The Effect of Hyperglycemia on Serum Transforming Growth Factor-β1 (TGF-β1) Level and Their Relations to Diabetic Nephropathy in Patients With Controlled Type 2 Diabetes Mellitus

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ABSTRACT

TGF-β1 plays a critical role in the pathogenesis of different types of nephropathy. The current work aimed at investigating the effects of hyperglycemia on serum TGF-β1 to clarify their relations to diabetic nephropathy in controlled type 2 diabetic patients. Fourty-eight patients were categorized according to the concentration of urinary microalbumin per 24h into normoalbuminuric, microalbuminuric and macroalbuminuric groups. Each group comprised 16 patients of both sex. Their age ranged from 42 to 75 years, with a mean value of 57.9 ± 9.1 years. These patients were compared to 10 healthy subjects, age and sex matched who served as controls. The results of the present work showed that; the mean values of serum TGF-β1 in normoalbuminuric, microalbuminuric and macroalbuminuric groups were significantly elevated compared to the control group ($p<0.05$). Also, diabetic patients with nephropathy showed that; the mean values of serum TGF-β1 in hypertensives were significantly elevated compared to normotensive patients ($p<0.05$). Furthermore, gender had non-significant effect on serum TGF-β1. Moreover, correlation study showed a significant positive correlation between urinary microalbumin per 24h and serum TGF-β1 in microalbuminuric and macroalbuminuric ($p<0.05$) groups. In addition, systolic and diastolic blood pressure showed significant positive correlation with serum TGF-β1 in macroalbuminuric group ($p<0.05$).

The results of this work showed that; the augmented effects of hyperglycemia and the subsequent increase in serum TGF-β1 could play a prominent role in the pathogenesis of diabetic nephropathy. This may be helpful when using TGF-β1 system as a new therapeutic target for treatment and prevention of diabetic nephropathy in the future.

INTRODUCTION

Transforming growth factor-beta (TGF-β) is a prototypical multifunctional cytokine isolated from platelets. The name was adopted because the ability of these molecules to confer, on fibroblast cell lines, functional properties associated with neoplastic transformation[1] .

Virtually every cell in the body produces TGF-β and has receptors for it. There are three isoforms of TGF-β: TGF-β1, TGF-β2 and TGF-β3. All three isoforms are highly conserved in mammals, suggesting a critical biologic function for each isoform. Increase or decrease in the production of TGF-β have been linked to numerous disease states[2].

Diabetic nephropathy is a common complication in patients with type 1 or type 2 diabetes. The pathogenesis of diabetic nephropathy is thought to involve both metabolic and vascular factors, leading to chronic accumulation of glomerular mesangial matrix[3].

The critical role of hyperglycemia in the genesis of diabetic nephropathy has been established by cell culture studies, experimental animal models and clinical trials. Certain cytokines have been identified as likely mediators of the effects of high ambient glucose on the kidney, but prominent among these is TGF-β, a prototypical hypertrophic and fibrogenic cytokine[4].

SUBJECTS AND METHODS

Fifty-eight volunteer subjects (29 males and 29 females) were selected from Outpatients Clinic of Internal Medicine Department, Benha University Hospital. They were categorized into 4 groups:

Control group: Comprised 10 healthy subjects (5 males and 5 females).They were age and sex matched.

Normoalbuminuric group: Comprised 16 controlled type 2 diabetic patients (8 males and 8 females) **.** Their urinary microalbumin levels were < 30 mg/24h

Microalbuminuric group: Comprised 16 controlled type 2 diabetic patients (8 males and 8 females). Their urinary microalbumin levels ranged 30-300 mg/24h

Macroalbuminuric group: Comprised 16 controlled type 2 diabetic patients (8 males and 8 females) . Their urinary microalbumin levels were > 300 mg/24h.

(N.B: The patients of the current study were categorized according to ***Sacks***[5] and considered controlled diabetics when HBA1c ranged 6.5-8.5%[9])

All the studied groups were subjected to full history and clinical examination, abdominal ultrasonography scanning as well as Plain X ray, duration of diabetes, duration of hypertension, blood pressure monitoring, body mass index (BMI), was calculated according to ***Garraw***[6], and laboratory investigations including complete blood picture (CBC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)[7], fasting serum glucose level (FSG)[8], glycosylated hemoglobin[9] (HbA_{1c}) by spectrophotometric method (Teco Diagnostics,USA), urinary microalbumin level per 24h[10] by ELISA (Orgentec Diagnostika Gmbh, Germany), serum creatinine[11], alanine aminotransferase[12] (ALT) and TGF-β1[13] by ELISA (BioSource International, Inc., USA.) were estimated.

