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Original Research Article

Serum malondialdehyde and adiponectin in albuminuric kidney disease patients

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ABSTRACT

Background: Diabetes, hypertension, oxidative stress, obesity, adipocytokine dysfunction, and dyslipidemia are causative factors in development of Chronic Kidney Disease (CKD). Adiponectin secreted from adipose tissue, has Reno protective effect against development of albuminuria in animal studies. The previous studies investigated the relationship between serum adiponectin level and urinary albuminuria in kidney disease patients, but the results are conflicting.
Methods: The pre diagnosed kidney disease patients were divided into microalbuminuria and macroalbuminuria groups, while control subjects were called as normoal buminuria group. The pre diagnosed adult kidney disease patients of both genders with age matching control subjects with no known comorbidity were included in the study. Whereas pregnant female patients and the patients with comorbidity were excluded from the study. The demographic data and the anthropometric data of control and kidney patients were recorded. The blood was analyzed for Glycosylated Hemoglobin (HbA1c), electrolytes, glucose, calcium, total protein, albumin, urea, creatinine adiponectin and malondialdehyde. The Urine was analyzed for Creatinine and albuminuria. The glomerular filtration rate was estimated.
Results: The blood pressure, blood urea, creatinine, glycated hemoglobin, malondialdehyde, adiponectin levels were higher in albuminuric kidney patients as compared to normal control subjects. The mean glomerular filtration rate was lowest in macroalbuminuric patients as compared to micro and normoalbuminuric patients. The serum adiponectin and serum malondialdehyde both showed positive correlation with serum creatinine, and with albuminuria/urinary creatinine ratio.
Conclusions: The study concludes that, positive correlation of serum malondialdehyde with adiponectin and albuminuria.

Keywords: Adiponectin, Albuminuria, Kidney disease, Malondialdehyde, Oxidative stress

INTRODUCTION

Oxidative stress is an instigator of the metabolic syndrome. The reactive oxygen species are produced by various cells, such as vascular cells, inflammatory cells and have different functions in different types of cells.[1] Reactive Oxygen Species (ROS) are highly reactive molecules that oxidize lipids and proteins and cause cellular injury. Within the kidney Nicotinamide Adenine Dinucleotide Phosphate oxidase (NADPH oxidase)

produce superoxide which affect renal epithelial ion transport and alters renal pressure, natriuresis, blood pressure and also contribute to proteinuria.[2] Systemic and tissue oxidative stress is also reported in chronic kidney diseases, which in turn increases the progressive reduction of renal function.[3] The increased extracellular glucose rapidly stimulate the generation of reactive oxygen species through NADPH oxidase and mitochondrial pathways. This increase of ROS is followed by apoptosis of podocytes.[4] Malondialdehyde is one of the markers of oxidative stress.

Adipose tissue play an active endocrine role via adipokines, which are produced by adipocytes or infiltrating macrophages.[5] The emerging evidences suggest that instead of being a consequence, oxidative stress may be a prerequisite for adipogenesis, and oxidative stress directly influence adiponectin synthesis.[6,7] Oxidative stress is the modulator of adiponectin expression of adipose tissues, and is also an active player in the regulation of adiponectin in chronic kidney diseases.[8] Adiponectin levels affect albuminuria through several pathways; inhibition of the adiponectin-AMPK pathway has now become established as a critical pathway, regulating inflammation in kidney diseases. Adenosine Monophosphate Kinase (AMPK) regulates Nuclear Factor Kappa B (NFkB) activation and is a potent regulator of NADPH oxidases.[9]

Adiponectin exhibits antioxidative and anti-inflammatory effects.[5] Adiponectin seems to exert beneficial effects in kidney's glomerulosclerosis and interstitial fibrosis, and lack of adiponectin increases glomerular permeability and albuminuria.[10] In podocytes, adiponection may increase the AMPK activity, and also reduces the protein levels of NADPH oxidase-4 (NOX-4), thus reducing oxidative stress and normalize albuminuria.[1] Adiponectin has been reported to exert beneficial renal effects protecting against the development of albuminuria in rodent experiments.[11] Several studies have been performed to investigate the relationship of albuminuria with adiponectin level but the results are conflicting.[12]

METHODS

The blood and urine samples of 30 control and 55 pre diagnosed kidney patients both male and female were collected. This study was carried out at the Department of Biochemistry at Al-Tibri Medical College Karachi. The ethical approval was taken from the Isra University.

Inclusion criteria

- Adults of both genders with age matching controls without any disease and the pre diagnosed adult kidney disease patients were included in the study.

Exclusion criteria

- Female patients with pregnancy and the patients suffering from the diseases related to hyperthyroidism, gout, urinary stones, liver disease, arthritis, malignancy, bone metabolism were excluded from the study.

