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Original Article

Loss of Inverse Association between Framingham Risk Score and Estimated Glomerular Filtration Rate in Moderate to Severe Diabetic Kidney Disease

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Abstract

Background: We investigated the association of estimated glomerular filtration rate (eGFR) with Framingham risk score (FRS), and actual cardiovascular disease (CVD) in patients with type 2 diabetes (T2DM). We also assessed improvement in FRS for prediction of CVD after inclusion of eGFR and albuminuria.

Methods: A total of 571 patients with T2DM and mean age 55 were divided into 2 groups based on the presence of CVD. Participants without CVD were then divided into three groups according to FRS. CVD is defined as an episode of CCU admission, Myocardial infarction, history of coronary artery bypass graft surgery or percutaneous intervention. FRS is calculated using the Wilson 1998 Circulation equation, which includes age, sex, high blood pressure, smoking, high-density lipoprotein (HDL), total cholesterol and diabetes as components to assess CVD risk in 10 years.

Results: An inverse adjusted association between eGFR and prevalent CVD was confirmed by multiple logistic regression analysis (OR = 0.84, 95% CI: 0.74, 0.94, $P = 0.03$). We observed every 10 mL/min/1.73 m^2 decrease in eGFR is related to 3% increase in FRS in patients without chronic kidney disease (CKD) (coefficient = -0.03, $P < 0.001$). The association between FRS and GFR and also CVD and eGFR were not significant in patients with CKD ($P = 0.12$; $P = 0.17$, respectively). Predictive values for FRS components with and without considering eGFR and albuminuria were calculated (0.74 and 0.75, respectively).

Conclusion: Inclusion of eGFR and albuminuria in the FRS formula did not improve the predictive value of the model. We showed an inverse association between eGFR and FRS in early stages of diabetic kidney disease, which was lost in patients with CKD.

Keywords: Cardiovascular disease, Diabetic nephropathy, eGFR, Framingham risk score, Type 2 diabetes

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Introduction

Diabetes and its complications constitute major causes of mortality and morbidity. Macrovascular disease is not specific to diabetes although it is more rapidly progressive and more extensive in diabetic patients. People with diabetes are 2-4 times more likely to experience cardiovascular diseases (CVD).[1] It has been said that cumulative burden of microvascular complications affect the future risk of cardiovascular events in patients with type 2 diabetes (T2DM).[2]

Diabetic nephropathy is a major cause of end stage renal disease and it is also a risk factor for cardiovascular events.[3,4] It has been suggested that microalbuminuria in patients with T2DM is a predictive factor of cardiovascular mortality both in the general population and in secondary prevention of CVD.[5,6] The decrease in estimated glomerular filtration rate (eGFR) is also known as an independent risk factor of CVD,[7] even in normoalbuminuric diabetic patients.[8] According to these studies, it can be intuitive to hypothesize an association between renal function and CVD prediction risk scores. Framingham risk score (FRS) is a sex-specific multivariable risk factor algorithm used to assess the individual risk of CVD events in 10 years.[9] An inverse link between FRS and eGFR has been found in previous studies.[10] In comparison of different cardiovascular risk estimation methods, the FRS has the strongest association with eGFR.[11,12]

Moreover, effect of race on relationship between renal disease and cardiovascular risks and events has been reported in previous studies.[13,14] This inspired us to investigate any relationship in Iranian patients as a representative of people in the Middle East, where diabetes

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seems to have the highest burden.[15] In this study, we aimed to investigate the association between renal function and FRS in type 2 diabetic patients. Since cardiovascular events and nephropathy are 2 major complications of diabetes, diabetic patients can be perfect models for study of any association between these 2. Furthermore, we questioned if the association between eGFR and FRS change through progression of nephropathy, which was not considered in previous studies. There have not been enough studies in diabetic populations studying this issue. The other goal of our study was to determine how eGFR is related to the occurrence of cardiovascular events. It has been said that FRS has underestimated the risk of CVD in people with chronic kidney disease (CKD).[16] Therefore, we also examined whether it is possible to improve FRS for prediction of CVD by adding eGFR and albuminuria to the existing parameters in patients with T2DM.