Exclusion criteria: patients using angiotensin converting enzyme inhibitors (ACEI) were excluded.

Sampling:

From all subjects, fasting venous blood samples (8.0 ml) and 24 hours urine samples were collected. Each blood sample was divided into 3 parts. The first part (1.0 ml) was collected on dipotassium EDTA (16.6 μl/1ml

blood) for determination of blood picture and HbA_{1c}. The second part (2.0 ml) was taken on 0.5 ml trisodium citrate solution (3.8%) for determination of erythrocyte sedimentation rate (ESR). The remaining part (5.0 ml) was allowed to clot. The separated serum was used for determination of C-reactive protein (CRP) , glucose, creatinine and ALT. Part of the sera were kept frozen at -80 ºC for later determination of TGF-β1. Also, 5.0 ml of 24 hours collected urine were kept frozen at -80 ºC for later determination of microalbumin.

Statistical analysis

The results of the present work were tabulated and statistically analyzed using student (t-test) and correlation coefficient (r). p values <0.05 were considered significant while p values >0.05 were insignificant[14].

RESULTS

Table (1) shows the mean values and ±SD of age, duration of diabetes mellitus (DM), duration of hypertension, systolic, diastolic blood pressure and body mass index (BMI) in all studied groups.

Table (2) shows the mean values and ± SD of fasting serum glucose (FSG), glycosylated hemoglobin (HbA_{1C}), serum creatinine, serum ALT, urinary microalbumin/24h and serum TGF- β1 in all studied groups. The mean values of serum TGF-β1 in normoalbuminuric (2.51±0.46 pg/l), microalbuminuric (2.74 ± 0.67 pg/l) and macroalbuminuric groups (3.57 ± 1.41 pg/l) were significantly elevated compared to the control group (1.86 ±0.52 pg/l) (p< 0.05).However, the mean value of serum TGF-β1 in microalbuminuric group (2.74 ± 0.67 pg/l) was non-significantly elevated compared to the normoalbuminuric group(2.51±0.46pg/l). Furthermore, the mean value of serum TGF-β1 in macroalbuminuric group (3.57±1.41 pg/l) was significantly elevated compared to the normoalbuminuric(2.51 ± 0.46 pg/l ; p<0.05) and microalbuminuric groups (2.74 ± 0.67 pg/l ; p< 0.05) .

Table (3) shows that the mean value of serum TGF-β1 in hypertensive (3.44±1.2 pg/l) was significantly elevated compared to normotensive patients (2.59 ± 0.72 pg/l; $p < 0.05$).

Table (4) shows that the mean value of serum TGF-β1 in male (2.94 ± 0.95 pg/l) was not significantly different compared to the female patients (2.95 ± 1.12pg/l).

Table (5) shows the correlation study between age, duration of diabetes mellitus (DM), duration of hypertension, systolic, diastolic blood pressure, BMI, FSG, glycosylated hemoglobin (HbA$_{1C}$), serum creatinine, urinary microalbumin and serum TGF-β1 in normoalbuminuric, microalbuminuric and macroalbuminuric groups. There was significant positive correlation between urinary microalbumin and serum TGF-β1 in microalbuminuric group (r=0.61; p<0.05). Also, there was significant positive correlation between systolic (r=0.60; p<0.05), diastolic blood pressure (r=0.54; p<0.05), urinary microalbumin (r=0.82; p<0.05) and serum TGF-β1 in macroalbuminuric group.

Table (1): mean values and ± SD of age, duration of diabetes mellitus (DM), duration of hypertension, systolic, diastolic blood pressure (B.P) and body mass index (BMI) in all studied groups.

Groups / Parameters	Controls (n=10)	Normo-albuminuric (n=16)	Micro-albuminuric (n=16)	Macro-albuminuric (n=16)
Age (Y)	54.1±9.64	55.38±7.92	59.81±11.39	58.56±7.36
Duration of D.M (Y)	-	6.44±3.88	8.72±4.39	12.31±3.94
Duration of hypertension (Y)	-	3.60±1.95	5.00±2.90	5.22±2.64
Systolic B.P (mmHg)	118.00±4.22	122.81±7.52	126.25±8.47	124.40±8.94
Diastolic B.P (mmHg)	74.50±4.97	77.50 ±7.53	79.69±6.94	78.79±7.39
BMI (Kg/m^2)	30.39±3.61	28.63±2.45	28.72±2.37	27.10±3.92

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Table (2): mean values and ± SD of fasting serum glucose (FSG), glycosylated hemoglobin (HbA$_{1C}$), serum creatinine, serum ALT, urinary microalbumin/24h and serum TGF- β1 in all studied groups.

