Early Biochemical Changes in the Development of Nephropathy in Type II Diabetics

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Abstract

Objectives: To detect the early biochemical changes showing the development of diabetic nephropathy in type II diabetics and to recommend some measures to slow down these changes.

Materials and Methods: It was cross-sectional analytical study and was conducted through nonprobability convenient sampling. It comprised of 50 recently diagnosed (within 2 years) patients of type II diabetes mellitus and 50 healthy subjects. Alcoholics, pregnant ladies and individuals having serious infection or disease or having neoplasia were not included in the study. Random blood glucose, blood urea, serum creatinine, urinary albumin and urinary creatinine were estimated and albumin to creatinine ratio (ACR) mg/g was calculated.

Results: Mean values of random plasma glucose level, serum creatinine, urine albumin, urine creatinine and ACR in diabetic group when compared with those of healthy group showed significant P values (≤0.05).

Conclusion: In our setup due to a lack of regular health care type II DM is coincidently diagnosed and it is very difficult to assess the exact duration of the disease and type II diabetics develop nephropathy due to continuous high plasma glucose levels.

Keywords: Diabetes Mellitus, Nephropathy, Albumin Creatinine Ratio

How to cite: *Siddiqui RA, Akram S, Fatima E, Mustansar M. Khan HA, Liaqat S. Early Biochemical Changes in the Development of Nephropathy in Type II Diabetics. Esculapio - JSIMS 2023;19(04):404-407.*

DOI: https://doi.org/10.51273/esc23.25131946

Introduction

Type II Diabetes Mellitus is a disease of miscellaneous causes marked by hyperglycemia, due to flaws in the action or secretion of insulin, or both.[1] The sufferers of diabetes mellitus on our planet as estimated in 2017 were 451 million (age 18–99 years). These figures were expected to increase to 693 million by 2045.[2] Diabetes type II causes destruction, loss of function and failure of different organs, especially blood vessels, heart, nerves and kidneys.[3]

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Submission Date: 07-09-2023
1st Revision Date: 27-09-2023
Acceptance Date: 12-12-2023

Diabetes is said to be linked with complications of microvascular nature such as nephropathy, neuropathy and retinopathy. These complications rout to kidney damage.[4] Diabetic nephropathy (DN) is a clinical diagnosis and its presentation can have diversity in patients of type II diabetes mellitus. In the initial phase, it is marked by glomerular hyperfiltration followed by albuminuria (microalbuminuria/macroalbuminuria), hypertension, and gradual loss of glomerular filtration rate (GFR) that results to end-stage nephropathy.[5]

The rate and incidence of diabetic nephropathy are not so much clear in type II diabetes mellitus mainly due to the highly inconsistent inception age and difficulty in explaining the inception time. There are marked racial variations. In epidemiology of diabetic nephropathy the racial variations are high which can be explained partially by the differences in dietary habits, smoking, environmental factors and health care services. The danger of the development and progression of diabetic nephropathy lies mainly in poor glycemic and blood pressure control, obesity, dyslipidemia and lack of exercise.[6] The duration of T2DM and genetic susceptibility

are also important factors. The majority of individuals who develop DN are sufferers of T2DM because it accounts for 90% of diabetes worldwide.[7] Diabetic nephropathy is a major cause of end-stage kidney disease (ESKD) throughout the world and it is linked to an increase in cardiovascular (CV) risk. Diabetic nephropathy increases morbidity and mortality in people living with diabetes. Risk factors for DN are chronic hyperglycemia and high blood pressure. The renin-angiotensin-aldosterone system blockade improves glomerular function and CV risk in these patients.[8]

In diabetic nephropathy, there is a gradual loss of kidney function which occurs in the time range of months and years as per the National Kidney Foundation. Kidney diseases are defined as shown in the table below.[9]

Stages	Description	GFR (ml / Min / 1.73 m^2)
1	Renal Damage + Normal GFR	≥ 90
2	Renal Damage + Mildly Decreased GFR	60-89
3	Moderately Decreased GFR	30-59
4	Severely Decreased GFR	15-29
5	Renal Failure	< 15

