Pak J Med Res
Vol. 59, No. 1, 2020

Original Article

Association of Estimated Glomerular Filtration Rate with HbA1c and Microvascular Complications in Type 2 Diabetes

Nazish Waris[1,2], Ambreen Shiraz[3], Muhammad Azfar Tanveer[4], Faisal Ahmed[5], Asher Fawwad[2,3], Iftikhar Ahmed Siddiqui[3], Abdul Basit[6]

Department of Biochemistry[1], University of Karachi, Department of Research[2], Baqai Institute of Diabetology and Endocrinology, Department of Biochemistry[3], Baqai Medical University, Karachi, Department of Medicine[4], Nishter Medical College, Multan, Department of Family Medicine[5], Baqai Medical University, Department of Medicine[6], Baqai Institute of Diabetology and Endocrinology, Karachi.

Abstract

Objective: To determine the association of estimated Glomerular Filtration Rate (eGFR) with HbA1c and microvascular complications in patients with type 2 diabetes.
Study design, settings & duration: This retrospective study was based on a hospital data record of patients visiting the outpatient department of Baqai Institute of Diabetology and Endocrinology, Baqai Medical University from January 2018 to October 2018.
Methodology: Data was obtained from hospital management system (HMS). Records of Patients with type 2 diabetes having data on eGFR were included. Calculation of eGFR was done by MDRD formula. Following clinical practice guideline (KIDGO) eGFR was grouped into five GFR Categories of CKD Stage 1, 2, 3, 4 and 5.
Results: Total of 3165 patients, 1773 (56%) males and 1392 (44%) females with type 2 diabetes were recruited. Mean age of patients was 50.4±10.84 years. Frequency of patients were higher 57.7% in eGFR category 2 (60-89 ml/min/1.73 m^2) and 32.1% eGFR category 3 (30-59 ml/min/1.73 m^2). Very low eGFR (<15 ml/min/1.73 m^2) was significantly associated with reduction of glycated HbA1c (%) and HDL-Cholesterol. While, decreased eGFR was significantly (p <0.0001) associated with increased risk of diabetic nephropathy, neuropathy, retinopathy and hypertension.
Conclusion: Overall, eGFR reduction especially in combination with longer disease duration is significantly associated with decreased HbA1c but increased risks of microvascular complications in patients with type 2 diabetes.
Key words: Microvascular complications, type 2 diabetes, eGFR, KIDGO.

Introduction

Glomerulus Filtration Rate (GFR) can be assessed by means of formulas stated as estimated GFR (eGFR). It shows the flow rate of filtered fluid via kidney.[1] In patients with diabetes, changes in eGFR have an early onset.[2] It was observed that rate of eGFR increases due to high blood sugar in early and in the later stages of diabetes mellitus (DM) it decreases reflecting a failure in renal functions.[1]

Around 20% to 40% of patients with diabetes develop kidney problems.[3] These medical disorders are characterized via constant albuminuria (> 300 mg/24 h, or 300 mg/g creatinine), persistent decrease in rate of glomerular filtration [eGFR (<60 mL/min/1.73 m2) for 3 months and more], raised blood pressure and higher risk of morbidity as well as mortality.[3-5] In Type 2 Diabetes Mellitus (T2DM) patients, direct association was also seen between HbA1c variability and decline in kidney functions. It demonstrates that strong association was present in

Corresponding Author:
Asher Fawwad
Department of Biochemistry
Baqai Medical University, Karachi.
Email: asherfawwad@bide.edu.pk

Received: 22 May 2019, **Accepted:** 10 April 2020,
Published: 24 June 2020

Authors Contribution

NW, AF & IAS conceptualized the project. NW & AF performed the data collection, literature search & statistical analysis. NW, AF & FA also did the data interpretation. Drafting, revision & writing of manuscript were done by NW, AF & MAT. KR also did the data collection literature search. NW, AF, AS, MAT, FA, IAS & AB edited and approved the manuscript.