The duration of study was from June 2017 to December 2017. Under aseptic conditions 10 ml of blood was drawn and serum was preserved at -700 C for analysis. The blood pressure was recorded. HbA1c were analyzed by Cobas c 111 (Roche) analyzers. The microlab (Merck) was used for estimation of blood sugar, total protein, albumin, urea and creatinine with the help of their respective kits. The estimation of serum adiponectin was performed by Elisa kit supplied by Glory science co. ltd. and malondialdehyde was estimated by ELISA (Enzyme-linked immunosorbent assay) kit supplied by Germany. 24hours urine was collected from which albuminuria, and Creatinine was estimated. Urine analysis was done by Cybow reader 300. The data was analyzed by SPSS version 21.0. For comparison between different quantitative variables one-way ANOVA was applied, p-value <0.05 was taken as significant. Correlation among the parameters was calculated by Bivariate Pearson's correlation (r).

RESULTS

The 30 normal control subjects having no kidney disease and were execrating albuminuria less than 30 mg/dl were included in group 1 called normoalbuminuric group. The kidney patients were divided into two groups, group-2 included 25 patients having albuminuria 30-299 mg/dl called microalbuminuria patients and group-3 includes 30 subjects whose albuminuria was more than 300 mg/dl called macroalbuminuria group.

The systolic and diastolic blood pressure in albuminuria kidney disease patients was significantly ($p<0.001$) higher as compared to normal control persons (Table 1). The mean value of blood urea, serum creatinine was higher in albuminuria kidney disease patients as compared to normal control subjects. The random blood sugar was significantly high among albuminuria kidney disease patients as compared to normal control subjects. The mean value of serum adiponectin and MDA in micro albuminuria and macroalbuminuria kidney patients was high as compared to normal control persons (Table 2).

The urine analysis results are tabulated in (Table 3). The mean value of albuminuria to urinary creatinine ratio among albuminuria kidney disease patients was significantly high as compared to normal control subjects. The mean value of glomerular filtration rate was high in normal control persons than albuminuria kidney disease patients.

Table 1: Variation in BMI and blood pressure of normal control and albuminuria kidney disease patients the results are given as Mean±SD.

Variables	Groups	Mean±SD	F	p value
Age (years)	Control	47.13±4.99	1.22	0.300
	Microalbuminuria	51.60±9.051		
	Macroalbuminuria	48.43±15.29		
Body mass index (kg/m^2)	Control	23.89±3.83	0.97	0.383
	Microalbuminuria	26.11±8.22		
	Macroalbuminuria	25.51±6.09		
Systolic blood pressure (mm hg)	Control	113.33±8.44	14.12*	0.001
	Microalbuminuria	133.60±23.43		
	Macroalbuminuria	141.67±27.30		
Diastolic blood pressure (mm hg)	Control	77.33±5.04	3.60*	0.032
	Microalbuminuria	84.00±14.72		
	Macroalbuminuria	86.17±17.00		

Table 2: Variation of biochemical parameters of normal control and albuminuria kidney disease patients the results are given as Mean±SD.

Variables	Groups	Mean±SD	F	p value
Urea mg/dl	Control	23.37±7.88	52.16*	0.0001
	Microalbuminuria	86.16±42.61		
	Macroalbuminuria	104.03±36.36		
Serum Creatinine Mg/dl	Control	0.79±0.18	41.36*	0.001
	Microalbuminuria	3.62±2.48		
	Macroalbuminuria	4.95±2.01		
Random blood sugar (RBS) mg/dl	Control	108.43±7.28	6.31*	0.003
	Microalbuminuria	152.60±64.94		
	Macroalbuminuria	155.47±74.72		
Glycated hemoglobin (Hba1c) %	Control	5.52±0.32	16.38*	0.001
	Microalbuminuria	5.89±0.36		
	Macroalbuminuria	5.97±0.28		
Adiponectin µg/ml	Control	8.69±0.91	54.14*	0.001
	Microalbuminuria	10.93±2.62		
	Macroalbuminuria	14.45±2.58		
Malondi-aldehyde µm/l	Control	1.65±0.47	808.37*	0.001
	Microalbuminuria	13.64±1.39		
	Macroalbuminuria	14.55±1.86		
Calcium mg/dl	Control	9.45±0.57	10.81*	0.001
	Microalbuminuria	8.77±0.97		
	Macroalbuminuria	8.42±1.01		

Table 3: Variation of urinary albuminuria, urinary creatinine and glomerular filtration rate in normal control and albuminuria kidney disease patients the results are given as Mean±SD.