Groups Parameters	Controls (n=10)	Normo-albuminuric (n=16)	Micro-albuminuric (n=16)	Macro-albuminuric (n=16)
FSG (mg/dl)	83.40 ±4.81	141.94±29.63	155.63±27.53	151.94±27.18
HbA$_{1C}$ (%)	7.57±0.48	7.54±0.73	7.76±0.66	7.75±0.63
Serum creatinine (mg/dl)	0.71±0.16	0.72±0.09	0.86±0.20	1.75±0.65
Serum ALT (U/l)	27.5±3.63	28.19±3.73	28.69±4.14	28.88±4.69
Urinary microalbumin (mg/24h)	11.70±3.40	23.04±5.17	53.83±23.56	435.56±47.66
Serum TGF-β1(pg/l)	1.86±0.52	2.51±0.46*	2.74±0.67* #	3.57±1.41* # #

* Significant differences between diseased groups and control group (p<0.05).

Non-significant difference between microalbuminuric group compared to normoalbuminuric group (p>0.05).

Significant differences between macroalbuminuric groups compared to normoalbuminuric and microalbuminuric groups (p<0.05).

Table (3): Mean ± SD, and p values of serum TGF-β1 in hypertensive patients compared to normotensive patients in all diseased groups.

Parameter Group	Serum TGF- β1(pg/l)		p
	Mean	± SD	
Normotensives (n = 28)	2.59	± 0.72	-
Hypertensives (n = 20)	3.44	± 1.20	< 0.05

p < 0.05: significant

p > 0.05 : non-significant (NS).

Table (4): Mean ± SD, and p values of serum TGF-β1 in the male compared to the female patients in all diseased groups.

Parameter / Groups	Serum TGF- β1(pg/l)		p
	Mean	**± SD**	**p**
Females (n = 24)	2.95	± 1.12	-
Males (n = 24)	2.94	± 0.95	NS

p < 0.05: significant
p > 0.05 : non-significant (NS).

Table (5): Correlation coefficient (r) between age, duration of diabetes mellitus (DM), duration of hypertension, systolic, diastolic blood pressure, BMI, FSG, glycosylated hemoglobin (HbA$_{1C}$), serum creatinine, urinary microalbumin and serum TGF-β1 in normoalbuminuric, microalbuminuric and macroalbuminuric groups.

Groups / TGF-β1	Normo-Albuminuric (n=16)		Micro-Albuminuric (n=16)		Macro-albuminuric (n=16)	
	r	**p**	**r**	**p**	**r**	**p**
Age (year)	0.32	NS	0.04	NS	0.18	NS
Duration of DM (year)	0.35	NS	0.34	NS	0.45	NS
Duration of hypertension (year)	0.34	NS	0.29	NS	0.49	NS
Systolic blood pressure (mmHg)	0.46	NS	0.45	NS	0.60	<0.05
Diastolic blood pressure (mmHg)	0.21	NS	0.46	NS	0.54	<0.05
BMI (kg/m^2)	0.13	NS	0.14	NS	0.43	NS
FSG (mg/dl)	0.19	NS	0.09	NS	0.22	NS
HbA$_{1C}$ (%)	0.14	NS	0.45	NS	0.02	NS
Serum creatinine (mg/dl)	0.21	NS	0.37	NS	0.31	NS
Urinary microalbumin (mg/24h)	0.06	NS	0.61	< 0.05	0.82	< 0.05

p < 0.05: significant
p > 0.05 : non-significant (NS).

DISCUSSION

Diabetic kidney disease affects about 15-25% of type 1 and 30-40% of type 2 diabetic patients[15]. Secondary microvascular complications, including nephropathy, develop some years after the onset of diabetes[16].

The results of the present study showed a significant elevation in the serum level of TGF- β1 in normoalbuminuric, microalbuminuric and macroalbuminuric groups compared to the control group ($p < 0.05$) .