microalbuminuria patients than in normo-albuminuria patients.[6] Conversely, consistency of glycemic control is also important for preserving kidney functions. Raised blood pressure (BP) and dyslipidemia were also associated with progression of microvascular complications in T2DM patients.[7,8] The guideline of kidney disease improving global outcomes (KDIGO) shows that staging of chronic kidney disease (CKD) is based on eGFR, the best index of kidney function and albuminuria as a kidney damage marker in health and diseases.[9] Earlier this staging was categorized by urinary albumin or protein excretion and no such strategy was defined to evaluate eGFR decline.[10] However later few formulas were developed to estimate GFR. Cockcroft and Gault (CG), Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease - Epidemiology Collaboration (CKD-EPI) are the most commonly used equations.[11] The Federation of American Diabetes (ADA) recommends the yearly screening of diabetic nephropathy and urinary excretion of albumin, meanwhile the Foundation of National Kidney (NKF) mentioned the MDRD equation for GFR estimation.[12]

Recent studies have focused on the correlation between levels of HbA1c and decrease eGFR in diabetes. However, very scarce data is present to determine direct association of eGFR with type 2 diabetic subjects in Pakistan. Therefore, the main objective of the current study is to find out the association and correlation of eGFR with HbA1c and microvascular complications in T2DM patients.

Methodology

This retrospective study is preceded by hospital data records of patients, who attended the outpatient department (OPD) of Baqai Institute of Diabetology and Endocrinology (BIDE), Baqai Medical University (BMU). The duration of study was from January 2018 to October 2018. Study was ethically approval by Institutional committee (IRB) of BIDE. Patients of both genders with T2DM having data of eGFR available with other biochemical parameters and baseline characteristics were included. Type 1 diabetes mellitus (T1DM) patients, pregnancy, malignant diseases, acute and chronic infections, renal transplantation, glomerulonephritis, liver diseases, hypo and hyperthyroidism were excluded.

Detail baseline demographics and anthropometric characteristics including age, gender, diabetes family history, diabetes duration, use of insulin duration, BMI, systolic and diastolic blood pressure were obtained from hospital BIDE management system (HMS). Height was measured when an individual standing in erect posture to the nearest of 0.1cm and weight 0.1 kilogram (kg) was measured with portable weighing scale. The ratio of weight (kg) and height squared (m^2) was considered BMI (body mass index). Blood pressure was recorded using mercury sphygmomanometer in sitting position via standardized technique. Blood pressure ≥130/85mmHg was considered as hypertension.[13]

Biochemical parameters (HbA1c, eGFR, serum creatinine, urine detailed report and lipid profile) and record of patients having any microvascular complications (nephropathy, neuropathy, and retinopathy) were also retrieved from HMS.

Nephropathy was diagnosed based upon finding of urinary albumin in the detailed urine analysis whereas protein and creatinine clearance was done by 24 hours' urine sample. As per the standardized guidelines, neuropathy was examined and determined after pin prick checking, ankle, knee reflex and vibration sense. Retinopathy was labeled after examining microdots, blot hemorrhage, hard exudates, soft exudates, and new vessel formation. HPLC technique on Bio-Rad D-10 was used to measure HbA1c.[14] In Erba Transasia autoanalyzer (XL-600) modified Jaffe's kinetic method was used for measuring serum creatinine. The eGFR calculation was done via MDRD formula as:

eGFR in mL/min per 1.73 m2 = 175 x SerumCr-1.154 x age-0.203 x 1.212 (if patient is black) x 0.742 (female) Or [186 × Serum Cr (mg/dL)-1.154] × [age (years)-0.203] × [0.742 female]. The 186 factor was used for creatinine non-compensated method.