Variables	Groups	Mean±SD	F	p value
Albuminuria mg/dl	Control	21.63±3.69	71.36*	0.001
	Microalbuminuria	91.20±53.02		
	Macroalbuminuria	643.33±364.53		
Urinary creatinine mg/dl	Control	1.41±0.84	0.12	0.88
	Microalbuminuria	1.54±1.05		
	Macroalbuminuria	1.55±1.57		
Albuminuria/urinary Creatinine Ratio (ACR)	Control	22.21±17.57	26.97*	0.001
	Microalbuminuria	73.04±42.24		
	Macroalbuminuria	708.57±669.03		
Glomerular Filtration Rate (GFR) ml/min	Control	98.77±18.99	248.89*	0.001
	Microalbuminuria	25.93±14.75		
	Macroalbuminuria	19.78±10.11		

Table 4: Correlation of blood and urinary biochemical parameters with serum malondialdehyde.

Variables	r value	p value
Blood		
Urea	0.711	0.000
Bun	0.723	0.000
Serum creatinine	0.679	0.000
Random blood sugar	0.361	0.001
Glycated hemoglobin	0.502	0.000
Adiponectin	0.625	0.000
Calcium	- 0.402	0.000
Urine		
Albuminuria	0.549	0.000
Urinary creatinine	0.061	0.579
Albuminuria/ urinary creatinine ratio	0.399	0.000
Glomerular filtration rate	- 0.907	0.000

Malondialdehyde was negatively correlated with calcium and glomerular filtration rate. The blood urea, urea nitrogen, serum creatinine, random blood sugar, glycated hemoglobin, adiponectin, albuminuria and albuminuria to urinary creatinine ratio were positively correlated with serum malondialdehyde (Table 4). Serum adiponectin showed a positive correlation with malondialdehyde (Table 5).

Table 5: Correlation of blood and urinary biochemical parameters with adiponectin.

Variables	r value	p value
Blood		
Urea	0.519	0.000
Blood urea nitrogen	0.529	0.000
Serum creatinine	0.541	0.000
Random blood sugar	0.304	0.005
Glycated hemoglobin	0.453	0.000
Malondialdehyde	0.625	0.000
Calcium	- 0.383	0.000
Urine		
Albuminuria	0.654	0.000
Urinary creatinine	0.226	0.037
Albuminuria/urinary creatinine ratio	0.461	0.000
Glomerular filtration rate	- 0.608	0.000

DISCUSSION

Kidney diseases are associated with a number of alterations in metabolic and physiological functions such as abnormalities in lipid, amino acid, bone and homocysteine, metabolism, malnutrition, insulin resistance, inflammation and oxidative stress etc. Many other factors such as dyslipidemia, diabetes and hypertension are also associated with kidney dysfunction.[13]

Serum creatinine and serum urea levels are the markers of renal function and renal damage and these markers assist the diagnosis, monitoring and prognosis of kidney disease.[14] In the present study an elevated level of serum creatinine and urea were found in micro and macro albuminuric kidney disease patients as compared to normal control subjects. Sarabandi et al, had found high level of serum urea in patients as compared to control. Stepien et al, had reported slightly increased but non-significant difference in the level of serum urea and creatinine in early stage of chronic kidney disease.[15,16]

A low serum calcium level but within normal reference range was observed in albuminuric kidney patients as compared to control subjects in the present study (table-2). It might be possible that kidney patients may have low vitamin D level. Both epidemiological and experimental studies have shown that vitamin D3 deficiency contributes in the progression of decline of kidney function.[17] Janmaat et al, had reported that low serum calcium is associated with a more rapid Chronic Kidney Disease (CKD) progression and the low serum calcium seem to be indicative of vitamin D deficiency.[18] According to Gallant and Spiegel a calcium balance is required for normal function of kidney.[19]

The characteristics of Chronic Kidney Disease (CKD) are loss of renal energy and uremia result in an imbalance between free radical production and antioxidant defense. In addition, hyperlipidemia, hypertension and diabetes mellitus trigger the inflammatory process and accelerate renal injury progression. Peroxidation of membrane polyunsaturated fatty acid by free radical produces malondialdehyde that could be a useful indicator for assessing oxidative damage. Elevated level of serum malondialdehyde level in Chronic Kidney Disease (CKD) patients with Cardiovascular Disease (CVD) had been reported earlier.[20] In the present study also the kidney patients with albuminuria had shown a significant increase in the level of serum malondialdehyde as compared to normal control patients, (Table 2) and oxidative stress marker malondialdehyde is positively correlated with albuminuria/Creatinine ratio (Table 4) so it is being proposed that a high oxidative stress which is seen in the vascular wall and in the glomeruli may be directly involved for vascular dysfunction in albuminuric kidney patients.[21,22]