Diabetic nephropathy is characterized by thickening of the glomerular and tubular basement membranes, hypertrophy of both tubuloepithelial and glomerular structures and deposition of extracellular matrix (ECM) components in the glomerular mesangium, due largely to the effects of hyperglycemia[4].

Hyperglycemia mediates these pathological changes of diabetic nephropathy either directly or indirectly, via stimulation of TGF-β1 production and/or activation. The direct effect of hyperglycemia has been studied in cell culture studies, in which high glucose concentration stimulated the production of ECM molecules such as fibronectin and type IV collagen by proximal tubular cells, mesangial cells and renal fibroblasts[4].

Meanwhile, the indirect effects of high glucose, in diabetic kidney injury, mediate TGF-β1 overproduction and activation through many molecular mediators and intracellular signaling pathways. These mediators encompass the following: First, Amadori protein and advanced glycation end products (AGEs) which are products of early and advanced non-enzymatic glycation of proteins, respectively. Recently, Amadori products and AGEs have been shown to induce a transcriptional activity of c-fos[17] and platelet derived growth factor (PDGF)[16]. Both, c-fos and PDGF, enhance TGF- β1 production and thus overexpression of collagen and other ECM components in diabetic nephropathy[18]. Second, in cells such as mesangial

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cells, in which glucose uptake is not regulated by insulin, high intracellular glucose is phosphorylated and cleaved to form glyceraldehyde 3-phosphate and dihydroxyacetone phosphate, and then into glycerol 3-phosphate which is transformed into phosphatidic acid and diacylglycerol. Elevated diacylglycerol levels greatly increases the affinity of protein kinase C (PKC) for calcium and phosphatidyl serine, thus allowing prolonged activation of PKC[19]. Third, high intracellular glucose, also, results in activation of aldose reductase enzyme in the polyol pathway. This leads to accumulation of sorbitol which is further converted to fructose by sorbitol dehydrogenase enzyme, using NAD^+. The ratio of NAD^+: NADH decreases and the conversion of glyceraldehyde-3-phosphate to 1,3-bisphosphoglycerate is blocked, leaving more substrate (glyceraldehyde-3-phosphate) for the synthesis of diacylglycerol which is a protein kinase C activator[20]. The net result of PKC activation is the stimulation of TGF- β1 production which in turn increases ECM accumulation through stimulating ECM synthesis and inhibiting its degradation[21]. Fourth, hyperglycemia leads to overproduction of intracellular reactive oxygen species by the mitochondrial electron transport chain. Reactive oxygen species may arise from multiple pathways including: glucose autoxidation, hydrogen peroxide (H_2O_2) generated from the oxidation of enediols formed from Amadori products and superoxide formed by the mitochondrial oxidation of NADH to NAD^+[22]. Mitochondrial superoxide overproduction stimulates aldose reductase activity leading to activation of PKC, also, reactive oxygen species can initiate intracellular formation of advanced glycation end products, thus increasing TGF- β1 levels and ECM accumulation[20]. Fifth, recent studies demonstrated that some of the effects of high glucose on cellular metabolism are mediated by hexosamine pathway in which glucose is phosphorylated and transformed into fructose-6-phosphate and then into glucosamine-6-phosphate. This last reaction is catalyzed by glutamine: fructose-6-phosphate amidotransferase

(GFAT)[19]. In kidney mesangial cells, glucosamine is more potent than glucose in stimulating TGF- β1 mRNA transcription and bioactivity[23], resulting in increase in the ECM components; laminin and fibronectin. These effects of TGF- β1 on the accumulation of fibronectin and laminin are mediated by protein kinase A (PKA) possibly through activation of c-AMP responsive element binding transcription factor (CREB)[24]. Sixth, hyperglycemia induces endothelin-1 overexpression in endothelial, epithelial and mesangial cells. Endothelin-1 can induce TGF- β1 synthesis and stimulates mesangial cells, smooth muscle cells and fibroblasts proliferation[20]. Finally, exposure to high glucose upregulates thrombospondin-1 (TSP-1) expression in mesangial cells. TSP-1 has been shown to enhance the synthesis of many ECM proteins through its ability to activate latent TGF- β1[25]. TSP-1 might mediate AGEs-induced distal renal tubular hypertrophy through increased activation of TGF- β1. Moreover, anti TSP-1 neutralizing antibodies attenuated the AGEs induced increase in TGF- β1 bioactivity[26]. The results of the current study were in agreement with the results of *Sharma et al.[3], Hellmich et al.[27], Bordin et al.[28] and Senatorski et al.[29]*