Following clinical guideline Kidney Disease: Improving Global Outcomes, KIDGO, eGFR was grouped into five GFR Categories of CKD Stage 1, 2, 3, 4 and 5. As, GFR Category 1 (or CKD Stage 1; usual or elevated GFR with kidney damage) was described as eGFR ≥90 ml/min/1.73 m^2, Category 2 of GFR (or CKD Stage 2; mildly low GFR with kidney damage) as eGFR 60–89 ml/min/1.73 m^2, Category G3 (G3a and G3b, or Stage 3 CKD; moderately decreased GFR) as eGFR 30–59 ml/min/1.73 m^2, Category G4 (stage 4 CKD; severely decreased GFR) as eGFR <30 ml/min/1.73 m^2, and Category G5 (stage 5 CKD; Kidney failure) as eGFR <15 ml/min/1.73 m^2.[15-17]

The GOD-PAP method on a Selectra Pro S fully automated analyzer was used to determine plasma triglycerides. Similarly, CHOD-PAP technique on Pro S Selectra analyzer was used for serum total cholesterol measurements. For HDL (High Density Lipoprotein) cholesterol, homogeneous enzymatic

colorimetric technique and for LDL (Low Density Lipoprotein)-cholesterol, direct method was used.

For analyzing data, SPSS (statistical package for social sciences) version 20 was used. Baseline characteristics, biochemical results were compared using ANOVA and Chi-square test. To determine correlation between eGFR and baseline, biochemical parameters, coefficient of Pearson's correlation was used. Variables which showed potential association (*p*-value <0.20) with eGFR in correlation analysis were selected for stepwise multiple linear regression. We additionally entered HbA1c level related to eGFR. Results were statistically significant at *p*-value <0.05.

Results

Eight thousand and one hundred two (8102) patients with T2DM visited the outpatient department (OPD) of BIDE. Of these, 3165 patients, 1773 (56%) males and 1392 (44%) females with T2DM having eGFR were included. Patients mean age was 50.4±10.84 years.

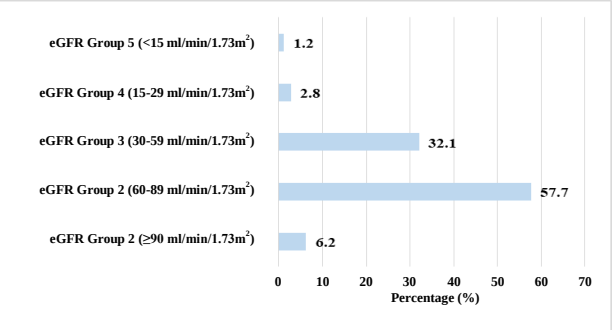

Figure 1: Percentage distribution of patients in 5 groups based on estimated glomerular filtration rate (eGFR).

Table 1: Baseline characteristics among 5 groups based on estimated glomerular filtration rate (eGFR).