Materials and Methods

Study Population

This cross-sectional study was a part of an open prospective cohort conducted in the diabetes clinic of Vali-Asr hospital (Tehran, Iran). Data collection for this cohort started from 2008 to 2017. Patients with T2DM who attended Vali-Asr diabetes clinic were enrolled in the original cohort. In the current study, we selected 600 diabetic participants, who had data from all needed examinations and laboratory measurements, including age, duration of diabetes diagnosis, gender, body weight, height, body mass index (BMI), blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides (TG), HbA1c, fasting blood sugar (FBS), and creatinine concentration. Ultimately 571 subjects were confirmed as participants after excluding people with age below 20 years and above 75 years. 130 patients had a history of cardiovascular events and the other 441were healthy.

Before enrollment, written informed consents were taken from all participants. The ethics committee of the Tehran University of Medical Sciences approved the study protocol. The ethics code is 8911215062.

Clinical and Laboratory Measurements

All the patient's characteristics including age, duration of diabetes diagnosis, gender, body weight, height, BMI, blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, TG, HbA1c, FBS, creatinine concentration, and medication (antihypertensive drug, cholesterol lowering drug and antidiabetic drug) were extracted from the computerized hospitalization records.

Age, medication and duration of diabetes were obtained from the participants through the interview at the first visit. Weight, height and the waist circumference were measured at baseline. BMI was computed as weight in kilograms divided by height per square meter (kg/m^2).

Systolic and diastolic blood pressure (SBP and DBP) measurement was performed on the arm of seated participants after 10 minutes of resting using a standard mercury sphygmomanometer. The measurement was repeated after 15 minutes and the average was reported.

After 12 hours of fasting, venous blood samples were collected for biochemical analysis. Fasting blood glucose and 1 hour post-prandial glucose was measured by the glucose oxidase method. Hba1c was measured by High-performance liquid chromatography. Measurement of Serum creatinine was performed by Jaffe method. Plasma total cholesterol, TG, HDL cholesterol (HDL-C), LDL-C were determined using direct enzymatic method (Parsazmun, Karaj, Iran). Patients were instructed in the collection of timed 24-hour urine for the measurement of urinary albumin excretion and were instructed to return in the morning after the end of the urine collection.

Outcome Measures and Definitions

The primary outcome of this study was set as CVD, which is defined as an episode of CCU admission, Myocardial infarction, history of coronary artery bypass graft surgery or percutaneous intervention. The diagnosis of diabetes was made based on fasting blood glucose ≥ 126 or 2 hour post prandial glucose ≥200 or randomized blood glucose ≥200 or Hba1c≥ 6.5.[17]

We calculated eGFR using the CKD-EPI equation based on age, gender, race (black vs other), and serum creatinine. We defined CKD as eGFR< 60 mL/min/1.73 m^2 or albuminuria >30 mg/24 h.

FRS is a sex-specific multivariable risk factor algorithm using to assess the individual risk of CVD events in 10 years. In the current study, we used the Wilson 1998 Circulation equation. Age, sex, high blood pressure, smoking, HDL, total cholesterol and diabetes are included as components of FRS. FRS categories are defined as 1) FRS<6% (low risk); 2) 6% ≤ FRS < 20% (medium risk); 3) FRS ≥ 20% (high risk). Cigarette smoking status was determined by self-reporting.

Statistical Analysis

Continuous variables were summarized as mean (SD) and categorical variables were presented as number (percentage). Differences in continuous variables among groups were examined using a one-way analysis of variance (ANOVA) and independent sample *t* test.

Multiple logistic regression model was used to assess the association between eGFR and CVD adjusted for potential confounders and the result was presented as OR per10 ml/min/1.73 m^2 increase in eGFR with 95% confidence interval. The association between FRS and eGFR adjusted for potential confounders was examined using multiple linear regression models and summarized as the mean decrease in risk score per 10 mL/min/1.73 m^2 increase in eGFR with 95% confidence interval.

The scale of eGFR in the multiple logistic and linear regression models was assessed using Lowes (locally weighted scatter plot smoother) and scatter plot, respectively.

