Effect of type 2 diabetes mellitus duration on fasting plasma glucose, serum creatinine, and urinary microalbumin in type 2 diabetics attending to Diabetic Centre at Teaching Hospital Jaffna

Ruwanpathirana, R. P. E.*, Kandeepan, K.** and Arasaratnam, V.**

Unit of Allied Health Sciences, Faculty of Medicine, University of Jaffna.
**Department of Biochemistry, Faculty of Medicine, University of Jaffna.*
erandika.r4@gmail.com

Abstract - Diabetes Mellitus is the most common non-communicable chronic metabolic disease worldwide. Renal complications are one of the major complications apart from cardiovascular, neurological and retinal complications. The objective of this study was to evaluate the effect of type 2 diabetes mellitus duration on fasting plasma glucose, serum creatinine and urinary microalbumin in type 2 diabetics attending to Diabetic Centre at Teaching Hospital Jaffna. A total of 98 patients diagnosed as type 2 diabetics without chronic kidney diseases were included. Fasting plasma glucose (Glucose Oxidase method), serum and urine creatinine (Jaffe Alkaline Picric Acid method) and random urine albumin (Immunoturbidimetry method) were estimated. The strength of correlation was determined by Pearson correlation. The mean (±SD) fasting plasma glucose, serum creatinine and urine albumin to creatinine ratio were 136.17 (±53.92) mg/dL, 1.25 (±0.64) mg/dL and 49.31 (±102.64) mg/g creatinine respectively. The mean (±SD) random urine creatinine, random urine albumin and duration of diabetes mellitus were 1.21 (±0.80) g/L, 34.38 (±54.04) mg/L and 9.28 (±7.20) years respectively. Out of 98 type 2 diabetics, 69 (70.41%), 25 (25.51%), and 4 (4.08%) had normoalbuminuria, microalbuminuria and macroalbuminuria respectively. When the duration of diabetes mellitus was increased, fasting plasma glucose level, serum creatinine, random urine albumin and urine albumin to creatinine ratio were gradually increased. But random urine creatinine was gradually decreased with the duration of diabetes mellitus. The longest duration of diabetes mellitus was 13.57 (±9.93) years in the sub-group of ≥201 mg/dL. The highest urine albumin to creatinine ratio ≥61 mg/g was resulted in the mean (±SD) duration of diabetes mellitus 14.27 (±7.70) years which was the longest duration of diabetes mellitus. On applying Pearson correlation, duration of diabetes mellitus showed a weak positive correlations with fasting plasma glucose (r = 0.251, p = 0.013) and serum creatinine (r = 0.097, p = 0.340). Urine albumin to creatinine ratio showed a weak positive correlation with duration of diabetes mellitus which was statistically significant (r= 0.430, p= 0.000). This study revealed that FPG, serum creatinine and albumin excretion were increased with the duration of diabetes mellitus in type 2 diabetics

Keywords: Creatinine, Duration of diabetes, Microalbuminuria, Plasma glucose.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder with the presence of chronic hyperglycemia as a result of derangement in metabolism of carbohydrate, protein and fat associated with relative or absolute deficiencies in insulin action, insulin secretion or both [1]. Estimated worldwide prevalence of diabetes was approximately 285 million (6.4%) in 2010 and it is anticipated to increase up to 438 million (7.7%) by 2030 and would be the seventh leading cause of death [2]. Approximately 90% of all cases of diabetes are constituted by type 2 diabetes [3]. Insufficient production of insulin hormone by the β- cells of pancreas or the insulin resistance means inadequate respond to the normal insulin levels by the peripheral receptors such as muscles, fat tissues and liver are leading to type 2 diabetes mellitus [1]. Diabetes mellitus may lead to cause severe cardiovascular, neurological, retinal and renal complications and chronic metabolic disorders [4].