Parameters	*eGFR Group 1 (≥90 ml/min/1.73 m²)*	*eGFR Group 2 (60-89 ml/min/1.73 m²)*	*eGFR Group 3 (30–59 ml/min/1.73 m²)*	*eGFR Group 4 (15–29 ml/min/1.73 m²)*	*eGFR Group 5 (<15 ml/min/1.73 m²)*	*p-value*	*Overall*
Age (year)	43.5±11.32	48.17±10.17	55.04±9.9	56.94±10.47	54.22±10.45	<0.0001 [a]	50.4±10.84
Gender							
Male	136(69.4%)	1172(64.1%)	405(39.9%)	42(47.2%)	18(48.6%)	<0.0001 [b]	1773(56%)
Female	60(30.6%)	655(35.9%)	611(60.1%)	47(52.8%)	19(51.4%)		1392(44%)
Height (cm)	163.43±11.1	163.59±9.87	158.86±10.78	160.41±8.93	159.96±10.45	<0.0001 [a]	161.96±10.46
Weight (kg)	75.98±17.91	77.43±15.32	74.18±15.57	71.29±14.45	66.52±16.65	<0.0001 [a]	76.08±15.67
BMI (kg/m²)	28.12±5.64	28.90±5.25	29.43±6.22	27.61±4.99	25.63±5.10	<0.0001 [a]	28.96±5.61
Pulse (BPM)	81.52±7.47	82.61±7.37	82.37±7.23	79.98±6.56	82.1±8.65	0.009 [a]	82.39±7.34
Systolic BP(mmHg)	124.16±16	125.21±15.99	129.44±18.13	127.68±21.15	125.31±24.23	<0.0001 [a]	126.55±17.06
Diastolic BP(mmHg)	79.79±9.46	80.18±9.15	79.59±10.04	78.57±10.88	77.97±11.84	0.230 [a]	79.9±9.54
Marital status							
Single	11(5.6%)	62(3.4%)	46(4.5%)	4(4.5%)	2(5.4%)	<0.0001 [b]	125(4%)
Married	183(93.8%)	1725(94.7%)	893(88.3%)	79(88.8%)	32(86.5%)		2912(92.4%)
Widow	1(0.5%)	34(1.9%)	72(7.1%)	6(6.7%)	3(8.1%)		116(3.7%)
Smoking habit							
Non-smoker	153(78.1%)	1496(81.9%)	900(88.6%)	81(91%)	32(86.5%)	<0.0001 [b]	2662(84.1%)
Smoker	28(14.3%)	196(10.7%)	54(5.3%)	4(4.5%)	2(5.4%)		284(9%)
Ex-smoker	15(7.7%)	135(7.4%)	62(6.1%)	4(4.5%)	3(8.1%)		219(6.9%)
Alcoholic							
Non-alcoholic	192(98%)	1810(99.1%)	1009(99.3%)	87(97.8%)	37(100%)	0.073 [b]	3135(99.1%)
Alcoholic	3(1.5%)	12(0.7%)	1(0.1%)	2(2.2%)	0(0%)		18(0.6%)
Ex-alcoholic	1(0.5%)	5(0.3%)	6(0.6%)	0(0%)	0(0%)		12(0.4%)
Family history of DM							
No	69(35.2%)	472(25.8%)	314(30.9%)	30(33.7%)	11(29.7%)	0.005 [b]	896(28.3%)
Yes	127(64.8%)	1355(74.2%)	702(69.1%)	59(66.3%)	26(70.3%)		2269(71.7%)
Duration of DM (years)	6.62±6.15	8.57±7.11	13.59±8.52	15.98±6.59	14.35±6.93	<0.0001 [a]	10.34±7.98
Duration of insulin use (years)	5.95±5.30	5.68±5.04	7.11±5.86	7.44±5.14	7.84±5.61	<0.0001 [a]	6.44±5.48
Hypertension							
No	92(48.2%)	862(47.7%)	379(38.5%)	40(47.6%)	16(50%)	<0.0001 [b]	1389(44.8%)
Yes	99(51.8%)	947(52.3%)	605(61.5%)	44(52.4%)	16(50%)		1711(55.2%)

Data presented as mean ± SD or n (%), *p*-value<0.05 considered to be statistically significant, a ANOVA and b Chi-square test were applied.

Table 2: Biochemical characteristics and complications among 5 groups based on estimated glomerular filtration rate (eGFR).