All analyses were repeated using a dichotomized version of eGFR: 1: eGFR ≥ 60 mL/min/1.73 m^2, 0: eGFR <60 mL/min/1.73 m^2. The C-statistics was used to assess the discriminatory power of FRS for prediction of CVD with and without considering eGFR alone and along with albuminuria. We compared the areas under the ROC curve (AUC) for these 3 models using the logistic linear predictors. All analyses were performed using Stata version 12.

Results

Study Characteristics

We had a total of 571 participants aged 20–75 (55 ± 9) years old, consisting of 244 males (42.7%) and 327 females (57.3%). Participants were divided into 2 groups based on history of CVD. There were 130 people with a history of CVD, consisting of 72 males (55.4%) and 58 females (44.6%); and 441 people with no history of CVD consisting of 172 males (39%) and 269 females (61%).

Age ($P < 0.001$), sex prevalence ($P < 0.001$), duration of diabetes ($P < 0.001$), diastolic blood pressure ($P = 0.008$), creatinine ($P < 0.001$), total cholesterol ($P = 0.002$), LDL-C ($P = 0.003$) and eGFR ($P < 0.001$) were significantly different between these 2 groups. There was no significant difference in BMI, waist circumferences, systolic blood pressure, smoking status, FBS, HBA1C, HDL-C, TG and albuminuria (Table 1).

We divided participants with no CVD into 3 groups according to FRS; low risk group: 5 persons consisting of 1 male (20%) and 4 females (80%); moderate risk group: 92 persons consisting of 18 males (19.6%) and 74 females (80.4%); high risk group: 344 persons consisting of 153 males (44.5%) and 191 females (55.5%). Because of the small number of participants in the low risk group, we combined the low and moderate risk groups and considered them as one group. Age ($P < 0.001$), percentage of females ($P < 0.001$) waist circumferences ($P = 0.009$), systolic blood ($P < 0.001$), diastolic blood pressure ($P < 0.001$), duration of diabetes ($P = 0.03$), creatinine ($P < 0.001$), total cholesterol ($P = 0.008$), LDL-C ($P = 0.003$), HDL-C ($P = 0.012$), eGFR ($P = 0.03$) and albuminuria ($P < 0.001$) were significantly different between low or moderate risk and high-risk groups (Table 2).

The Association between eGFR and CVD

The mean (SD) eGFR in the entire study population was 82.13 (25.01). There was a statistically significant difference in eGFR between participants with and without a history of CVD.

An inverse association between eGFR and CVD was confirmed by logistic regression (OR per 10 mL mL/min/1.73 m^2 increase in eGFR = 0.75 [95% CI: 0.68, 083]; $P < 0.001$). Multiple logistic regression model was used to adjust for confounding factors, such as age, sex, SBP, duration of diabetes, smoking, FBS, HBA1C, TC, HDL, and BMI. The inverse association was still

Table 1. Baseline Characteristics of Participants According to Presence of CVD

	No CVD n = 441	CVD n = 130	Total N = 571	*P* Value
Age (y)	54 (9)	60 (8)	55 (9)	<0.001
Male/female (%)	172 (39%)/269 (61%)	72 (55%)/58 (45%)	244 (43%)/327 (57%)	<0.001
Smoking	44 (10.0%)	21 (16.2%)	65 (11.4%)	0.083
BMI (kg/m^2)	28.66 (5.28)	28.14 (4.58)	28.54 (5.13)	0.312
WC (cm)	96.7 (13.41)	96.75 (11.02)	96.71 (12.89)	0.968
SBP (mm Hg)	132 (23)	131 (22)	131 (23)	0.082
DBP (mm Hg)	80 (14)	76 (12)	79 (14)	0.008
DDM (y)	7.17 (6.69)	10.18 (7.56)	7.86 (7)	<0.001
Cr (mg/dL)	0.97 (0.25)	1.12 (0.35)	1.01 (0.28)	<0.001
eGFR (mL/min/1.73 m^2)	85.44(25.14)	70.88(21.06)	82.13(25.01)	<0.001
FBS (mg/dL)	182.9 (73.27)	174.72 (64.73)	181.04 (71.44)	0.252
HbA1C (%)	8.27 (1.97)	8.42 (1.93)	8.3 (1.96)	0.437
TG (mg/dL)	179 (115)	168 (120)	176 (117)	0.355
Cholesterol (mg/dL)	181 (43)	168 (50)	178 (45)	0.002
LDL-C (mg/dL)	102.56 (32.29)	91.9 (35.95)	100.15 (33.42)	0.003
HDL-C (mg/dL)	45.45 (13.3)	44.39 (13.84)	45.21 (13.42)	0.428
Albuminuria (mg/24 h)	35.94(25.86)	56.05(27.94)	41.93(26.52)	0.284

