Austin Journal of Endocrinology and Diabetes

Open Access

Austin Publishing Group

Research Article

Combination of Estimated Glomerular Filtration Rate and Diabetic Retinopathy May be Useful for Diagnosing Diabetic Kidney Disease (DKD) in Patients with Type 2 Diabetes Mellitus

Xie Ying[1], Lu Bin[1] and Hu Renming[1]*

[1]Department of Endocrinology and Metabolism, Fudan University, China

***Corresponding author:** Hu Renming, Department of Endocrinology and Metabolism, Fudan University, Shanghai, China, Fax: +86-21-62481305; Email: renminghuhs@163.com

Received: January 27, 2015; **Accepted:** March 22, 2015; **Published:** March 25, 2015

Abstract

Background: Estimated Glomerular Filtration Rate (eGFR) and Diabetic Retinopathy (DR) are associated with Diabetic Kidney Disease (DKD). This study investigated the use of DR and eGFR for the diagnosis of DKD in patients with type 2 diabetes mellitus (T2DM).

Methods: This cross-sectional study examined 490 inpatients with T2DM. Binary logistic regression analysis and receiver operating characteristic (ROC) curve analysis were performed to evaluate the utility of using eGFR alone and using eGFR and DR together for the diagnosis of DKD.

Results: ROC analysis indicated that the area under the curve (AUC) of ROC curve for using eGFR alone for the diagnosis of DKD was 0.663 (95% CI:0.595, 0.730, $p < 0.001$). AUC for using DR and eGFR together was 0.860 (95% CI:0.819, 0.901, $p < 0.001$). Combined use of DR and eGFR with the cut-off value of 60 ml/min/1.73m2 for the diagnosis of DKD had a positive predictive value of 0.720, a sensitivity of 0.221, and a specificity of 0.990. Among the 28 patients diagnosed with DKD by this criterion, 5 had normo-albuminuria.

Conclusion: The combined use of eGFR and DR is useful for the diagnosis of DKD in patients with T2DM, especially in those with normo-albuminuria.

Keywords: Diabetic kidney disease; Estimated glomerular filtration rate; Diabetic retinopathy; Normo-albuminuria; Diagnosis

Introduction

Diabetic kidney disease (DKD) is the main cause of chronic kidney disease (CKD) in patients with type 2 diabetes mellitus (T2DM). Persistent albuminuria is considered as the earliest sign of DKD and is associated with adverse cardiovascular and renal events [1-3]. According to the current clinical diagnostic criteria, persistent albuminuria is the key condition to diagnose DKD in patients with T2DM [4, 5]. Most patients with DKD also have Diabetic Retinopathy(DR) [6,7], so the presence of DR may also be useful for the diagnosis and screening of DKD[4-8] .In fact, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative(NKF's KDOQI) guidelines recommend consideration of DR in the diagnosis of DKD in patients with T2DM[4]. However, some patients with DKD had normo-albuminuria [9], so the KDOQI criteria may need further refinement. Normo-albuminuria is prevalent in patients with CKD and T2DM [10,11]. GFR less than 60ml/min/1.73m^2 is the main criterion used for the diagnosis of CKD. Other research reported that low estimated GFR (eGFR) correlated with more pathologically severe DKD in patients with T2DM and proteinuria [12]. In the present study, we investigated the use of eGFR alone and the combined use of DR and eGFR for the diagnosis of DKD in patients with T2DM.

Method

We conducted a cross-sectional study in Huashan Hospital affiliated with Fudan University in Shanghai, China. The inpatients who had been diagnosed as T2DM between Jan 2010 to Jan 2013 were included. Exclusion criteria included acute fever, acute infection, heart failure, other known kidney diseases, dialysis and other types of diabetes. 490 patients were enrolled in this study. The data of age, gender, duration of diabetes and hypertension history were collected from the clinical records of patients. Height and weight were measured at the admission day. The fasting serum samples were used to measure HbA1c, total Cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), uric acid (UA) and serum creatinine. The morning urinary samples were used to measure ACR. Diabetic retinopathy was detected by ophthalmoscopy or the fundus photographic imaging with a 45-degree digital nonmydriatic camera.

