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High Incidence of Chronic Kidney Disease among Iranian Diabetic Adults: Using CKD-EPI and MDRD Equations for Estimated Glomerular Filtration Rate

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Background: To investigate the population based incidence rate of chronic kidney disease (CKD) and its potential risk factors among Iranian diabetic adults during over 14 years of follow-up.
Methods: Two different equations (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] and Modification of Diet in Renal Disease [MDRD]) were applied for the calculating the estimated glomerular filtration rate (eGFR). Among a total of 1,374 diabetic Tehranian adults, 797 and 680 individuals were eligible for CKD-EPI and MDRD analyses, respectively. CKD was defined as eGFR lower than 60 mL/min/1.73 m^2. Multivariable Cox proportional hazard models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CI) for all potential risk factors.
Results: The incidence rates (95% CI) of CKD per 1,000 person-years were 43.84 (39.49 to 48.66) and 55.80 (50.29 to 61.91) based on CKD-EPI and MDRD equations, respectively. Being older, a history of cardiovascular disease, and having lower levels of eGFR were significant risk factors in both equations. Moreover, in CKD-EPI, using glucose-lowering medications and hypertension, and in MDRD, female sex and fasting plasma glucose ≥10 mmol/L were also independent risk factors. Regarding the discrimination index, CKD-EPI equation showed a higher range of C-index for the predicted probability of incident CKD in the full-adjusted model, compared to MDRD equation (0.75 [0.72 to 0.77] vs. 0.69 [0.66 to 0.72]).
Conclusion: We found an incidence rate of more than 4%/year for CKD development among our Iranian diabetic population. Compared to MDRD, it can be suggested that CKD-EPI equation can be a better choice to use for prediction models of incident CKD among the Iranian diabetic populations.

Keywords: Diabetes mellitus; Glomerular filtration rate; Incidence; Iran; Renal insufficiency, chronic; Risk factors

INTRODUCTION

Chronic kidney disease (CKD) is defined as kidney damage or glomerular filtration rate (GFR) lower than 60 mL/min/1.73 m^2 lasting at least 3 months. It was a considerable public health challenge, with a global prevalence of 13.4% [1]. Previous studies have indicated a greater CKD burden in low- and middle-income countries, responsible for about 80% of overall CKD cases [2]. We previously reported that about 2.9% of women and 1.3% of men developed CKD annually among the Iranian adult population [3]; this issue was more prominent among those with type 2 diabetes mellitus (T2DM) constituting 11.37% of the Iranian adult population in 2011 [4].

It is well-known that diabetes mellitus (DM) plays a strong role in CKD development, almost tripling this phenomenon's probability in both sexes [5]. Pro-inflammatory processes, glo-

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merular injuries such as thickening of basal glomerular membranes, tubular injuries such as the diabetic kidney's premature senescence, intra-renal vascular disease, and renin-angiotensin system insufficiency have been suggested to explain renal impairment in patients with T2DM [6]. The annual incidence rate of CKD varies from 2.2% to 4.3% in different populations with T2DM [7]. Moreover, it was shown that incident CKD was increased by female sex, obesity, older age, albuminuria, longer duration of diabetes, poor glycemic control, presence of macro-vascular complications, and higher blood pressure (BP), as well as low baseline estimated glomerular filtration rate (eGFR) [7-9]. Recently, Jiang et al. [10] established a model for predicting diabetic kidney disease (DKD) in a meta-analysis. They found huge heterogeneity (all $I^2 \geq 70\%$) among included cohort studies conducted in Europe, Americas, and Eastern Asia for risk factors of DKD (apart from smoking), especially for eGFR with $I^2 = 100\%$ [10].

Previous studies have reported some differences in the methodological aspects of GFR estimation, due to applied equations [11,12]. The most common equations used to estimate GFR are the Modification of Diet in Renal Disease (MDRD) study equation and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [12]. In a study on 24,516 adults with diabetes, in comparison with CKD-EPI equation, smaller bias and higher accuracy were observed for MDRD equation [13]. On the other hand, in a meta-analysis of 1,130,472 adults, CKD-EPI was found to have more accurate categorization for the risk of mortality and end stage renal disease among diabetic, high risk, and general populations [14].