Values are mean (SD) for continuous variables, and No. (%) for categorical variables.
BMI, body mass index; WC, waist circumferences; SBP, systolic blood pressure; DBP, diastolic blood pressure; DDM, duration of diabetes diagnosis; Cr, serum creatinine; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; HbA1C, hemoglobin A1C; TG, triglyceride; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol.

Table 2. Baseline Characteristics of Participants without CVD According to FRS

	Low & Intermediate n = 97	High n = 344	Total N = 441	*P*-Value
Age (y)	47 (8)	56 (8)	54 (9)	<0.001
Male/female (%)	19 (19.6%)/78 (80.4%)	153 (44.5%)/1 (55.5%)	172 (39.0%)/69 (61.0%)	<0.001
Smoking	14 (14.4%)	30 (8.7%)	44 (10.0%)	0.232
BMI (kg/m^2)	28.43 (5.88)	28.72 (5.11)	28.66 (5.28)	0.569
WC (cm)	93.46 (17.5)	97.62 (11.87)	96.7 (13.41)	0.009
SBP (mm Hg)	110 (14)	138 (21)	132 (23)	<0.001
DBP (mm Hg)	71 (11)	82 (14)	80 (14)	<0.001
DDM (y)	5.79 (5.66)	7.56 (6.91)	7.17 (6.69)	0.030
Cr (mg/dL)	0.89 (0.16)	1 (0.26)	0.97 (0.25)	<0.001
eGFR (mL/min/1.73 m^2)	95.61(29.49)	82.58(23.02)	85.44(25.14)	0.030
FBS (mg/dL)	192.34 (79.51)	180.24 (71.31)	182.9 (73.27)	0.137
HbA1C (%)	8.24 (1.89)	8.28 (1.99)	8.27 (1.97)	0.293
TG (mg/dL)	156 (81)	185 (123)	179 (115)	0.059
Cholesterol (mg/dL)	171 (43)	184 (42)	181 (43)	0.008
LDL-C (mg/dL)	93.81 (31.97)	105 (32)	102.56 (32.29)	0.003
HDL-C (mg/dL)	48.92 (17.65)	44.47 (11.64)	45.45 (13.3)	0.012
Albuminuria (mg/24 h)	17.46(42.69)	41.43 (41.13)	35.94(25.86)	<0.001

Values are mean (SD) for continuous variables, and No. (%) for categorical variables.
BMI, body mass index; WC, waist circumferences; SBP, systolic blood pressure; DBP, diastolic blood pressure; DDM, duration of diabetes diagnosis; Cr, serum creatinine; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; HbA1C, hemoglobin A1C; TG, triglyceride; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol.

significant after adjustment (OR per 10 mL mL/min/1.73 m^2 increase in eGFR = 0.84 [95% CI: 0.74, 0.94], *P* = 0.03). We analyzed the association between CVD and eGFR separately in patients with and without CKD. The association was significant in patients without CKD. (OR per 10 mL mL/min/1.73 m^2 increase in eGFR = 0.98 [95% CI: 0.97, 0.99); *P* = 0.001] but we did not observe a significant association in patients with CKD. (*P* = 0.17)

Cardiovascular events were significantly higher in people with eGFR <60 mL/min/1.73 m^2 compared to people with eGFR ≥60 mL/min/1.73 m^2 (*P* < 0.001, OR = 0.37 [CI: 0.24, 0.59]). After adjustment for confounding factors such as age, sex, SBP, duration of diabetes, smoking, FBS, HBA1C, TC, HDL-C, and BMI, the difference was no longer significant (*P* = 0.32, OR = 0.75 [CI: 0.41, 1.25]) LOWESS showed that the inverse association between eGFR and CVD is almost linear (Figure 1).