Parameters	*eGFR Group 1 (≥90 ml/min/ 1.73 m²)*	*eGFR Group 2 (60-89 ml/min/1.73 m²)*	*eGFR Group 3 (30–59 ml/min/1.73 m²)*	*eGFR Group 4 (15–29 ml/min/1.73 m²)*	*eGFR Group 5 (<15 ml/min/1.73 m²)*	*p-value*	*Overall*
Serum creatinine (mg/dl)	0.85±0.11	1.06±0.14	1.38±0.3	2.56±0.53	5.81±1.95	<0.0001	1.25±0.64
HbA1c (%)	9.64±2.18	9.31±2.12	9.41±2.22	9.49±2.4	8.23±2.31	0.009	9.36±2.17
HDL-Cholesterol (mg/dl)	33.99±9.43	35.83±9.35	35.16±10.94	31.18±9.97	26.94±10.44	<0.0001	35.24±10.01
LDL-Cholesterol (mg/dl)	83.35±31.6	86.54±31.88	85.53±35.51	76.38±33.34	71.97±37.85	0.010	85.59±33.23
Cholesterol (mg/dl)	151.9±48.3	157.46±42.64	155.04±46.98	149.21±48.45	137.41±47.66	0.041	155.82±44.77
Triglyceride (mg/dl)	192.6±163.6	219.77±161.6	217.27±138.7	219.55±110.7	209.69±160.1	0.381	217.12±153.3
Nephropathy							
No	84(46.4%)	764(45.2%)	277(29.7%)	7(9.3%)	0(0%)	<0.0001	1132(38.9%)
Yes	97(53.6%)	927(54.8%)	657(70.3%)	68(90.7%)	29(100%)		1778(61.1%)
Retinopathy							
No	84(79.2%)	887(85.2%)	411(73.7%)	19(47.5%)	3(25%)	<0.0001	1404(79.9%)
Yes	22(20.8%)	154(14.8%)	147(26.3%)	21(52.5%)	9(75%)		353(20.1%)
Neuropathy							
No	145(89.5%)	1294(82.5%)	561(66.1%)	30(42.9%)	11(42.3%)	<0.0001	2041(76.3%)
Yes	17(10.5%)	275(17.5%)	288(33.9%)	40(57.1%)	15(57.7%)		635(23.7%)

Data presented as Mean±SD or n (%), *p*-value<0.05 considered to be statistically significant, ANOVA and Chi-square test were applied.

Figure-1 shows frequency of patients in eGFR groups. Frequency of patients was 6.2%, 57.7%, 32.1%, 2.8%, and 1.2% in groups 1, 2, 3, 4 and 5, respectively.

Table-1 presents the patients baseline characteristics among eGFR groups. Most of the male patients were observed in eGFR groups 1 and 2, and females in groups 3, 4 and 5. Mean BMI of eGFR group 5 was lower as compared to other groups. Most patients were married, non-smokers and non-alcoholic in all eGFR groups. In group 1, mean value of diabetes duration (years) was 6.62±6.15, in group 2 was 8.57±7.11, in group 3 was 13.59±8.52, in group 4 was 15.98±6.59 and in group 5 was 14.35±6.93 (p <0.0001). Significant results were observed between all eGFR groups for hypertension (<0.0001), family history of diabetes (years) (p =0.005) and duration of insulin use (years) (<0.0001).

Table-2 shows the biochemical parameters and complications of T2DM patients among eGFR groups. Mean glycemic control (HbA1c%) at baseline was 9.64±2.18 in group 1, 9.31±2.12 in group 2, 9.41±2.22 in group 3, 9.49±2.4 in group 4 and 8.23±2.31 in group 5, while serum creatinine (mg/dl) was 0.85±0.11, 1.06±0.14, 1.38±0.3, 2.56±0.53 and 5.81±1.95, respectively. Significant results were observed for HDL-Cholesterol, LDL-cholesterol and total cholesterol, while results for triglycerides were non-significant.

Frequency of nephropathy was significantly higher in all eGFR groups, 97 (53.6%) in group 1, 927 (54.8%) in group 2, 657 (70.3%) in group 3, 68 (90.7%) in group 4, and 29 (100%) in group 5 (p <0.0001). Frequency of retinopathy and neuropathy was significantly higher 21 (52.5%) and 40 (57.1%) in group 4 and 9(75%) and 15 (57.7%) in group 5, respectively (p <0.0001).

Table 3: Correlation of estimated glomerular filtration rate (eGFR) with baseline and bio-chemical parameters.