In the current study we examined the incidence rate and risk factors of CKD among Iranians with T2DM aged over 20 years, using MDRD and CKD-EPI equations for calculation of eGFR, in the oldest cohort of the Middle East and North Africa region, a zone with high burden of T2DM and CKD [15].

METHODS

Study design

This study was done within the framework of the Tehran Lipid and Glucose Study (TLGS), which is a community-based cohort study on a representative sample of Tehran's citizens in district 13. The TLGS aims to determine the epidemiologic aspect of non-communicable diseases (NCDs) and their risk factors. It also aims to prevent NCDs by advancing healthier lifestyles. The TLGS enrollment was conducted in two phases; phase one (January 31, 1999 to July 3, 2001) and phase two (October 20, 2001 to September 22, 2005). Data gathering for follow-up was conducted up to phase VI in 3-year intervals (i.e., phase III: 2005 to 2008; phase IV: 2008 to 2011; phase V: 2011 to 2014; and phase VI: 2015 to 2018). Further details on the TLGS design and enrollment have been previously published [16].

Study population

Among a total of 12,288 individuals aged >20 years, 1,374 subjects (1,163 individuals from phase I and 211 new individuals from phase II) were considered as diabetic population. Considering CKD-EPI equation, we initially excluded 325 subjects with prevalent CKD stages 3 to 5 at baseline (i.e., eGFR <60 mL/min/1.73 m^2) [17]. Furthermore, the subjects with missing information on covariates such as body mass index (BMI), waist circumference (WC), creatinine levels, fasting plasma glucose (FPG), triglyceride level (TG), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), systolic blood pressure (SBP), diastolic blood pressure (DBP), physical activity level, smoking status, and educational level at baseline were excluded ($n=53$, considering overlap features between numbers). After excluding those with no follow-up measurement ($n=199$), 797 participants who successfully followed until April 2018 (the 6th examination cycle) were eligible for analysis. A similar approach was applied to 1,374 diabetic participants based on MDRD equation. After the exclusion for prevalent CKD ($n=471$), those with missing data ($n=49$), those without any follow-up after recruitment ($n=174$), 680 eligible participants remained for MDRD analysis. Moreover, we had only three cases with type 1 of diabetes with a history of diabetic ketoacidosis at the time of presentation. Hence considering a very few number of patients with type 1 in our study sample, we generally considered our participants as a T2DM population.

This study was approved by the Institutional Review Board (IRB) of the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Science (code number: IR.SBMU.ENDOCRINE.REC.1399.054). All subjects provided written informed consent. All methods of this study were performed following the relevant guidelines and regulations.

Clinical and laboratory measurements

Using standard questionnaires, a trained interviewer gathered data on demographic characteristics, past medical history,

drug history, family history of cardiovascular disease (CVD) and T2DM, educational level, smoking habits and physical activity level.

Considering the TLGS protocol [16], we measured weight with shoes removed and wearing light clothing to the nearest 100 g. The height of subjects was measured in a standing position, using a tape measure. The mean of two measurements of SBP and DBP on the right arm, which were taken after a 15-minute rest in a sitting position, was defined as the subject's BP.

A blood sample was taken after 12 to 14 hours of overnight fasting between 7:00 and 9:00 AM from all participants. A 82.5 g glucose monohydrate solution (equivalent to 75 g anhydrous glucose) was orally taken by participants (only for those without a history of using glucose-lowering medications). Then a blood sample was taken 2 hours later, for the oral glucose tolerance test. FPG and 2-hour post-challenge plasma glucose (2h-PCPG) were measured using enzymatic colorimetric glucose oxidase method, both inter-and intra-assay coefficient of variations (CVs) were less than 2.2%. Measurements of serum creatinine (SCr) levels were done using kinetic colorimetric Jaffe with a sensitivity of 0.2 mg/dL (range, 18 to 1,330 mmol/L [0.2 to 15 mg/dL]). Based on the manufacturer's recommendation, reference intervals were 80 to 115 mmol/L (0.9 to 1.3 mg/dL), 53 to 97 mmol/L (0.6 to 1.1 mg/dL) in men and women, respectively. Both the baseline and follow-up phases had intra-assay, and inter-assay CVs of less than 3.1%. More details on laboratory data including TG, TC, and HDL-C were previously expounded [16].