Persistent glomerular injury produces hypertension, capillary vessels increasing Glomerular Filtration Rate (GFR) in every single nephron and protein leak in tubular fluids. Protein urea increase angiotensin II production. Accumulated cytokine induces the mononuclear cell accumulation in the interstitial tissues. The interstitial neutrophils will be replaced by macrophages and produces interstitial neutrophils inflammation causes formation of fibroblast which disrupts capillaries and tubular nephron and produces fibrosis. Glomerular hyper proliferation causes damage in podocyte cells, endothelial cells and mesangial cell proliferation resulting in

systemic hypertension which damage the glomerulus and worsen chronic kidney disease.[23] Albuminuria/urinary creatinine ratio had been increased in albuminuric kidney patients as compared to control subjects in the present study (Table 3) as was earlier reported by Hurtado et al.[24]

Adiponectin is a multifunctional cytokine which regulates inflammation and plays a role in the pathogenesis of acute renal injury and it may be a potential therapeutic agent.[25] In the present study an increased level of adiponectin was found in kidney disease patients as compared to control subjects (Table 2). Higher levels of serum adiponectin are positively associated with Chronic Kidney Disease (CKD) in Asian population.[26] In patients with chronic kidney disease loss of renal function results with an increase of serum adiponectin concentration.[27] Iwashima et al, performed a study in which the patients were grouped into CKD stages on the basis of estimated creatinine clearance and found a significant association between higher plasma adiponectin level and worse degree of CKD.[28] The adiponectin gene expression in adipocytes is decreased with the advancement of chronic kidney disease. The reduced gene expression may be related to negative feedback and results in elevation of total serum adiponectin level.[29]

Shen et al, had found that the expression of receptors adipo R1 and adipo R2 were increased on peripheral blood mononuclear cells in end stage renal disease patients as compared to controls and these levels were correlated with subcutaneous and visceral fat.[30] This shows that increased level of adiponectin is not only due to decreased renal excretion but may be a response to other factors within the system. This finding is consistent to Tsigalon et al, results.[31]

In the present study the serum adiponectin level increases with the progression of albuminuria as was earlier reported by Kacso et al.[32] There is an up regulation of circulating adiponectin due to decreased renal clearance of adiponectin in subjects with advanced albuminuria and decrease in GFR. The up regulation of adiponectin production rate is a compensatory mechanism to mitigate further renal injury, appears to be the main cause of increased serum adiponectin levels in patients with advanced albuminuria. The elevation of adiponectin expression and production was demonstrated in end stage renal disease human patients.[33] Although the subtotal nephrectomised rats showed a decreased expression of adiponectin in adipose tissue. This may be, that subtotal nephrectomy may accompanied by changes in fat mass and insulin sensitivity, that may interfere with altered adiponectin expression in adipose tissue. So further studies are needed to confirm the mechanism for elevated adiponectin expression by human adipose tissue in renal diseases.

Albuminuria is positively correlated with serum adiponectin in the present study (Table 5). The present results are in consistent to the previous findings.[34-36] However in studies with type-2 diabetic subjects with albuminuria, a decreased level of circulating adiponectin level was found as compared to non-albuminuric subjects.[37] This may be due to increased insulin resistance in diabetics with albuminuria as compared to diabetics without albuminuria, which may account for down regulation of serum adiponectin level in patients with type-2 diabetes whereas in patients who were suffering from type-1 diabetes and diabetic nephropathy, the serum adiponectin level progressively increased from normo to micro and macro albuminuria.[38]

A positive correlation of adiponectin to advanced albuminuria indicates the counter acting up regulation of serum adiponectin to reduce renal injury. The reno protective effect of adiponectin is based on data from non-human experiments. So, there is a need to explore the exact route of biodegradation of adiponectin in human for understanding the role of adiponectin in renal physiology.[39] Adiponectin receptors are present on epithelial cells of human kidney tubules. Adiponectin activate AMPK and cAMP signal transduction pathways and inhibits angiotensin II induced NADPH oxidase activation in these cells, an effect which depends on adipo R1. Adiponectin also attenuated the increase in NF-Kβ- activity and fibronectin expression. So, vitro findings support the hypothesis that adiponectin may impact progression of CKD by limiting Angiotensin-II induced oxidative stress, inflammation and fibrosis in kidney.[40]

Adiponectin control anabolic process and oxidative stress in glomerulus through AMPK-activated pathways. It is likely that adiponectin also play an important role in the development of albuminuria through podocytes. Hopefully, further research in renal physiology related to adiponectin may lead to therapeutic approaches for albuminuria and kidney disease.

CONCLUSION

The kidney disease patients had shown a progressive increase in albuminuria with the increase of oxidative stress and adiponectin.

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