Parameters	*r*	*p-value*
Age	-0.358	<0.0001
BMI	-0.016	0.372
Gender-male	0.206	<0.0001
Duration of diabetes	-0.355	<0.0001
Duration of insulin use	-0.145	<0.0001
Systolic blood pressure	-0.106	<0.0001
Diastolic blood pressure	0.035	0.052
Serum creatinine	-0.649	<0.0001
HbA1c	0.019	0.320
HDL-Cholesterol	0.053	0.011
LDL-Cholesterol	0.034	0.069
Cholesterol	0.018	0.397
Triglyceride	-0.028	0.170
Hypertension	-0.063	<0.0001
Nephropathy	-0.194	<0.0001
Retinopathy	-0.188	<0.0001
Neuropathy	-0.266	<0.0001

Pearson's correlation and point-biserial correlation was applied.
p-value <0.05 considered to be statistically significant.

In Table-3, correlation of eGFR with baseline and bio-chemical parameters are shown. Estimated GFR shows a significantly negative correlation with age (r =-0.358, *p* <0.0001), diabetes duration (years) (r =-0.355, *p* <0.0001), insulin use duration (years) (r =-0.145, *p* <0.0001), hypertension (r =-0.063, *p* <0.0001), and creatinine levels in blood (mg/dl) (r =-0.649, *p* <0.0001). No correlation of eGFR was found for BMI (Kg/m²), triglycerides, HbA1c (%) and HDL Cholesterol. Significantly inverse relation was observed for eGFR with nephropathy (r =-0.194, *p* <0.0001), neuropathy (r =-0.266, *p* <0.0001), and retinopathy (r =-0.188, *p* <0.0001).

By applying multiple stepwise linear regression, association of eGFR was found for male gender (β±S.E =11.26±1.03, *p* <0.0001), age (β±S.E =-0.29±0.05, *p* <0.0001), diabetes duration (β±S.E =-0.26±0.08, *p* =0.001), serum creatinine (β±S.E =-14.44±0.69, *p* <0.0001), nephropathy (β±S.E =-2.99±1.07, *p* =0.006) and neuropathy (β±S.E =-2.96±1.25, *p* =0.019) (Table-4).

Table 4: Stepwise multiple linear regression of estimated glomerular filtration rate (eGFR) with baseline and bio-chemical parameters.

Parameter	*β±S.E*	*p-value*
Serum creatinine	-14.44±0.69	<0.0001
Gender-male	11.26±1.03	<0.0001
Age	-0.29±0.05	<0.0001
Duration of DM	-0.26±0.08	0.001
Nephropathy	-2.99±1.07	0.006
Neuropathy	-2.96±1.25	0.019

β: Unstandardized coefficient; S.E: standard error.
p-value<0.05 considered to be statistically significant.

Discussion

Overall, high frequency of patients was observed in eGFR group 2 (60–89ml/min/1.73 m^2) and group 3 (30–59ml/min/1.73 m^2) similar to Alwakeel JS et al study.[18] In our study, very low eGFR (<15ml/min/1.73 m^2) was significantly linked with glycated HbA1c reduction. It was statistically related with high microvascular complications risk, including diabetic nephropathy, neuropathy and retinopathy. Our results are consistent with previous study that eGFR is considered as a rational non-invasive mode to assess microvascular complications risk and renal status in T2DM patients.[19]

In best of our knowledge, no such study from Pakistan reported direct association of eGFR with HbA1c and all three microvascular complications on the same type 2 diabetes patients. Jelinek HF et al established the association of good glycemic control by means of low incidence of micro- and macrovascular complications in T2DM subjects.[20] From previous study, we were unable to determine whether low eGFR was associated directly with decline rate of HbA1c in T2DM patients.[6] In current study, non-significant correlation was identified between HbA1c and low eGFR, but very low values of HbA1c in eGFR groups 5 was observed, which is known as functional renal failure- a stage of progressive functional loss, observed in CKD, T2DM patients. No such details are found in other studies, but findings somehow are similar to the study conducted in Oman that younger Omani adults shows poorer glycemic levels when compared to adults posing a difficult task to diabetes care teams.[21] Similarly, Kuo IC et al study demonstrates that at earlier CKD stages stronger HbA1c level is observed.[22]