(i) Determinations of variables

Albuminuria includes Microalbuminuria (ACR30-300mg/g) and macroalbuminuria (ACR>300mg/g) [13].

eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula: eGFR(ml/min per1.73m^2)

Citation: Ying X, Bin L and Renming H. Combination of Estimated Glomerular Filtration Rate and Diabetic Retinopathy May be Useful for Diagnosing Diabetic Kidney Disease (DKD) in Patients with Type 2 Diabetes Mellitus. Austin J Endocrinol Diabetes. 2015;2(1): 1031.

$=141\times (sCr/0.9)^{-1.209}\times 0.993^{age}$ (sCr>0.9 mg/dl, if male);

$=141\times (sCr/0.9)^{-0.411}\times 0.993^{age}$ (sCr<=0.9 mg/dl, if male);

$=144\times (sCr/0.7)^{-1.209}\times 0.993^{age}$ (sCr>0.7 mg/dl, if female);

$=144\times (sCr/0.7)^{-0.329}\times 0.993^{age}$ (sCr<=0.7mg/dl, if female)

(sCr: serum creatinine (mg/dl)) [14].

DR was classified by International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scales. The patients were diagnosed as non-DR, non-proliferative diabetic retinopathy (NPDR, with microaneurysms, intraretinal hemorrhages, definite venous beading, or prominent intraretinal microvascular abnormalities) or proliferative diabetic retinopathy (PDR, with neovascularization or vitreous/preretinal hemorrhage) [15] respectively.

By the criteria of DKD for patients with T2DM in NKF-KDOQI guideline, most patients had one or two of the following conditions were considered to have DKD (NKF): (i) macroalbuminuria was present (ii) microalbuminuria was present in the presence with diabetic retinopathy [4].

Statistical analyses were performed by the software package SPSS 16.0. Data of continuous variables were expressed as mean±standard deviation (SD). Data of continuous variables were expressed as number or percentage. The differences between groups were analyzed by ANOVE analysis for continuous variables and Chi-square tests for categorical variables. Binary logistic regression analysis was performed to obtain the predictive probabilities to predict DKD. The predictive probabilities of eGFR were saved as pre-1 and the predictive probabilities of combined use of DR and eGFR were saved as pre-2. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the efficiency of combined use of DR and eGFR to diagnose DKD. In the ROC analysis, DKD diagnosed by criteria of NKF-KDOQI guideline was set as state variable, and pre-1 and pre-2 were set as the tested variables. Significance level was set as p-value less than 0.05.

Table 1: Characteristics of the participants.

Characteristics	N=490
Age(years)	61.04±11.44
Male (n (%))	274(55.9%)
Duration of T2DM(years)	9.85±7.33
Hypertension (n (%))	222(45.4%)
BMI(kg/m^2)	24.18±3.36
HbA1c (%)	8.60±2.14
TC(mmol/L)	4.73±1.15
TG(mmol/L)	1.95±1.73
HDLC(mmol/L)	1.09±0.31
LDLC(mmol/L)	2.79±0.88
UA(mmol/L)	0.33±0.12
DR (n (%))	171(34.9%)
ACR(mg/g)	235.01±769.44
eGFR(ml/min/1.73m^2)	89.93±22.15
DKD (NKF) (n (%))	104(21.2%)

T2DM: type 2 diabetes mellitus, BMI: body mass index, HbA1c: glycosylated hemoglobin, TC: total cholesterol, TG: triglycerides, HLDC: high-density lipoprotein cholesterol, LDLC: low-density lipoprotein cholesterol, UA: uric acid, DR: diabetic retinopathy, ACR: albuminuria creatinine ratio, eGFR: estimated glomerular filtration rate calculated by CKD-EPI equation, DKD: diabetic kidney disease diagnosed by the criteria of NKF-KOQI guideline.

Result

Table 1 showed the baseline characteristics of the 490 enrolled patients and all of them had T2DM. The means of age and duration of diabetes were 61.04±11.44 years and 9.85±7.33 years, respectively. A total of 34.9% of patients had DR, 21.2% of patients had DKD based on NKF-KDOQI guidelines. The mean of urinary ACR was 235.01±769.44mg/g, and the mean of eGFR was 89.93±22.15ml/min/1.73m^2. (Table 2) showed the coefficients of binary logistic regression analysis for combined use of eGFR and DR to diagnose DKD. Using the results in Table 2, pre-2 was calculated by the following equation:

Predictive probability (eGFR=X,DR=1) $=1/[1+e^{-(0.083-0.033*X+2.839*1)}]=1/[1+e^{-(2.922-0.033*X)}]$[1]. In the ROC curve analysis, area under the curve (AUC) of eGFR to diagnose DKD was 0.663 (95%CI 0.595 ,0.730, p<0.001) (Figure 1). AUC of combined use of DR and eGFR to diagnose DKD was 0.860 (95%CI 0.819, 0.901, p<0.001) (Figure 1).

