF-β level increases in patients of both type 1 and type 2 diabetes and in those with diabetic nephropathy. TGF-β is considered one of the major mediators of diabetic renal fibrogenesis that results in end-stage renal disease.

Keywords:
angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diabetic nephropathy, transforming growth factor-β

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Introduction

Diabetic nephropathy is an important cause of end-stage renal disease worldwide. The pathology of diabetic nephropathy consists of glomerulopathy, tubulointerstitial changes, and extracellular matrix (ECM) expansion culminating in renal fibrosis [1]. A partial list of the pathogenesis of diabetic nephropathy includes glomerular hyperfiltration, renal hypertrophy, tubular transdifferentiation, oxidative stress, and dysregulation of cell cycle proteins and transforming growth factor-β (TGF-β) [2].

TGF-β is an important factor in diabetic renal hypertrophy both *in vivo* and *in vitro* [3]. TGF-β is a family of multifunctional cytokines composed of disulfide polypeptides that was isolated from platelets. It is also produced by many normal tissues including the placenta, macrophages, and B and T lymphocytes. TGF-β plays a key role in regulation of ECM accumulation. Its overexpression can cause tissue fibrosis and organ failure [4].

The fibrogenic action of TGF-β has been implicated in the development of pathologic renal fibrosis [5]. Factors known to be associated with the development and progression of diabetic nephropathy including hyperglycemia, increased intraglomerular pressure, mesangial cell stretch, activation of the renin–angiotensin system, and hypertension have been shown to induce TGF-β

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production in the kidney or in cultured mesangial or tubular cells [6]. Moreover, high-glucose-induced hypertrophy and growth inhibition in cultured proximal tubular cells are mediated by endogenous TGF-β [3].

It was found that control of ECM expansion is crucial for the development and progression of diabetic renal disease. Inhibiting renal TGF-β activity can partially reverse the thickening of the glomerular basement membrane and expansion of the mesangial matrix [7].

Patients and methods

Our study comprised 80 individuals divided into three groups:

(1) Group I included 25 patients with type 2 diabetes.
(2) Group II included 15 patients with type 1 diabetes (insulin-dependent diabetes).
(3) Group III included 40 healthy volunteers (controls).

All groups were sex and age matched.

The 40 patients with diabetes were randomly selected, and included 14 (35%) men and 26 (65%) women, their ages ranging from 18 to 65 years (mean ± SD 52.4 ± 10.5 years). The 25 (62.5%) patients of type 2 diabetes had overt nephropathy (proteinuria >0.5 g/24 h), whereas the 15 (37.5%) patients of type 1 diabetes did not. The duration of diabetes ranged from 1 to 25 years (mean 16.7 ± 5.9 years). A total of 23 (57.5%) patients were receiving oral antidiabetic drugs and 17 (42.5%) were on insulin therapy. A total of 28 (70%) patients had hypertension (blood pressure >140/90) and 12 (30%) were normotensive. Twelve of the hypertensive patients (42.86%) were on angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs), whereas 16 (57.14%) were on other antihypertensive drugs (Table 1).

Patients were selected from among the inpatients of the Department of Internal Medicine of Al-Zahraa University Hospital and National Institute of Nephrology, Cairo. The exclusion criteria included presence of autoimmune diseases, hepatitis, HIV (excluded by serology), or malignancies. Patients with any acute inflammatory state or rheumatic activity were also excluded from the study.

The control group III comprised 40 normal healthy volunteers, including 25 (62.5%) men and 15 (37.5%) women with ages ranging from 20 to 60 years (mean 50.1 ± 7.6 years). Both patients and controls were nonsmokers.

The patients and controls were subjected to the following:

(1) Detailed history taking and full clinical examination including neurological examination to detect 'neuropathy' and fundus examination for detection of diabetic retinopathy as signs of microvascular complication associated with nephropathy in patients with diabetes.
(2) Abdominal ultrasound to determine the sonographic grade of nephropathy by assessing the echogenicity of the kidneys.