In 1926, Rehberg originated the use of serum creatinine as a perfect filtration marker of glomerular filtration rate (GFR) [5]. It is a more sensitive indicator of renal function [3]. Reduction in glomerular filtrate and increase in serum creatinine represent abnormal renal function [6]. Low creatinine might reflect glomerular hyperfiltration and low muscle mass volume [7]. By glomerular filtration, the concentration of plasma creatinine is maintained within narrow range predominantly [3]. Diabetes nephropathy is a leading cause of end stage renal disease and affects 20 to 30% of all diabetics [6]. Type 2 diabetes mellitus less commonly develop diabetic nephropathy, but due to the higher incidence, approximately 60% of all cases are found in type 2 diabetics. Increased rate of albumin escaping through the capillary membrane is indicated by increased urinary albumin excretion and used as a marker of microvascular disease [3]. Lower levels of albumin in urine are normal and upper levels of albumin excretion represent macroalbuminuria or clinical proteinuria. Most sensitive and simplest prognostic factor is represented by microalbuminuria which is one of the earliest sign of progressive diabetic nephropathy, increased vascular permeability and vascular function abnormality in type 2 diabetics [2].

According to the International Diabetes Federation, South-East Asia, estimated prevalence of diabetes in the South-East Asia Region is 78 million and it will rise to 140 million by 2040. In Sri Lanka, there were 1.16 million (8.5%) diabetes in 2015 [8]. This means diabetes mellitus may be a big burden to Sri Lanka in near future with presence of diabetic nephropathy. This study reveals the importance of assessing

the effect of duration of diabetes mellitus on fasting plasma glucose, serum creatinine and urinary microalbumin based on a study involving patients attending to Diabetic Centre at Teaching Hospital, Jaffna.

METHODOLOGY
Subjects
Blood and urine samples of the patients who had been diagnosed to have type 2 diabetes mellitus and attending Diabetic Centre, Teaching Hospital, Jaffna were selected for this study. The sample size was 98 [9],which was approximately one third (1/3) of the total population attending the clinic in a month. Informed written consents were obtained for the collection of additional 4 mL venous blood during the blood collection for routine investigations and random urine samples.

Patients with fever, obstructive liver disease, thyroid disease, already diagnosed as chronic kidney disease or pyelonephritis or glomerulonephritis and on treatment, evidence of proteinuria due to other ill-health and congestive cardiac failure or history of heart failure of any stage were excluded from this study. Data extraction sheet was used to enter the data and filled by the interviewer administered way.

Ethical clearance was obtained from the Ethics Review Committee of the Faculty of Medicine, University of Jaffna.

ANALYTICAL METHODS
Height, weight, sex, fasting (8h) plasma glucose concentration [Glucose Oxidase, 10], serum and urine creatinine concentration (Colorimetric Jaffe Alkaline Picric Acid, 11]and urinary Microalbumin concentration (Immunoturbidimetry, 12]were measured. Obtained data was entered in Statistical Packages for Social Sciences (SPSS) Version 21. Basic descriptive statistics named mean and standard deviation, Independent t-test and Pearson chi squared test were used.

RESULTS AND DISCUSSIONS
Out of 98 diabetics, 60 were females (61.23%). Mean age was 59.9 (±10.4) with the range of 40 to 85 years. The males were not significantly older than the females (p=0.572). Majority of type 2 diabetic patients [36 nos.] were in the age group of 60-69 years. It was the same age group with the highest number of both males [15 (15.31%)] and females [21 (21.43%)]. The mean (±SD) body mass index (BMI) was 24.85 (±4.59) [(24.06 (±3.33) males, 25.34 (±5.21) females] kg/m2. There was no significant difference between their body mass index (p= 0.182). Mean FPG level was 136.17 (±53.92) mg/dL [144.59 (±70.09) and 130.85 (±40.3) mg/dL in males and females respectively but did not differ significantly (p = 0.221)], which was significantly higher than the glycaemic control based on the FPG level (<126mg/dL). However, FPG level of the 17.4, 31.6 and 51 % of the patient were <100mg/dL (controlled), 100-126 mg/dL (like that of prediabetics) and >126mg/dL (uncontrolled glycaemic control) respectively. The mean serum creatinine, urine albumin, urine creatinine and urine albumin to creatinine ratio were 1.25(±0.64)mg/dL, 18.9(±16.2)mg/L, 1.21(±0.80)g/L and 17.11(±14.16) mg/g creatinine respectively.