(Table 3) showed the clinical utility of the combined use of DR and eGFR to diagnose DKD. When the cut-off value of eGFR was set as 90 ml/min/1.73m^2, the predictive probability, sensitivity and specificity to diagnose DKD were 0.488, 0.462 and 0.925, respectively.

Table 2: Coefficient, standard error and p-value of Binary Logistic Regression for eGFR and DR*.

Covariates	B(coefficient)	Standard error	p-value
eGFR	-0.033	0.006	<0.001
DR	2.839	0.300	<0.001
Constant	0.083	0.536	0.877

Dependent variate was set as DKD using the criteria of NKF-KDOQI guideline.

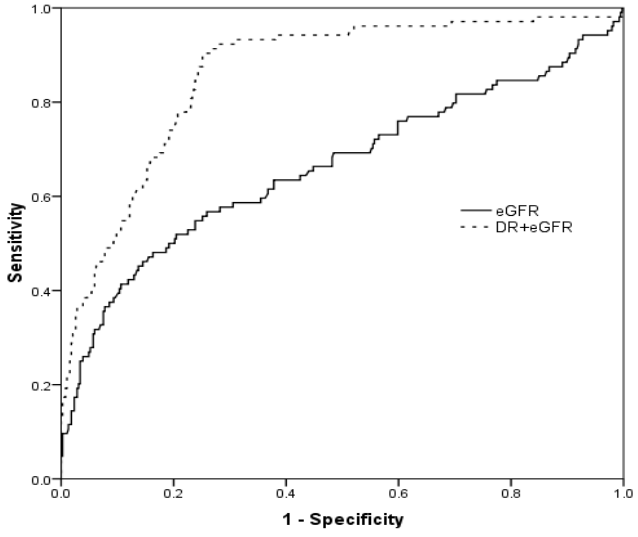

Figure 1: ROC curve of eGFR alone and combination of DR and eGFR to diagnose DKD in patients with T2DM.

Table 3: The clinical utility of combination of DR and eGFR to diagnose DKD.

Cut-off value of eGFR (ml/min/1.73m^2)	Predictive probability*	Sensitivity	Specificity	Diagnosed patients(n)**	Diagnosed patients with normo-albuminuria(n)
30	0.873	0.058	1.000	6	0
60	0.720	0.221	0.990	28	5
90	0.488	0.462	0.925	77	29

*: Predictive probability was calculated by the formula(1) obtained in binary logistic regression analysis.
**: Patients who had diabetic retinopathy and eGFR less than the cut-off value was considered to be the diagnosed patients.

At this cut-off value, 77 patients were diagnosed with DKD and 29 out of these patients had normo-albuminuria. When the cut-off value was set as 60 ml/min/1.73m^2, the predictive probability, sensitivity and specificity to diagnose DKD were 0.720, 0.221 and 0.990, respectively. At this cut-off value, 28 patients were diagnosed with DKD and 5 of these patients had normo-albuminuria. When the cut-off value was set as 30 ml/min/1.73m^2, 6 patients were diagnosed with DKD and all of them had albuminuria.

Discussion

The results of the present study demonstrated that the use of eGFR was effective for the diagnosis of DKD. Moreover, our ROC curve analysis indicated that the combined use of eGFR and DR was more effective than the use of eGFR alone for the diagnosis of DKD in patients with T2DM.

The eGFR reflects renal function and is used for staging of CKD[16] However, eGFR is normal or elevated in patients with early-stage DKD[4] , so it has not been used for diagnosis of DKD. Oh WS et al. analyzed the relationship between clinical characteristics and pathological classification by Tervaert et al [17]. in proteinuric patients with T2DM. In 50 patients with pure DKD and 11 patients with mixed DKD [12], eGFR was declined with the later class except class I [12]. Classification of DKD, percentage of global sclerosis and grade of interstitial fibrosis were all inversely correlated with eGFR [12]. In agreement, we found that eGFR was effective for the diagnosis of DKD, supporting the use of eGFR for diagnosing DKD in patients with T2DM.