Laboratory tests

(1) Routine laboratory tests for determination of complete blood count, liver enzymes, and erythrocyte sedimentation rate.
(2) Kidney function tests including estimation of serum creatinine and blood urea nitrogen.
(3) Complete urine analysis.
(4) 24-h urine collection for quantitative estimation of proteinuria (albuminuria).
(5) Estimation of creatinine clearance, which was performed as follows:
   (a) Measurement of 24-h urine volume.
   (b) Measurement of urine creatinine.
   (c) Measurement of plasma creatinine.
   (d) Creatinine clearance was finally calculated as follows:

$$\text{Creatinine clearance (ml/min)} = [\text{urinecreatinine (mg/dl)} \times \text{urine volume (ml)} / \text{plasmacreatinine (mg/dl)}] \times \text{time (min)}.$$

(6) Tests for microalbuminuria were performed only for patients with type 1 diabetes, using a competitive enzyme-linked immunosorbent assay (ELISA) (Table 2).

Principles of the tests

An undiluted sample and conjugate solution are added to microtiter wells precoated with albumin. Albumin from

Table 1 Demographic data of the 40 patients with diabetes and the 40 controls

Groups	Age (range) (mean ± SD)	Sex (male) (female)	Type of DM (type I) (type II)	Duration of DM (range) (mean ± SD)	Hypertension (%)	Diabetic neuropathy	Diabetic retinopathy
Group I type 2 DM (n=25)	18–65 years 52.4 ± 10.5 years	14 (35%) 26 (65%)	15 (62.5%) 25 (37.5%)	1–25 years 16.7 ± 5.9 years	70% with hypertension 30% without hypertension	17 (68%) with neuropathy	25 (100%) with retinopathy
Group II type 1 DM (n=15)							
Group III (n=40)	20–60 years 50.1 ± 7.6 years	25 (62.5%) 15 (37.5%)	–	–	–	–	–

DM, diabetes mellitus.

Table 2 Biochemical data of group I and group II patients

Variables	Group I	Group II	*P*-value
Serum creatinine (mean) (mg/dl)	2.9 ± 1.7	0.77 ± 0.28	< 0.01
Blood urea nitrogen (mean) (mg/dl)	41.8 ± 19.9	12.5 ± 3.6	< 0.01
Creatinine clearance (mean) (ml/min)	24.3 ± 15.6	95.9 ± 6.4	< 0.01
24 h urine protein (mean) (g/24 h)	1.9 ± 1.2	0.03 ± 0.02	< 0.01
Fasting blood sugar (mean ± SD) (mg%)	280 ± 31.8	260 ± 36	< 0.08
Postprandial blood sugar (mg%) (mean ± SD)	320 ± 26	308 ± 42	
AST (mg/dl)	32 ± 24	30 ± 21	> 0.05
ALT (mg/dl)	56 ± 48	54 ± 47	> 0.05
Hemoglobin (mg/dl)	13.1 ± 11.2	14.8 ± 11.5	> 0.05
WBCs ($\times 10^3$/Cumm)	8.6 ± 5.3	7.5 ± 4.2	> 0.05
ESR (mm/h)	12 ± 7	9 ± 5	> 0.05

ALT, alanine aminotransferase; AST, aspartate aminotransferase, ESR, erythrocyte sedimentation rate; WBC, white blood cell.

the urine sample and that coated onto the microtiter well compete for binding sites on the antibody conjugate.

After incubation, the plate is washed and a substrate for alkaline phosphatase enzyme is added. Reaction with the enzyme produces a colored product, which can be measured at 409 nm. The color intensity is inversely proportional to the amount of albumin in the urine sample.

The reference range for microalbuminuria is between 20 and 200 mg/l. Measurement of plasma or serum TGF-β level for both patients and controls was made using ELISA.

Principles of the MEDGENIX transforming growth factor-β enzyme-linked immunosorbent assay

The MEDGENIX TGF-β ELISA (Biosource Europe S.A. Zoning Industrial, Nivelles, Belgium) is a solid-phase ELISA performed on a microtiter plate. A fixed amount of TGF-β labeled with horseradish peroxidase competes with unlabeled TGF-β present in standard or extracted samples for a limited number of binding sites on a specific coated antibody. After 2 h of incubation at room temperature with continuous shaking, the microtiter plate is washed to stop the competition reaction.