The mean (±SD) fasting plasma glucose level was 144.59 (±70.09) and 130.85 (±40.3) mg/dL in males and females respectively (p = 0.221). Although, the mean (±SD) fasting plasma glucose level was high in males than females, there was no statistically significant difference between fasting plasma glucose levels of males and female (p>0.05). The mean (±SD) serum creatinine concentration of all 98 type 2 diabetic patients was 1.25 (±0.64) mg/dL and those of males and females were 1.28 (±0.72) mg/dL and 1.23 (±0.59) mg/Dl respectively. The mean (±SD) random urine albumin excretion of all 98 type 2 diabetic patients was 34.38 (±54.04) mg/L while those of males and females were 49.30 (±74.83) and 24.93 (±32.49) mg/L respectively. The mean (±SD) of random urine creatinine excretion of all 98 type 2 diabetic patients was 1.21 (±0.80) g/L and those of males and females were 1.36 (±0.96) and 1.11 (±0.68) g/L respectively. The mean (±SD) of urine albumin to creatinine ratio of all 98 type 2 diabetic patients was 49.31 (±102.64) mg/g. Mean (±SD) urine albumin to creatinine ratio of males and females were 73.03 (±140.55) and 34.28 (±65.88) mg/g respectively.

Serum creatinine level, urine albumin concentration, random urine creatinine concentration and urine albumin to creatinine ratio in of type 2 diabetic patients Classified based on duration of type 2 diabetes mellitus.

For all 98 type 2 diabetic patients, the mean (±SD) duration of diabetes mellitus was 9.28 (±7.20) years while those of males and females were 9.76 (±7.67) years and 8.97 (±6.92) years respectively. The mean (±SD) duration of diabetes mellitus was higher in males than the females. But the duration difference between males and females was not significant (p=0.596).

The patients were grouped into based on the fasting plasma glucose levels, it was observed that the plasma glucose level increases as the duration of diabetes increases. The longest duration of diabetes mellitus was 13.57 (±9.93) years in the sub-group of plasma glucose ≥201 mg/dL. Males [16.33 (±8.33) years] showed a similar observation of longest duration of diabetes mellitus in the sub-group of fasting plasma glucose ≥201 mg/L. But the sub-group of fasting plasma glucose 161-180 mg/dL showed the longest duration of diabetes mellitus in females [12.50 (±0.71) years]. Duration of diabetes mellitus was longer in males than the females. Finding of this study showed that with the increased duration of diabetes mellitus, random urine albumin and urine albumin to creatinine ratio was also increased. The sub-group of highest urine albumin to creatinine ratio ≥61 mg/g was observed in the mean (±SD) duration of diabetes mellitus 14.27 (±7.70) years which was the longest duration of diabetes mellitus. Similar results were observed in both males [17.11 (±5.30) years] and females [10.00 (±9.21) years] in the same sub-group. The duration of diabetes of all 98 type 2 diabetic patients were sub-grouped into 1-5,6-10, 11-15, 16-20 and ≥20 years. Based on the results, majority of type 2 diabetic patients [39 (39.80%)] were in the duration of 1-5 years and was true for both the males [15 (15.31%)] and females [24 (24.49%)] (Table 1). It was clearly observed that, when the duration of

diabetes mellitus was increased, fasting plasma glucose level, serum creatinine, random urine albumin and urine albumin to creatinine ratio were gradually increased (Table 1). But random urine creatinine was a gradually decreased with the duration of diabetes mellitus. Fasting plasma glucose and random albumin to creatinine ratio gradually increased with the duration of diabetes mellitus in both males and females except for the duration range of 1-5 years (Table 1).