The Association Between eGFR and FRS

The inverse association between eGFR and FRS was seen in patients without CKD using linear regression (*P* value < 0.001, coef = -0.03 [95% CI: -0.04, -0.02]) (Figure 2).

Multiple linear regression models were used to adjust for confounding factors, such as duration of diabetes, FBS, HBA1C and BMI. The inverse association was still significant after adjustment (*P* value < 0.001, coef = -0.03 [95% CI: -0.05, -0.02]). This association was not significant in patients who had developed CKD (*P* value = 0.12, coef = -0.02 [CI: -0.09-0.02]) (Figure 3).

FRS was significantly higher in people with eGFR <60 mL/min/1.73 m^2 compared to people with eGFR ≥60 mL/min/1.73 m^2 (*P* < 0.001). The association remained significant after adjusting for potential confounding factors (*P* < 0.001).

In order to examine the predictive value of FRS with and without including eGFR and albuminuria, C-statistic analysis was done. We examined all the parameters included in FRS (AUC = 0.75). Then we added eGFR and albuminuria separately to the components used in FRS and assessed the discriminatory power of the models for prediction of CVD (AUC = 0.76, 0.73, respectively). After including both eGFR and albuminuria to the model

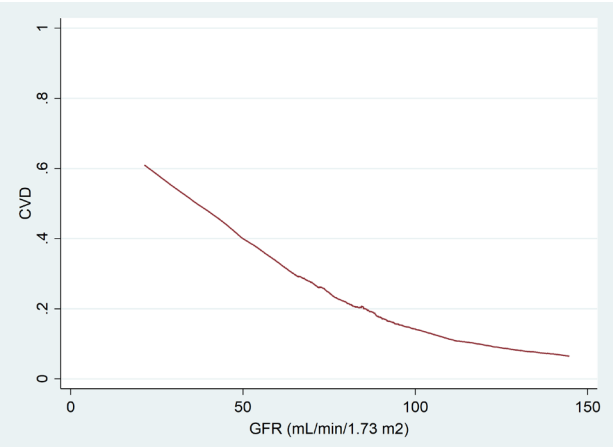

Figure 1. Locally Weighted Scatterplot Smoothing (LOWESS) for the Logit of Probability of CVD versus GFR ml/min/1.73m2. An inverse association between eGFR and CVD was confirmed by logistic regression (OR per 10 mL/min/1.73 m^2 increase in eGFR = 0.75 (95%CI: 0.68, 083); *P* < 0.001).

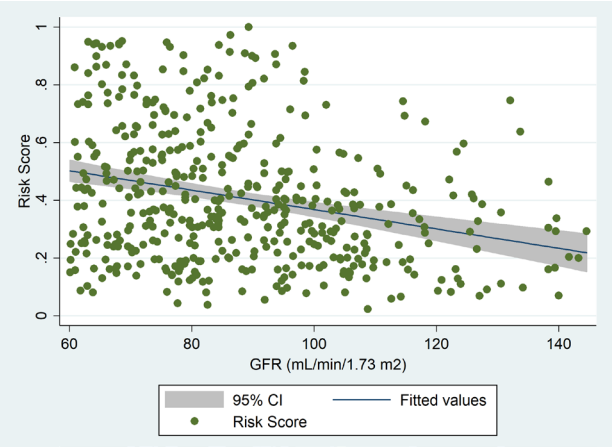

Figure 2. Scatter Plot for Risk Score versus eGFR Along with Regression Line with 95% Bond in Patients without CKD. The inverse association between eGFR and FRS was seen in patients without CKD using linear regression (P < 0.001, coef = -0.031; 95% CI: -0,044, -0.019).