The chromogenic solution (TMB) is added and incubated for 60 min. The reaction is stopped with the addition of the stop solution and the microtiter plate is read at the appropriate wavelength. The amount of substrate turnover is determined colorimetrically by measuring the absorbance, which is inversely proportional to the TGF-β concentration. A standard curve is plotted and TGF-β concentrations in the samples are determined by interpolation from the standard curve.

Statistical analysis

Statistical analysis was performed using SPSS (version 12.0; SPSS Inc., Chicago, Illinois, USA). The parameters are expressed as frequency and percentage for qualitative variables. Quantitative variables are expressed as mean ± SD and range. For comparison between groups with regard to quantitative data, the independent sample *t*-test was used. For correlation studies, the *r*-test (correlation coefficient) was used to find linear relationships between certain variables. A *P*-value of less than 0.05 was considered statistically significant, a *P*-value of less than 0.01 was considered highly significant and a *P*-value of more than 0.05 was considered insignificant.

Table 3 Mean plasma level of transforming growth factor-β in 40 patients with diabetes and 40 controls

Group I (25 diabetes type 2)	786.7 ± 401.3 pg/ml
Group II (15 diabetes type 1)	482.2 ± 185.8 pg/ml
Group III (40 healthy controls)	286.9 ± 99.4 pg/ml

Results

The serum level of TGF-β in the 40 patients with diabetes ranged from 278.29 to 843.03 pg/ml. The mean level of TGF-β in group I was 786.7 ± 401.3 g/ml, in group II it was 482.2 ± 185.8 pg/ml, and in group III (controls) it was 286.9 ± 99.4 pg/ml (Table 3). The mean serum TGF-β level in group I (type 2 diabetes) was significantly increased compared with the levels observed in group II (type 1 diabetes) ($P = 0.046$) and the control group ($P = 0.04$). The mean TGF-β level in patients with diabetes with diabetic retinopathy was 493.8 ± 212.2 pg/ml, which was higher than the mean TGF-β level in patients without it (408.4 ± 120.2 pg/ml), and this was statistically significant ($P = 0.044$; Table 4). Patients with diabetes with diabetic neuropathy had a mean TGF-β level of 402.3 ± 112.2 pg/ml, whereas patients without diabetic nephropathy had a mean TGF-β level of 388.4 ± 98.4 pg/ml, and this was statistically nonsignificant ($P > 0.05$; Table 4). The 12 patients with diabetes taking ACEI or ARBs had a mean serum TGF-β level of 323.3 ± 43.1 pg/ml, whereas in those not taking these medications the mean level was 766.8 ± 332.4 pg/dl. The serum TGF-β levels were statistically significantly decreased in patients with diabetes who were using ACEI or ARBs compared with those not using these medications ($P = 0.038$; Table 5). Nine (60%) patients with type 1 diabetes had microalbuminuria, with the microalbumin levels ranging from 23.785 to 195.2 mg/l, whereas the remaining six (40%) patients were negative for microalbuminuria as their levels ranged between 11.326 and 18.134 mg/l (Table 6). Serum TGF-β levels in patients with microalbuminuria ranged from 455.92 to 677.53 pg/ml (mean 602.2 ± 134.7 pg/ml), and these were statistically significantly higher than the levels observed in the six patients without microalbuminuria who had

Table 4 Mean plasma transforming growth factor-β level in patients with diabetes with or without diabetic complications

Parameters	TGF-β with complications (pg/ml)	TGF-β without complications (pg/ml)	*P*-value
Diabetic nephropathy	786.7 ± 401.3	482.2 ± 185.8	< 0.04
Diabetic retinopathy	493.8 ± 212.2	408.4 ± 120.2	0.044
Diabetic neuropathy	402.3 ± 112.2	388.4 ± 98.4	> 0.05

TGF-β, transforming growth factor-β.