Also, this study showed that the level of serum TGF- β1 was not significantly elevated in microalbuminuric patients compared to normoalbuminuric patients while, there was a significant elevation in the mean level of serum TGF- β1 in macroalbuminuric group compared to normoalbuminuric and microalbuminuric groups ($p<0.05$). These results are, also, compatible to those reported by *Chaturvedi et al[30].* , who suggested that none of the factors known to be responsible for TGF- β1 production and activation have been shown to be influenced by mild renal dysfunction. They, also, suggested that adjustment of blood pressure markedly attenuated the differences in circulating TGF-β1 in normoalbuminuric and microalbuminuric patients but not in macroalbuminuric patients.

Moreover, *Korpinen et al[31].,* found that, the secretion of TGF- $\beta1$ by peripheral blood mononuclear cells, was increased only in patients with macroalbuminuria. These results were compatible with the findings of *Korpinen et al[31].* and in agreement with the results of *Chaturvedi et al[30].*

The findings of the present study showed a significant positive correlation between 24 hours urinary microalbumin and serum TGF-$\beta1$ in the microalbuminuric and macroalbuminuric groups ($p < 0.05$).However, there was no significant correlation between 24 hours urinary microalbumin and serum TGF-$\beta1$ in the normoalbuminuric group.

Menne et al[32]., found that the glucose-induced albuminuria seems to be mediated by PKC via downregulation of heparan sulfate proteoglycan in the glomerular basement membrane. Decreased heparan sulphate diminished the glomerular capillary wall electrostatic charge barrier, increasing the excretion of negatively charged albumin. The filtered proteins are taken up by the tubular cells and overwhelming this system may lead to tubular synthesis of various cytokines including TGF-$\beta1$[33].These results are in agreement with *Hellmich et al[27].*

Furthermore, this work showed a significant elevation in the serum TGF-$\beta1$ of diabetic hypertensive patients compared to normotensive patients ($p<0.05$) .

Moreover, the results of the present study, showed a significant positive correlation between systolic and diastolic blood pressure levels and serum TGF-$\beta1$, in the macroalbuminuric group ($p<0.05$) while, there was non-significant correlation between systolic, diastolic blood pressure and serum TGF-$\beta1$ in normoalbuminuric and microalbuminuric groups. These results are compatible with the results of *Chaturvedi et al[30].*Additionally, there was non-significant correlation between the duration of hypertension and serum TGF-$\beta1$ in all diseased groups.

Li et al.[34], supported the idea that TGF-β1 may regulate blood pressure via stimulation of endothelin-1 and/or renin secretion. In addition, cyclic stretching and relaxation of mesangial cells in culture (mimicking intraglomerular hypertension) increased the production of TGF-β1[35].

Moreover, mechanical strain due to systemic and/or glomerular hypertension, together with high glucose stimulate angiotensin II production, which exerts hemodynamic as well as profibrogenic effects mediated by increased TGF-β1 production[33]. These mechanisms explain why serum TGF-β1 was significantly elevated in hypertensives compared to normotensive patients. This finding was in consistence with the results of *Li et al*[34]. *and Suthanthiran et al*[36]. Meanwhile, the finding of non-significant correlation between systolic, diastolic blood pressure and serum TGF-β1 in normoalbuminuric and microalbuminuric patients was compatible with the results of *Chaturvedi et al*[30].

This study showed non-significant decrease in serum TGF-β1 in males compared to female patients. *Kwan et al*[37]., reported that neither estradiol nor testosterone affected the TGF-β1 mRNA level in cultured mesangial cells. However, estradiol suppressed collagen synthesis by mesangial cells, suggesting a protective effect of female gender on the progression of renal disease. This result was in accordance with the findings of *Kwan et al*[37]. and contradictory to the results of *Lane et al*[38]. The latter suggested that TGF-β1 becomes more active and efficient in males after puberty, while the reduced activation and efficiency, in females, appears to be compensated by the significant increase in serum TGF-β1.

In addition, this work showed no significant correlation between age, duration of diabetes mellitus, body mass index, fasting serum glucose, glycosylated hemoglobin, serum creatinine and serum TGF-β1 in all diseased groups. These results were in consistence with the results reported by *Hellmich*

et al[27]. and *Azar et al*[39]. However, *Hellmich et al*[27]. found a significant positive correlation between serum creatinine and TGF- β1 in patients with diabetic nephropathy. They suggested that metabolic changes due to impairment of renal function might affect the activation of TGF-β1.