Previous guidelines have used DR as an accessory component for the diagnosis of DKD [4]. Previous renal biopsy studies reported that most patients with DKD also had diabetic retinopathy [6, 7-18]. In particular, a meta-analysis by Huang et al. indicated that the sensitivity and specificity of DR to predict DKD in patients with T2DM were 0.65 and 0.72, respectively [8]. In the present study, the addition of DR made it more effective for the diagnosis of DKD. Moreover, the specificity of the combined use of DR and eGFR approximated 1 in all the cut-off values of eGFR we tested in this study (i.e.,30, 60 and 90) . The sensitivity was low at the cut-off value of 30 and the predictive probability was lower at the cut-off value of 90, so 60 might be a better cut-off value. It was coincident that 60 was also the cut-off value for the diagnosis of CKD. The current diagnostic criteria for DKD in T2DM were all base on albuminuria. In the present study, the combined use of DR and eGFR was able to recognize DKD in patients with normo-albuminuria. We were able to diagnose 5 additional patients with DKD who had normo-albuminuria at the cut-off value of 60. The reasons underlying normo-albuminuria in certain patients with CKD are elusive. Age, hypertension, uric acid metabolism, ischemic renal vessel diseases, rapid kidney progressive disease may participate in the rapid progression of eGFR decline before the onset of albuminuria [9,19-21]. Alternatively, use of renin-angiotensin-aldosterone system (RAAS) inhibitors or natural evolution of kidney disease may induce remission of micro-albuminuria without normalization of eGFR [22-24]. Some previous studies showed that DKD progressed without development of albuminuria or hypertension [9-25]. Regardless of the underlying mechanisms, our results indicated that DKD could manifest in the presence of normo-albuminuria, and that normo-albuminuria should therefore not be used to exclude a diagnosis of DKD. In particular, for the combined use of DR and eGFR less than 30ml/min/1.73m^2, none of the patients with non-albuminuric DKD were recognized. This result demonstrated that the combination of DR and eGFR could not recognize the non-albuminuric DKD at stages 4-5 of CKD.

Conclusion

Combination of eGFR and DR is useful in diagnosing DKD in patients with T2DM, especially in those with normo-albuminuria.

References

1. Sasso FC, Chiodini P, Carbonara O, De Nicola L, Conte G, Salvatore T, et al. Nephropathy In Type 2 Diabetes Study Group.High cardiovascular risk in patients with Type 2 diabetic nephropathy: the predictive role of albuminuria and glomerular filtration rate. The NID-2 Prospective Cohort Study. Nephrol Dial Transplant. 2012; 27: 2269-2274.
2. Wada T, Haneda M, Furuichi K, Babazono T, Yokoyama H, Iseki K, et al. Erratum to: Clinical impact of albuminuria and glomerular filtration rate on renal and cardiovascular events, and all-cause mortality in Japanese patients with type 2 diabetes.Clin Exp Nephrol. 2014; 18: 621-622.
3. Nitsch D, Grams M, Sang Y, Black C, Cirillo M, Djurdjev O, et al. Chronic Kidney Disease Prognosis Consortium. Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis.BMJ. 2013; 29: 346- 324.
4. KDOQI. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. Am J Kidney Dis. 2007; 49: S12-154.
5. SIGN 116 Management of Diabetes. NHS Quality Improvement Scotland. 2010.
6. Bi H,Chen N, Ling G, Yuan S, Huang G, Liu R. Nondiabetic renal disease in type 2 diabetic patients: a review of our experience in 220 cases. Ren Fail. 2011; 33: 26–30.
7. Chawarnkul O,Vareesangthip K, Ongajyooth L, Cheunsuchon B, Parichatikanond P. Non-diabetic glomerular disease in type II DM: 10 years experience. J Med Assoc Thai. 2009; 92: S57–S60.
8. He F, Xia X, Wu XF, Yu XQ, Huang FX. Diabetic retinopathy in predicting diabetic nephropathy in patients with type 2 diabetes and renal disease: a meta-analysis. Diabetologia. 2013; 56: 457-466.
9. López-Revuelta K, Galdo PP, Stanescu R, Parejo L, Guerrero C, Pérez-Fernández E. Silent diabetic nephropathy.World J Nephrol. 2014; 3: 6-15.
10. Lu B, Song X, Dong X, Yang Y, Zhang Z, Hu R, et al. High prevalence of chronic kidney disease in population-based patients diagnosed with type 2 diabetes in downtown Shanghai. J Diabetes Complication. 2008; 22: 96-103.