Table 5 Mean plasma level of transforming growth factor-β in the 12 patients with diabetes on treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and in 16 patients not on angiotensin-converting enzyme inhibitor treatment

Groups	TGF-β (mean) (pg/ml)	Significance
Patients on ACEI (*N* = 12)	323.3 ± 43.1	*P*-value = 0.038
Patients not on ACEI (*N* = 16)	766.8 ± 332.4	

ACEI, angiotensin-converting enzyme inhibitors; TGF-β, transforming growth factor-β.

levels ranging from 278.29 to 368.42 pg/ml (mean 314.3 ± 16.5 pg/ml) ($P = 0.039$; Table 6).

There was a significant positive correlation between serum TGF-β levels and duration of diabetes in patients of groups I and II ($P = 0.03$; Table 7). There was a nonsignificant positive correlation between serum TGF-β level and age of the patients in group I, group II, and controls ($P = 0.78$; Table 7). There was no significant difference between serum level of TGF-β and sex of the patients in group I, group II, and controls ($P = 0.38$; Table 7). Diabetic retinopathy was found in all patients of group I. Proliferative diabetic retinopathy was found in 20 (80%) patients, nonproliferative changes were found in three (12%), whereas a combination of both lesions was found in two (8%) (Table 8). The patients of group II and the control group had no retinopathy on fundus examination.

There was a significant positive increase in the level of TGF-β and microalbumin in patients with type 1 diabetes ($P = 0.039$; Table 7). There was no correlation between the level of TGF-β and serum creatinine and blood urea nitrogen in either group I or II ($P = 0.25$ and 0.11, respectively; Table 7). Ultrasound examinations in group I showed two (8%) patients with a normal renal ultrasound with respect to the size and echogenicity of both kidneys, 10 (40%) with grade I nephropathy, six (24%) with grade II nephropathy, and seven (28%) with grade III nephropathy (Table 9). The patients of group II and the control group had normal renal ultrasound findings.

Discussion

Renal failure is a common and serious complication of long-standing diabetes mellitus. Diabetes is the most common cause of end-stage renal failure requiring dialysis, accounting for almost 40% of all new dialysis patients [8]. Diabetic nephropathy refers to a characteristic set of structural and functional kidney abnormalities that occur in patients with diabetes, including hypertrophy of the kidney, thickening of the glomerular basement membranes, accumulation of ECM components, fibrosis with intraglomerular hypertension, proteinuria, systemic hypertension, and eventual loss of renal function [9]. These changes, although best described in patients with type 1 diabetes, are also known to occur in patients with type 2 diabetes [10].

Studies have shown that the factors responsible for the deposition and accumulation of ECM within the kidney are of considerable interest in the pathogenesis of diabetic nephropathy. Of these, the cytokine TGF-β emerged as having a key role in the development of renal hypertrophy and fibrosis in diabetes [11].

The current study showed that TGF-β levels are much higher in patients with diabetes compared with those without diabetes, which is in accordance with the study carried out by Ziyadeh [12], who reported that the hypertrophic and fibrogenic cytokine TGF-β is a mediator of the effects of high ambient glucose on the kidney. Furthermore, Ziyadeh [12] showed that TGF-β levels were also increased not only in the plasma but also in the urine of diabetic mice. This can be explained by the increased local production of TGF-β proteins by the kidneys of those with diabetes.

The present study showed that plasma level of TGF-β was higher in patients with overt nephropathy than in those without it. This result was also reported by Hellmich *et al.* [13], who showed markedly elevated levels of TGF-β in the serum of patients with diabetic nephropathy compared with patients with diabetes without nephropathy and in nondiabetic controls.

The current study showed significantly increased serum TGF-β levels in patients with diabetes with retinopathy, whereas the levels were not increased in diabetic patients without neuropathy. However, Tesfaye *et al.* [14] reported a high level of TGF-β in patients with diabetes with proliferative retinopathy and neuropathy compared with patients without these complications. As the initial stages of retinopathy are associated with loss of retinal capillaries and pericytes, the inhibitory action of TGF-β may contribute to capillary loss by preventing the replacement of damaged cells.