In our study, significant association of low eGFR was found for older age, male gender, long duration of diabetes and high serum creatinine similar to Fontela PC, et al study.[12] Reduced renal functions are based on levels of serum creatinine. In this study, inverse relation was observed for serum creatinine as the value of eGFR decreased, serum creatinine level increased mainly in group 4 and 5. Frequency of nephropathy was significantly higher in all eGFR groups, while, neuropathy and retinopathy was found to be significantly higher in group 5 and group 4, respectively as compared to other groups. Age with renal functions was used as predictors of complications of T2DM. Considering long duration of T2DM as reported in previous study, eGFR was also identified as a potential single predictor for diabetes complications development.[20]

The eGFR evaluation has clinical significance in early diagnosis of diabetic nephropathy, neuropathy and retinopathy similar to previous reports.[1,23] Significantly inverse correlation was observed for hypertension between all groups in our study. Although, normal serum total cholesterol was observed in all groups, but decreased HDL in group 5 was found which might be due to lipid metabolism disturbance that potentially precedes the disease by several years.[24]

Overall, eGFR reduction especially in combination with longer disease duration is significantly associated with decreased HbA1c but, increased risk of microvascular complications (nephropathy, neuropathy and retinopathy) in T2DM patients. Thus, eGFR measurements will help to predict microvascular complications at early stages, especially in low resource country like Pakistan.

Use of retrospective data is the limitations and hence, data regarding lifestyle interventions

such as regular exercise, diet modifications and macrovascular complications were scarce. Secondly, the eGFR values were only estimated by using MDRD formula and hence, no correlation could be established using other formula. We, did not use any gold standard marker (insulin or iothalamate clearance) for comparison, however, details of demographic characteristics, anthropometric measurements, biochemical parameters and microvascular complications at baseline can reflect the intensity of disease severity.

Acknowledgement

We all authors acknowledge the Nida Mustafa (Statistician) for result analysis and research department for their kind support at Baqai Institute of Diabetology and Endocrinology.

Conflict of interest: None declared.