The results may be varied due to the different number of male and female patients. On the other hand, 1-5 years of duration means that this is the initial years in which they found that they were suffering from diabetes mellitus.

It was observed that the highest amount of fasting plasma glucose, serum creatinine, random urine albumin and urine albumin to creatinine ratio were found in the sub-group of duration of diabetes mellitus ≥21 years (Table 1). This was true for both males and females who had duration of diabetes mellitus ≥21 years except for serum creatinine for males which showed highest amount in the sub group of 11-15 years (Table 1). Random urine creatinine did not gradually increase with the duration of diabetes mellitus and show the highest amount of random urine creatinine in the sub group of 6-10 years. It was true for males, but for females. Females showed the highest amount of random urine creatinine in the sub group of ≥21 years.

Classification of type 2 diabetic patients with normoalbuminuria, microalbuminuria and macroalbuminuria based on duration of Diabetes Mellitus

Significant difference was found with the duration of diabetes mellitus and the type 2 diabetic patients with normoalbuminuria, microalbuminuria and macroalbuminuria (p=0.000). The mean (±SD) duration was 8.14 (±6.80), 10.36 (±6.74) and 22.00 (±2.71) years in normoalbuminuria, microalbuminuria and macroalbuminuria patients with type 2 diabetes respectively. All 98 type 2 diabetic patients were classified based on the duration of diabetes mellitus (Table 2). It was observed that the majority of patients were in the duration of 1-5 years resulting number was 39 (39.80%). But there were not patients suffered from macroalbuminuria. Similar observation was found in the 6-10 and 11-15 year groups which was absent of macroalbuminuria patients. The least number of patients [10 (10.20%)] were observed in the patients with ≥21 years of duration of diabetes mellitus (Table 2). There were 59 diabetic patients with disease duration >5 years. Out of them, 38 (64.41%) had normoalbuminuria, 17 (28.81%) had microalbuminuria and 4 (6.78%) had macroalbuminuria. Correlation between duration of Diabetes Mellitus with fasting plasma glucose level of type 2 diabetic patients
On applying Pearson correlation, duration of diabetes mellitus was compared with fasting plasma glucose. There was a weak positive correlation between duration of diabetes mellitus and fasting plasma glucose with correlation coefficient of r = 0.251 and p = 0.013). The correlation coefficient (r value) for duration of diabetes mellitus and fasting plasma glucose in males was r= 0.297. It was not significant (p = 0.070). For

females, similar observations were observed. Relationship between duration of diabetes mellitus and fasting plasma glucose was not significant (r=0.200, p=0.125). According to the results, both in males and females, the duration of diabetes mellitus showed a weak positive correlation with fasting plasma glucose.

Correlation between duration of Diabetes Mellitus with serum creatinine concentration of type 2 diabetic patients Duration of diabetes mellitus was correlated with serum creatinine on applying Pearson correlation. Weak positive correlation was observed between duration of diabetes mellitus and serum creatinine (r = 0.097) which was not significant (p = 0.340). There was a weak negative correlation which was observed between duration of diabetes mellitus and serum creatinine in males [r= (-0.089)] which was not significant (p= 0.595). Duration of diabetes mellitus showed a weak positive correlation with serum creatinine (r=0.252) which was not significant (p=0.052) in females.