The results of the current study in conjugation with those of the previous studies on humans and experimental animals strongly implicate TGF-β as a prime candidate promoting the development of pathological manifestations of diabetic nephropathy.

TGF-β stimulates the synthesis of key ECM molecules, including type I and IV collagen, fibronectin, and laminin [15]. TGF-β also decreases matrix degradation

Table 6 Frequency of microalbuminuria and transforming growth factor-β in the 15 patients with type 1 diabetes mellitus

Microalbuminuria	Frequency (%)	TGF-β (mean) (pg/ml)	*P*-value
Present (positive microalbuminuria)	9 (60)	602.2 ± 134.7	0.039
Absent (negative microalbuminuria)	6 (40)	314.3 ± 16.5	

TGF-β, transforming growth factor-β.

Table 7 Correlation between plasma level of transforming growth factor-β and other variables

Groups	Variables	*r*-value	*P*-value	Correlation
Group I (type 2 DM)	Age	0.4923	0.78	Positive correlation
	Sex	–	0.38	No correlation
	Duration of DM	0.2162	0.03	Positive correlation
	Creatinine	–	0.76	No correlation
	Blood urea nitrogen	–	0.82	No correlation
Group II (type 1 DM)	Age	0.5947	0.91	Positive correlation
	Sex	–	0.16	No correlation
	Microalbuminuria	0.4887	0.039	Positive correlation

DM, diabetes mellitus.

Table 8 Frequency of retinopathy and mean transforming growth factor-β levels in patients with type 1 diabetic retinopathy

Fundus examination	Frequency (%)	TGF-β (mean ± SD) (pg/ml)
PDR	20 (80)	493.8 ± 344.3
Non-PDR	3 (12)	
PDR in one eye + nonproliferative in the other eye	2 (8)	

PDR, proliferative diabetic retinopathy; TGF-β, transforming growth factor-β.

Table 9 Ultrasound-based kidney findings in type 2 (group I) diabetic patients

Ultrasound findings (grading of nephropathy)	*N* (%)
Grade I	10 (40)
Grade II	6 (24)
Grade III	7 (28)
Normal	2 (8)

by inhibiting proteases and by activating protease inhibitors such as plasminogen activator inhibitor-1. In addition, TGF-β promotes cell–matrix interactions by upregulating integrins, the cell surface receptors for matrix accumulation.

Almost all of the molecular mediators and intracellular signaling pathways that have been identified in diabetes-related kidney injury have also been found to stimulate the renal TGF-β activity as an intermediary step [12].

These mediators encompass the following: high glucose concentration; early and advanced glycated end products; oxidative stress and overproduction of superoxide ions; cyclic stretch and relaxation of the mesangial cells in culture; de-novo synthesis of diacylglycerol and protein kinase C; activation and stimulation of the mitogen-activated protein kinase; overproduction of glucosamine; and high levels of vasoactive substances such as intrarenal angiotensin II, endothelin, and thromboxane [16].

The present study showed that serum levels of TGF-β were higher in patients with diabetes compared with healthy individuals (nondiabetics), as previously shown by Hellmich *et al.* [13]. This might be because the kidney in nondiabetic individuals functions to remove circulating TGF-β, whereas in patients with diabetes there is a substantial net renal production of TGF-β that 'spills over' into the renal veins and the urine.

Ardura *et al.* [17] and Sheets *et al.* [18] showed that a high glucose concentration induced TGF-β production in cultured mesangial and renal tubular cells and stimulates the production of matrix molecules such as fibronectin and collagen in these cells and in epithelial, endothelial, and fibroblastic cells. In almost all renal cell types, high glucose upregulates the expression and bioactivity of TGF-β, and in some cases upregulates the TGF-β type II receptor [15].

The current study showed decreased serum TGF-β levels in patients with diabetes with diabetic nephropathy who were receiving ACEI treatment compared with those who were not. This is in agreement with the studies that report that blockade of the renin–angiotensin aldosterone system decreases expression of TGF-β and matrix proteins [15].