Also, the present result regarding glycosylated hemoglobin was contradictory to the results of *Iwano et al*[40]. They proposed that poor glycemic control is a key factor in inducing TGF- β1 in diabetic kidney, evidenced by increased TGF- β1 production by cultured renal cells after exposure to high glucose. However, our diabetic patients were controlled and this could explain the discrepancy between these results.

So, it could be concluded that hyperglycemia affects the pathogenesis of diabetic nephropathy not only by its direct effect but, also, through various pathways in which TGF-β1 plays a prominent role. This is may be of help when using   TGF-β1 system as a new therapeutic target for treatment and prevention of diabetic nephropathy in the future.

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الملخص العربى

تأثير زيادة مستوى الجلوكوز بمصل الدم على عامل النمو المحول بيتا-1وعلاقتهما المسببة لإعتلال الكلى الوظيفى فى مرضى البوال السكرى المنضبط من النوع الثانى.

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طب بنها-جامعة الزقازيق

يعتبر إعتلال الكلى الوظيفى الناتج عن مرض البوال السكرى أحد أشهر الأمثلة على أمراض التليف، كذلك يعد واحداً من المضاعفات الناتجة عن مرض البوال السكرى من النوع الأول أو النوع الثانى على السواء.

يهدف هذا البحث إلى دراسة تأثير زيادة مستوى الجلوكوز بمصل الدم على عامل النمو المحول بيتا-1 وعلاقتهما المسببة لإعتلال الكلى الوظيفى الناتج عن مرض البوال السكرى من النوع الثانى.

أجريت هذه الدراسة على ثمانية وخمسين شخصاً من الجنسين (نصفهم من الذكور والنصف الآخر من الإناث) ممن تتراوح أعمارهم 42 – 75 عاماً، وقد تم تقسيمهم إلى 4 مجموعات. إشتملت الأولى على عشرة أشخاص من المتطوعين الأصحاء كمجموعة ضابطة و الثانية على ستة عشر مريضاً بداء الكلى الناتج عن مرض البوال السكرى من النوع الثانى، ولديهم مستويات طبيعية من الزلال فى البوال و الثالثة على ستة عشر مريضاً بداء الكلى الناتج عن مرض البوال السكرى من النوع الثانى، ولديهم مستويات دقيقة من الزلال فى البوال و الرابعة على ستة عشر مريضاً بداء الكلى الناتج عن مرض البوال السكرى من النوع الثانى، ولديهم مستويات كبيرة من الزلال فى البوال.

أوضحت هذه الدراسة أن هناك زيادة ذات دلالة إحصائية فى مستوى عامل النمو المحول بيتا-1 بمصل الدم فى جميع المرضى وذلك عند مقارنتهم بالمجموعة الضابطة.كذلك وجد أن هناك زيادة ذات دلالة إحصائية فى مستوى عامل النمو المحول بيتا-1 بمصل الدم فى مرضى البوال السكرى المصابين بارتفاع ضغط الدم وذلك عند مقارنتهم بمرضى البوال السكرى الذين لا يعانون من ارتفاع ضغط الدم. وعلى الجانب الآخر، فقد لوحظ أن هناك علاقة إرتباط طردية ذات قيمة إحصائية بين مستوى الزلال فى البوال ومستوى عامل النمو المحول بيتا-1 بمصل الدم فى مرضى البوال السكرى ذوى المعدلات الدقيقة والكبيرة من الزلال فى البوال. كذلك لوحظ وجود علاقة

1-إرتباط طردية ذات قيمة إحصائية بين ارتفاع ضغط الدم الإنقباضى والإنبساطى ومستوى عامل النمو المحول بيتا
فى مرضى البوال السكرى من النوع الثانى ذوى المستويات الكبيرة من الزلال فى البوال.

ويستخلص من نتائج هذه الدراسة أن زيادة مستوى الجلوكوز بمصل الدم قد تتسبب فى حدوث إعتلال
الكلى الوظيفى الناتج عن مرض البوال السكرى ليس فقط نتيجة لتأثيرها المباشر على الكلى ولكن أيضاً من خلال
العديد من الطرق التى يلعب فيها عامل النمو المحول بيتا ─1 دوراً فعالاً.