Correlation between duration of Diabetes Mellitus with urine albumin to creatinine ratio of type 2 diabetic patients By applying Pearson correlation, the correlation between duration of diabetes mellitus and urine albumin to creatinine ratio was observed. Duration of diabetes mellitus showed a weak positive correlation with urine albumin to creatinine ratio (r = 0.430). There was a significant relationship between duration of diabetes mellitus and urine albumin to creatinine ratio (p = 0.000). A moderate positive correlation was found between duration of diabetes mellitus and urine albumin to creatinine ratio resulting r= 0.571 which was statistically significant (p = 0.000). Duration of diabetes mellitus showed a weak positive correlation with urine albumin to creatinine ratio (r= 0.273) which was shown a significant correlation (p=0.035) in females. Duration of diabetes mellitus in both females and males showed significant correlations with urine albumin to creatinine ratio.

DISCUSSION
Based on the study conducted by Mishra et al., 2015 [4], fasting plasma glucose level and serum creatinine was significantly increased with the increased duration of diabetes in diabetic patients. The duration of diabetes was divided into three groups as 0-5, 2-5 and >5 years and the resulted fasting plasma glucose levels were 111 (±25.2), 134 (±45.2), 187. (±81.2) mg/dL and resulted serum creatinine levels were 1.05 (±0.38), 1.07 (±0.24), 1.3 (±0.32) mg/dL respectively which indicated the gradual increased with the duration of diabetes. In our study, similar results were found. The fasting plasma glucose and serum creatinine were increased with the duration of diabetes indicating mean (±SD) fasting plasma glucose 125.02 (±38.50), 128.39 (±38.84), 138.39 (±33.96), 159.22 (±79.24), 162.82 (±100.18) mg/dL and serum creatinine 1.22 (±0.6), 1.25 (±0.4), 1.29 (±0.8), 1.30 (±0.4) and 1.54 (±1.0) in the sub-groups of duration of diabetes 1-5, 6-10, 11-15, 16-20 and ≥21 years respectively.

Considering the duration of diabetes, Bamanikaret al. [6], 2016 found that patients with more than six years duration were

found to be had higher serum creatinine levels compared to lesser duration of diabetes. According to our results, highest mean (±SD) serum creatinine was shown in patients suffered from diabetes mellitus more than ≥21 years [1.54 (±1.0) mg/dL]. They had shown that the duration and severity of diabetes strongly correlated with serum urea levels, but not so with serum creatinine level.

CONCLUSION

This study revealed that increased in duration and poor glycemic control would cause increasing in the serum creatinine level, urine albumin to creatinine level and increase the chances of suffering from diabetic nephropathy. Good glycemic control is absolute requirement in diabetic patients with increased duration to prevent progressive renal impairment and diabetic nephropathy which is one of the major causes of chronic renal failure. Serum creatinine is a simple test helpful in diabetics who are poorly controlled to access the renal function. Microalbuminuria is a reliable marker of diabetic nephropathy in type 2 diabetic patients. All patients with type 2 diabetes mellitus should be screened with microalbuminuria at the time of diagnosis and subsequent yearly thereafter.

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Table 1 : The mean (±SD) serum creatinine, random urine albumin, random urine creatinine and urine albumin to creatinine ratio duration of Diabetes Mellitus Type 2 S (males 38, females 60 and Total 98), patients grouped on their fasting plasma glucose levels.