Of clinical interest is the fact that ACEI therapy protected the kidney by lowering the levels of TGF-β. Van den Heuvel *et al.* [19] showed that, in captopril-treated patients, the decrease in the circulating TGF-β level predicted a better preservation of the glomerular filtration rate.

Angiotensin II is a potent stimulus for TGF-β production by kidney cells and acts in synergy with elevated glucose concentrations to stimulate matrix production by renal epithelial cells [20]. Thus, it is likely that some of the beneficial effects of ACEI in diabetic nephropathy (and perhaps other kidney diseases) are related to the suppression of TGF-β production [21]. However, the inability of ACEI treatment to completely halt the progression of diabetic nephropathy may be related to the

incomplete suppression of TGF-β production by these agents [22].

ACEI effectively limit renal fibrosis with no effect on systemic blood pressure. In addition, ACEI significantly slow the progression of renal failure even in the absence of high blood pressure [23]. Studies have shown that in hypertensive type 2 diabetic patients, ACEI or ARB treatment reduced proteinuria independent of lowering of blood pressure [24].

The classical view of angiotensin II as a vasoactive agent has been changed to consider it as a true cytokine with an active role in the renal pathology and as a renal growth factor that modulates cell growth and ECM production [25]. The effects of angiotensin II stimulating mesangial cell matrix expression, renal tubular hypertrophy, and renal interstitial fibrosis seem to be mediated by release of TGF-β.

The current study showed that TGF-β levels were positively related to microalbuminuria in type 1 diabetic patients. This is in agreement with the study carried out by Hellmich *et al.* [13], who showed that TGF-β levels were correlated with the albumin excretion rate in patients with diabetes. Microalbuminuria is a marker of diabetic injury and cardiovascular risk in patients with type 1 diabetes. Caramory *et al.* [26] reported that patients with microalbuminuria have a 10-fold increased risk of developing proliferative retinopathy compared with those without microalbuminuria over a 5-year period, following the development of albuminuria. Studies have also shown a strong correlation between microalbuminuria and background retinopathy and between overt and proliferative retinopathy [27].

Detection of microalbuminuria is important because, once detected, it is an indication for the initiation of antiangiotensin II therapy, with the purpose of preventing or delaying the advance of progressive diabetic nephropathy [27].

Although the development of diabetes-related kidney disease is similar in patients with type 1 and type 2 diabetes, the issues involving the time course of the process are blurred by the insidious onset of type 2 diabetes. In patients with type 2 diabetes mellitus, the presence of microalbuminuria may be more reflective for generalized vascular disease compared with diabetic glomerulopathy [28]. Although the positive predictive value of microalbuminuria for progressive diabetes nephropathy is less than what was estimated, it remains a standard clinical test with important ramifications for patient management [26.]

The TGF-β complex system provides numerous levels of regulation and numerous targets for intervention. However, it remains to be seen whether any of these steps can be manipulated in a clinically meaningful way to reduce the progression of diabetic nephropathy and other chronic renal diseases [4].

Summary and conclusion

The current study estimated the level of TGF-β in 40 patients with diabetes compared with 40 normal healthy controls, and it was found that TGF-β levels were higher in the diabetic group than in normal individuals. Serum TGF-β levels were higher in patients with diabetes with overt nephropathy compared with those without it. There was a significant decrease in serum TGF-β levels in patients with diabetes receiving ACEI therapy compared with those not receiving such medications.

Studies have shown that inhibition of TGF-β attenuated both the increased renal TGF-β expression and the increased TGF-β levels, reduced the diabetes-associated renal and glomerular hypertrophy, and partially reversed established diabetic nephropathy in both experimental diabetes and human diabetes. However, because TGF-β has critical antiproliferative (tumor suppressor) and anti-inflammatory effects, defective TGF-β signaling is involved in the development of several (epithelial) tumors. This makes TGF-β a less suitable target for therapeutic intervention. In the future, it might be possible to combine both ACEI and anti-TGF-β antibodies as a possible route for renoprotection and for treatment of diabetic nephropathy in patients who did not respond to ACEI alone.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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