In diabetes type II, high level of blood glucose accelerates the activation of Beta and Delta types of protein kinase C in the cortex of kidneys. This process activates the nuclear factor Kappa Light Chain Enhancer of activated B cells and causes interleukin II release[6] as well as release of the Tumor Necrosis Factor (TNF) Alpha by the mesangial and endothelial cells.[10] The molecular mechanisms which are involved in renal damage in diabetes describe the pathogenesis of proinflammatory molecules and mechanisms related to the development and progression of DN. The potential utility of agents has been discussed that target inflammatory-related factors or pathways, including inflammatory cytokines, oxidative stress or pro-inflammatory pathways such as Signal transducers and activator of transcription (STAT/JAK) or Nuclear Factor-kB.[11] One of the studies has highlighted the importance of one of these inflammatory processes, the 17th immune response, in the pathogenesis of diabetic renal injury. So according to current information there is involvement of Th17/IL-17A in diabetes and diabetes-induced end-organ, with special attention to the kidney.[12] Microalbuminuria is an initial symbol of diabetic nephropathy. For screening purpose assessment of microalbuminuria is performed as a routine by clinicians but the renal damage may be there without microalbuminuria. It is important to adopt different methods for early assessment of diabetic nephropathy. This may allow earlier diagnosis and treatment, which minimize diabetic nephropathy or turn down the development of diabetic nephropathy.[13]

Materials and Methods

This study was according to the Helsinki Declaration, approved by the ethics committee of the institution and was performed on the newly diagnosed patients of type II diabetes mellitus.

The study was performed in the Department of Biochemistry Sheikh Zayed Hospital Lahore and patients were taken from the Department of Medicine, Nephrology and Diabetic Clinic.

The biomarkers used for the detection of kidney disease include serum creatinine, creatinine clearance (eGFR), and microalbuminuria. In microalbuminuria, an abnormally high amount of albumin is excreted in urine falling in the range of 30-299 mg/g creatinine. To detect increased excretion of urinary proteins, the urinary albumin to creatinine ratio (ACR) in mg/g is calculated.

This was a Cross-sectional Analytical study. The study was done through nonprobability convenient sampling. The clinical examination and the lab values of the study parameters were recorded on the designed proforma. The total sampling was one hundred individuals between the age of 35-75 years comprising an equal number of males and females. Group 1 comprised of 50 healthy individuals and Group 2 having 50 patients of type II diabetes mellitus diagnosed for the last 2 years. Individuals on steroids or anti-oxidant drugs were not included in the study. Similarly alcoholics, pregnant ladies and individuals with active infection, serious disease and neoplasia were also excluded from the study. After consent 5 ml of the venous blood was drawn for biochemical analysis. A wide-mouth bottle was used for the collection of urine samples. Random plasma glucose, blood urea, serum creatinine, urinary albumin and creatinine (spot) tests were performed on all the participants. Creatinine clearance (e-GFR) was calculated from serum creatinine by using CG (Cockcroft and Gault) formula. The urinary albumin to creatinine ratio was calculated in mg/g. The tests were performed in the biochemistry lab of Sheikh Zayed Hospital Lahore on the Beckman Coulter AU 480 Auto analyzer. SPSS 24.0 was used for data entry and analysis. Simple frequencies were drawn. The biochemical parameter of group 1 and 2 were compared and p-values < 0.05 were considered as significant. The P value was calculated by 2 Tail T Test.

Results

Table No: 1& 2 show the distribution of subjects according to gender and age in the present study. The biochemical tests for random blood glucose, blood urea, serum creatinine, urinary albumin and creatinine were conducted on healthy subjects and patients having diabetes mellitus type II for about 2 years. The results of these 2 groups were compared with each other. The results of these groups are shown in the table. Group 1 – Healthy Subjects Group 2 – Type II Diabetes Mellitus with Nephropathy. In Groups 1 and 2, the P values for age, blood urea and eGFR were non-significant. However the P values for random blood glucose level, S/creatinine and urine albumin creatinine ratio were significant. The parameters serum creatinine, urine albumin, urine creatinine and albumin creatinine ratio indicate early diabetic nephropathy.