Duration (Years)	Patients No. (%)			Fasting Plasma Glucose (SD) (mg/dL)			Serum creatinine (SD) (mg/dL)			Urine albumin (SD) (mg/L)			Urine creatinine (SD) (g/L)			Urine albumin to creatinine ratio (SD) (mg/g)		
	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
1-5	15 (15.3)	24 (24.5)	39 (39.8)	120.46 (30.3)	127.87 (43.2)	125.02 (38.5)	1.31 (0.8)	1.16 (0.5)	1.22 (0.6)	10.94 (11.5)	21.82 (23.6)	17.64 (20.4)	1.70 (1.1)	0.95 (0.6)	1.24 (0.9)	7.08 (5.4)	29.89 (29.2)	21.12 (25.5)
6-10	7 (7.1)	12 (12.3)	19 (19.4)	142.02 (55.3)	120.44 (24.8)	128.39 (38.8)	1.16 (0.5)	1.16 (0.5)	1.25 (0.4)	62.32 (59.2)	13.60 (7.7)	31.55 (42.3)	1.79 (1.0)	1.07 (0.5)	1.34 (0.8)	30.75 (30.6)	16.56 (17.2)	22.83 (23.5)
11-15	5 (5.1)	13 (13.3)	18 (18.4)	163.68 (19.9)	128.66 (33.7)	138.39 (34.0)	1.69 (1.3)	1.14 (0.4)	1.29 (0.8)	67.83 (50.9)	23.08 (19.9)	35.51 (36.3)	1.20 (0.4)	1.30 (0.8)	1.27 (0.7)	74.90 (73.2)	21.42 (16.5)	36.27 (45.4)
16-20	6 (6.1)	6 (6.1)	12 (12.3)	172.49 (104.9)	145.94 (48.8)	159.22 (79.2)	1.29 (0.4)	1.09 (0.4)	1.30 (0.4)	60.10 (62.8)	41.74 (60.8)	50.92 (59.6)	0.71 (0.5)	1.05 (0.7)	1.01 (0.6)	147.23 (147.4)	57.00 (82.8)	102.11 (123.4)
≥21	5 (5.1)	5 (5.1)	10 (10.2)	167.98 (137.8)	157.66 (59.3)	162.82 (100.2)	0.94 (0.2)	2.13 (1.0)	1.54 (1.0)	114.67 (163.7)	51.71 (67.9)	83.19 (122.7)	0.72 (0.6)	1.55 (1.1)	1.14 (0.9)	239.16 (294.1)	104.06 (201.1)	171.61 (248.0)

Table 2: Classification of type 2 diabetic patients with normoalbuminuria, microalbuminuria and macroalbuminuria based on duration of Diabetes Mellitus.

Duration (years)	Mean (±SD)									Number of patients (%)									Total (n=98)
	Normo-albuminuria (n=69)			Micro-albuminuria (n=25)			Macro-albuminuria (n=4)			Normo-albuminuria (n=69)			Micro-albuminuria (n=25)			Macro-albuminuria (n=4)			
	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T	T
1-5	7.08 (5.35)	13.7. (8.48)	10.50 (7.79)	0.00	62.27 (29.04)	62.27 (29.04)	0.00	0.00	0.00	15 (38.46)	16 (41.03)	31 (79.49)	0 (0.00)	8 (20.51)	8 (20.51)	0	0	0	39 (39.80)
6-10	11.93 (2.73)	11.90 (5.99)	11.91 (5.22)	55.84 (33.88)	67.90	58.86 (28.31)	0.00	0.00	0.00	4 (21.05)	11 (57.90)	15 (78.95)	3 (15.79)	1 (5.26)	4 (21.05)	0	0	0	19 (19.39)
11-15	16.71 (2.67)	13.57 (7.80)	14.09 (7.21)	113.70 (71.23)	47.58 (5.35)	80.64 (57.90)	0.00	0.00	0.00	2 (11.11)	10 (55.56)	12 (66.67)	3 (16.67)	3 (16.67)	6 (33.33)	0	0	0	18 (18.37)
16-20	16.41 (17.06)	13.43 (6.89)	14.62 (9.95)	158.22 (103.68)	100.56 (106.85)	129.39 (99.31)	375.90	0.00	375.90	2 (16.67)	3 25.00	5 (41.67)	3 (25.00)	3 (25.00)	6 (50.00)	1 (8.33)	0	1 (8.33)	12 (12.25)
≥21	13.74 (12.01)	1418 (9.27)	14.03 (8.97)	80.23	0.00	80.23	544.05 (181.70)	463.58	517.22 (136.62)	2 (20.00)	4 (40.00)	6 (60.0)	1 (10.00)	0	1 (10.0)	2 (20.00)	1 (10.00)	3 (30.0)	10 (10.20)