11. Dwyer JP, Parving HH, Hunsicker LG, Ravid M, Remuzzi G, Lewis JB. Renal Dysfunction in the Presence of Normoalbuminuria in Type 2 Diabetes: Results from the DEMAND Study. Cardiorenal Med. 2012; 2: 1-10.

12. Oh SW, Kim S, Na KY, Chae DW, Kim S, Chin HJ, et al. Clinical implications of pathologic diagnosis and classification for diabetic nephropathy. Diabetes Res Clin Pract. 2012; 97: 418-424.

13. American Diabetes Association. Standards of medical care in diabetes-2014. Diabetes Care. 2014; 37: S14-80.

14. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF,Coresh J, et al. CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150: 604–612.

15. Wilkinson CP, Ferris FL, Klein RE, Lee PP, Agardh CD, Verdaguer JT, et al. Global Diabetic Retinopathy Project Group.Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology. 2003; 110: 1677-1682.

16. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Eckardt KU, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2011; 80: 17–28.

17. Tervaert TW, Mooyaart AL, Amann K, Cohen AH, Cook HT,Bruijn JA, et al. Renal Pathology Society. Pathologic classification of diabetic nephropathy. J Am Soc Nephrol. 2010; 21: 556-563.

18. Chong YB, Keng TC, Tan LP, Ng KP, Kong WY, Tan SY, et al. Clinical predictors of non-diabetic renal disease and role of renal biopsy in diabetic patients with renal involvement: a single centre review. Ren Fail. 2012; 34: 323–328.

19. Ritz E. Type 2 diabetes: absence of proteinuria does not preclude loss of renal function (editorial). J Am Soc Nephrol 2004; 16: 284–285.

20. Bruno RM, Daghini E, Landini L, Versari D, Salvati A,Solini, et al. Dynamic evaluation of renal resistive index in normoalbuminuric patients with newly diagnosed hypertension or type 2 diabetes. Diabetologia. 2011; 54: 2430-2439.

21. Perkins BA, Krolewski AS. Early nephropathy in type 1 diabetes: the importance of early renal function decline. Curr Opin Nephrol Hypertens. 2009; 18: 233–240.

22. Gaede P, Tarnow L, Vedel P, Parving HH, Pedersen O, et al. Remission to normoalbuminuria during multifactorial treatment preserves kidney function in patients with type 2 diabetes and microalbuminuria. Nephrol Dial Transplant 2004; 19: 2784–2788.

23. Araki S, Haneda M, Sugimoto T, Isono M, Isshiki K,Koya D, et al. Factors associated with frequent remission of microalbuminuria in patients with type 2 diabetes. Diabetes. 2005; 54: 2983–2987.

24. Yamada T, Komatsu M, Komiya I, Miyahara Y, Shima Y, Aizawa T, et al. Development, progression, and regression of microalbuminuria in Japanese patients with type 2 diabetes under tight glycemic and blood pressure control: the Kashiwa study. Diabetes Care. 2005; 28: 2733–2738.

25. Yagil C, Barak A, Ben-Dor D, Rosenmann E, Bernheim J, Yagil Y, et al. Nonproteinuric diabetes-associated nephropathy in the Cohen rat model of type 2 diabetes. Diabetes 2005; 54: 1487–1496.

Austin J Endocrinol Diabetes - Volume 2 Issue 1 - 2015
ISSN : 2381-9200 | www.austinpublishinggroup.com

Citation: Ying X, Bin L and Renming H. Combination of Estimated Glomerular Filtration Rate and Diabetic Retinopathy May be Useful for Diagnosing Diabetic Kidney Disease (DKD) in Patients with Type 2 Diabetes Mellitus. Austin J Endocrinol Diabetes. 2015;2(1): 1031.