References

1. Wu J, Geng J, Liu L, Teng W, Liu L, Chen L. The relationship between estimated glomerular filtration rate and diabetic retinopathy. J ophthalmol 2015; 2015: 326209.
2. Luo Y, Wang X, Wang Y, Wang C, Wang H, Wang D, et al. Association of glomerular filtration rate with outcomes of acute stroke in type 2 diabetic patients: results from the china national stroke registry. Diabet Care 2014; 37(1): 173-9.
3. Oshima M, Toyama T, Haneda M, Furuichi K, Babazono T, Yokoyama H, et al. Estimated glomerular filtration rate decline and risk of end-stage renal disease in type 2 diabetes. PloS One 2018; 13(8): e0201535.
4. Rossing P, Persson F, Frimodt-Møller M. Prognosis and treatment of diabetic nephropathy: Recent advances and perspectives. Nephrol Ther 2018; 14: 31-7.
5. Ito H, Komatsu Y, Mifune M, Antoku S, Ishida H, Takeuchi Y, et al. The estimated GFR, but not the stage of diabetic nephropathy graded by the urinary albumin excretion, is associated with the carotid intima-media thickness in patients with type 2 diabetes mellitus: a cross-sectional study. Cardiovasc Diabetol 2010; 9(1): 18.
6. Takenouchi A, Tsuboi A, Terazawa-Watanabe M, Kurata M, Fukuo K, Kazumi T. Direct association of visit-to-visit HbA1c variation with annual decline in estimated glomerular filtration rate in patients with type 2 diabetes. J Diabet Metabol Disor 2015; 14(1): 69.
7. Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000; 321(7258): 412-9.
8. Rutledge JC, Ng KF, Aung HH, Wilson DW. Role of triglyceride-rich lipoproteins in diabetic nephropathy. Nat Rev Nephrol 2010; 6(6): 361.
9. Levey AS, Becker C, Inker LA. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. JAMA 2015; 313(8): 837-46.
10. Ito H, Takeuchi Y, Ishida H, Antoku S, Abe M, Mifune M, et al. High frequencies of diabetic micro-and macroangiopathies in patients with type 2 diabetes mellitus with decreased estimated glomerular filtration rate and normoalbuminuria. Nephrol Dial Transplant 2009; 25(4): 1161-7
11. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150: 604-12.
12. Fontela PC, Winkelmann ER, Ott JN, Uggeri DP. Estimated glomerular filtration rate in patients with type 2 diabetes mellitus. Revista da Associação Médica Brasileira 2014; 60(6): 531-7.
13. Watson RR. Nutrition in the Prevention and Treatment of Abdominal Obesity, 2nd Edition; 2014. (Accessed on 5th July 2018) Available from URL: https://www.elsevier.com/books/nutrition-in-the-prevention-and-treatment-of-abdominal-obesity/watson/978-0-12-813780-2.
14. Fawwad A, Butt AM, Siddiqui IA, Khalid M, Sabir R, Basit A. Neutrophil-to-lymphocyte ratio and microvascular complications in subjects with type 2 diabetes: Pakistan′ s perspective. Turk J Medi Sci 2018; 48(1): 157-61.
15. Eknoyan G, Lameire N, Eckardt K, Kasiske B, Wheeler D, Levin A, et al. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int 2013; 3(1): 5-14.
16. Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med 2013; 158(11): 825-30.
17. Fung CS, Wan EY, Chan AK, Lam CL. Association of estimated glomerular filtration rate and urine albumin-to-creatinine ratio with incidence of cardiovascular diseases and mortality in chinese patients with type 2 diabetes mellitus - a population-based retrospective cohort study. BMC Nephrol 2017; 18(1): 47.
18. Alwakeel JS, Isnani AC, Alsuwaida A, AlHarbi A, Shaikh SA, AlMohaya S, et al. Factors affecting the progression of diabetic nephropathy and its complications: a single-center experience in Saudi Arabia. Ann Saudi Med 2011; 31(3): 236.
19. Babaliche P, Nadpara RA, Maldar A. Association Between Estimated Glomerular Filtration Rate and Microvascular Complications in Type II Diabetes Mellitus Patients: A 1-Year Cross-Sectional Study. J Nation Med Assoc 2019; 111(1): 83-7.
20. Jelinek HF, Osman WM, Khandoker AH, Khalaf K, Lee S, Almahmeed W, et al. Clinical profiles,

comorbidities and complications of type 2 diabetes mellitus in patients from United Arab Emirates. BMJ Open Diabet Res and Care 2017; 5(1): e000427.
21. Al-Lawati JA, Barakat MN, Al-Maskari M, Elsayed MK, Al-Lawati AM, Mohammed AJ. HbA1c levels among primary healthcare patients with type 2 diabetes mellitus in Oman. Oman Med J 2012; 27(6): 465.
22. Kuo IC, Lin HY, Niu SW, Hwang DY, Lee JJ, Tsai JC, et al. Glycated hemoglobin and outcomes in patients with advanced diabetic chronic kidney disease. Scient Rep 2016; 6: 20028.
23. Lovrenčić MV, Biljak VR, Božičević S, Prašek M, Pavković P, Knotek M. Estimating glomerular filtration rate (GFR) in diabetes: the performance of MDRD and CKD-EPI equations in patients with various degrees of albuminuria. Clin Biochem 2012; 45(18): 1694-6.
24. Farasat T, Sharif S, Naz S, Fazal S. Significant association of serum creatinine with HbA1C in impaired glucose tolerant Pakistani patients. Paki J Med Sci 2015; 31(4): 991.