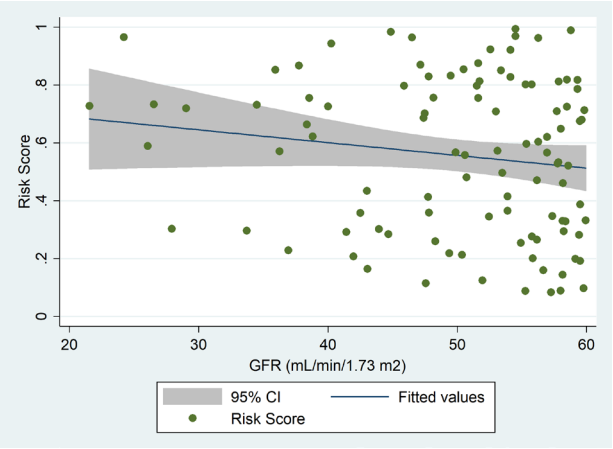

Figure 3. Scatter Plot for Risk Score versus eGFR Along with Regression Line with 95% Bond in Patients with CKD. There was no significant association between eGFR and FRS.

the AUC changed to 0.74. There was not a significant difference between the discriminatory power (AUC) of these three models and FRS (P = 0.08, 0.14, 0.31, respectively) (Figure 4).

Discussion

We investigated the association between CVD as a marker of macrovascular complication and nephropathy as a marker of microvascular complication in our diabetic patients. Our analyses found that every 10 mL/min/1.73 m^2 decrease in eGFR was related to 3% increase in FRS in patients without CKD. Of course, age was an important component in both eGFR and FRS, which may cause the inverse association between these 2 but interestingly the association between FRS and eGFR was lost in patients who had developed CKD.

We showed moderate to severe decrease in GFR and microalbuminuria in patients with T2DM which leads to loss of association between FRS and eGFR. Although

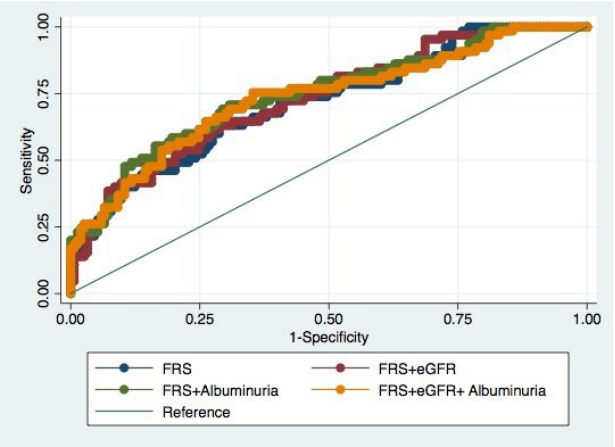

Figure 4. The Discriminatory Power of FRS Components with and without Consideration to eGFR and Albuminuria for Prediction of CVD.

there have been studies indicating association between FRS and renal function, most of these studies have been limited to healthy individuals and general population.[10, 11] This inverse correlation between GFR and FRS has been reported in the general population.[11, 16] Jin et al examined the association between GFR and FRS in the general population with no CKD and demonstrated an inverse association between these 2 parameters. In agreement with the Jin et al study, this current study also showed an inverse association in patients with T2DM without CKD. However, this association was lost in patients with CKD. These results highlight the role of eGFR in predicting CVD in patients with T2DM who are in early stages of diabetic kidney disease.

We also examined the association between CVD and eGFR in patients with and without established CKD. According to our data, we found that every 10 mL/min/1.73 m^2 decrease in eGFR is related to 15% increase in the probability of CVD and this association was significant in patients without CKD. This result is in favor of prior studies, which have reported the inverse association of eGFR and CVD risk.[18,19] Wang et al claimed that reduced eGFR (eGFR < 60 mL/min/1.73 m^2) from baseline is associated with increase in CVD risk.[20] We also showed that eGFR is significantly lower in patients with CVD compared to patients without CVD even after adjusting for potential confounders. Previous studies have reported nephropathy as an independent risk factor for CVD in patients with diabetes.[3] Albuminuria amplifies the incidence, mortality and poor prognosis of cardiovascular events even in a normal range.[5,21-23] There is limited data regarding the association of eGFR and CVD risks in the diabetic population. Therefore, the current study focused on eGFR as a risk factor.