Table 1: *Group 1: Age & sex distribution in Healthy Subjects*

Age in years	Males N=25		Females N=25	
	No	%	No	%
40-45	8	32	9	36
46-50	1	4	5	20
51-55	5	20	3	12
56-60	6	24	3	12
61and above	5	20	5	20

Table 2: *Group 2: Age & sex distribution in type II diabetics*

Age in years	Males N=25		Females N=25	
	No	%	No	%
40-45	7	28	13	52
46-50	6	24	6	24
51-55	5	20	1	4
56-60	5	20	2	8
61and above	2	8	3	12

Table 3: *Comparison of Statistics of Group 1 and 2.*

	Group 1 (n= 50)	Group 2 (n= 50)		
Variable	Mean±SD	Mean±SD	P-Value	Significant
Age (Years)	49.6 ± 7.7	51.5±10.9	0.316	NS
Random Plasma Glucose (mg/dl)	118.4±8.5	253 ± 24.3	0.001	S
Blood Urea (mg/dl)	26.7±4.9	26.8 ± 5.3	0.822	NS
Serum Creatinine (mg/dl)	0.87±0.15	0.89±0.15	0.001	S
Urine Albumin (mg/dl)	1 ± 0.0	1.14±0.35	0.001	S
Urine Creatinine (mg/dl)	104.5±11.2	90.6±26.9	0.001	S
Albumin Creatinine ratio (mg/g)	9.7 ± 1.1	13.7 ± 5.1	0.001	S
e GFR	116 ± 18.2	77.7±17.1	0.275	NS

Discussion

This study was performed on 50 type II diabetics diagnosed within 2 years duration. A control sample of 50 healthy subjects was selected for comparison. Both male and female individuals in the age group of 35-75 years were included. There was no significant difference in age between the two groups as shown in the Table. The duration of DM in patients with diabetic nephropathy was 2 years. This criterion has got a likeness with the study conducted by Selvi V S et al (2015).[14] The random plasma glucose level in group 2 was determined to be significantly higher than that of group 1 (healthy controls) (p-value < 0.001) (Table). It shows that, usually, there is poor glycemic control in complicated cases of DM. Kashinakunti SV (2016) and Raghavani PH, Sirajwala H (2014) observed much the same results in their studies.[15,16] The median level of blood urea in group 1 (healthy controls) was found to be nonsignificant than that of group 2. The median level of serum creatinine in groups 1 and 2 showed a significant difference (P value 0.001). These differences have also been reported by Oluba OM and Festuso.[17] The median urine albumin level in groups 1 and 2 showed a significant difference (P value 0.04). Similarly, the mean values for urine creatinine and albumin creatinine ratio were also significantly different. Tarig Karar et al[18] also described that early markers of diabetic nephropathy are microalbuminuria and urinary albumin creatinine ratio. Microalbuminuria is taken as the gold standard for the diagnosis of diabetic nephropathy. However, it cannot catch almost half of the patients of early diabetic nephropathy.[19] The estimated Glomerular Filtration Rate (eGFR) in the present study was non-significant (P value 0.275) as compared to the healthy group. According to Kidney Disease Improving the Global Outcome Work Group (KDIGO) guidelines, the patients who have albuminuria but normal eGFR are in stages I & II and those who have albuminuria and low eGFR are in stages III, IV & V of kidney disease.[20]

Conclusion

In our setup, due to lack of regular health monitoring patients of type II DM are accidentally diagnosed and it is very difficult to determine the exact duration of the disease. Type II diabetics develop nephropathy due to persistent high plasma glucose levels. Regular monitoring and maintenance of the aforesaid parameters and healthy changes in lifestyle can delay nephropathy.

Conflict of interest: *None*
Funding source: *None*

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Authors Contribution

RAS: Conceptualization of Project
HAK: Data Collection
SA: Literature Search
SL: Statistical Analysis
EF: Drafting, Revision
MM: Writing of Manuscript