An interesting finding in our study was that we observed a positive correlation and a loss of correlation of eGFR with FRS and CVD at different levels of CKD in our diabetic patients.

Loss of Physiologic associations in inflammatory conditions and appearance of pathologic correlations have been seen before in chronic disease states such as diabetes and rheumatoid arthritis.[24-26] This is a manifestation of the chaos theory. In a chaotic system, different pathways can affect the outcome of a process, which causes the unpredictable nature of diseases. It has been already shown that inflammatory responses and cytokine networks do not obey a linear behavior.[27] In a real biological (cytokine) system, a small number of simple but nonlinear interactions can lead to very complex behavior.[28] Considering the role of inflammatory cytokines such as IL6 and IL18 in the underlying mechanisms of the association between nephropathy and CVD,[3] we hypothesize that our findings can be explained by the chaotic behavior of inflammatory responses.

We used AUC to assess the predictive value of FRS components with and without considering eGFR and albuminuria. The aim of this analysis was to find out if it is valuable to include eGFR and albuminuria in FRS predictors in patients with T2DM. Our results indicated that the predictive value of FRS components didn't change significantly after considering eGFR alone or along with albuminuria. The original area under the ROC curve was 0.75 and after the addition of eGFR, it changed to 0.76; therefore, minimal improvement in discrimination was seen. Adding albuminuria to the model did not improve the discriminatory power either.

Previous studies in non-diabetic populations have reported controversial results. Our result is similar to a study by Ito et al which is a population-based study of participants without CVD at baseline.[29] Weiner et al studies also acclaimed CKD does not improve discrimination of the FRS equation in the general population and also in high-risk hypertensive patients[30, 31] while Nerpin et al suggested that combination of eGFR and albuminuria can be useful for prediction of cardiovascular outcomes in elderly men.[32] Unlike our study, they focused on cardiovascular death while we mainly studied coronary heart disease. Our study population was also different. We analyzed the role of eGFR in improving FRS in patients with T2DM. Chen et al study reported that the addition of GFR can improve the FRS equation for prediction of cardiovascular events in people with stage 3–5 CKD.[33] In our study, we did not see an improvement in both groups with eGFR above and less than 60 mL/min/1.73 m^2. Use of CKD to enhance prediction of CVD in the moderate risk group has also been reported,[34] but a great portion (78%) of our population was in the high risk group. A collaborative Meta analysis demonstrated that eGFR and albuminuria could improve the discrimination of CVD beyond FRS in patients with diabetes along with the general population but the improvement was more evident for cardiovascular mortality and heart failure.[35] According to our analyses, considering eGFR and albuminuria in the FRS equation has minimal effect in people with T2DM.

There have been limitations in our study. First, in order to measure kidney function, we used eGFR (CKD-EPI equation), which can lead to measurement bias. Second, since FRS is a 10-year risk assessment, we did not calculate the lifelong risk in participants. One another important limitation of this study was the cross-sectional design. Prospective studies are needed to help describe directionality of association, reduce possible reverse causation and incidence-prevalence bias.

In conclusion, in this study, we showed an inverse association between eGFR and FRS in patients with T2DM, which is lost when patients enter moderate to severe stages of CKD. We also found an association between eGFR and CVD. We hypothesize control of CKD in the early course of the disease and this may slow progression of cardiovascular events. We also showed that including eGFR and albuminuria in FRS variables is not helpful for better prediction of cardiovascular events in people with T2DM.

Authors' Contribution

Conception or Design of the work: PK, MN. Data analysis and interpretation: MAM, SSS. Drafting the article: PK, HA, SR. Critical revision of the article: MN, AE, MJB, MHM, HM. All the authors approved the final version of the manuscript and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

Ethical Statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Patient Consent

For this type of study, formal consent is not required.

Data Sharing Statement

At present, there is no additional unpublished data from this study.

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