Definition of outcomes and variables

Incident CKD was defined as eGFR lower than 60 mL/min/1.73 m^2 occurring at any time during the follow-up period. This equals to stage 3 to stage 5 CKD according to the Kidney Disease Outcome Quality Initiative (KDQOI) guidelines [17]. GFR was estimated from SCr values using both CKD-EPI and MDRD equations.

CKD-EPI equation [18]: Firstly, creatinine values were multiplied by 0.95 before eGFR calculation to standardize SCr [19,20].

$eGFR = 141 \times [\text{the minimum of standardized SCr (mg/dL)}/\kappa \text{ or } 1]^{\alpha} \times [\text{the maximum of standardized SCr (mg/dL)}/\kappa \text{ or } 1]^{-1.209} \times 0.993^{age} \times (1.018 \text{ if female}) \times (1.159 \text{ if black})$, where κ is 0.7 for females and 0.9 for males and α is −0.329 for females and −0.411 for males.

MDRD equation [20]:

$eGFR = 186 \times [\text{SCr (mg/dL)}]^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female})$.

Diabetes was defined as taking any glucose-lowering medications (known DM) or having FPG ≥7 mmol/L and/or 2h-PCPG ≥11.1 mmol/L (newly diagnosed DM). According to TLGS protocol, glycosylated hemoglobin (HbA1c) measurement was not performed at the recruitment phases; hence, FPG categories were used as a surrogate for HbA1c; it categorized as FPG <7.22 mmol/L, 7.22≤ FPG <10.0 mmol/L, and FPG ≥10 mmol/L, corresponding to HbA1c levels of <7%, 7% to 8%, and ≥8%, respectively [21]; a similar approach was applied in our previous study [22]. Hypercholesterolemia was defined as having TC ≥5.1 mmol/L or using lipid-lowering medications. Hypertriglyceridemia was considered as having TG ≥1.695 mmol/L and low HDL-C was defined as having HDL-C <1.036 mmol/L for men and <1.295 mmol/L for women or using lipid-lowering medications. Since the distribution of eGFR was left skewed among our population, we preferred the categorical presentation of this variable as tertile rather than using predefined cut-off points. Participants divided into three tertiles according to eGFR; top tertile: eGFR >79.4 mL/min/1.73 m^2; middle tertile: 70.0≤ eGFR ≤79.4 mL/min/1.73 m^2; and bottom tertile: 60≤ eGFR <70.0 mL/min/1.73 m^2 for CKD-EPI analysis. For MDRD analysis participants were also divided into top tertile: eGFR >72.8 mL/min/1.73 m^2; middle tertile: 66.2≤ eGFR ≤72.8 mL/min/1.73 m^2; and bottom tertile: 60≤ eGFR <66.2 mL/min/1.73 m^2. General obesity was classified in three groups: BMI <25 kg/m^2 (normal); 25≤ BMI ≥30 kg/m^2 (overweight); and ≥30 kg/m^2 (obese). Central obesity was defined as WC ≥90 cm for both sexes [23]. According to the seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure [24], BP was categorized into three groups; normal: SBP <120 mm Hg and DBP <80 mm Hg; prehypertension: SBP 120 to 139 mm Hg and/or DBP 80 to 89 mm Hg; and hypertension: SBP ≥140 mm Hg or DBP ≥90 mm Hg or using anti-hypertensive medications. Age was classified into three groups: 21–40, 41–60, and >60 years. The TLGS used the Lipid Research Clinic questionnaire for those who were enrolled in phase I, in which low physical activity was defined as having physical activity less than 3 days per week. Moreover, using the Modifiable Activity Questionnaire (MAQ), for those participants who were enrolled at phase II, individuals who had less than 600 minutes per week of metabolic equivalent tasks were considered as the low physical activity group [16,25]. Educational levels were categorized as

having <6, 6 to 12, and >12 years of formal education. Smoking status was classified as current smokers, former smokers, and never smokers. A positive family history of premature CVD was considered as any history of coronary heart disease/stroke in a male first-degree relative younger than 55 years or female first-degree relative younger than 65 years. A positive family history of DM was considered as any history of DM in a first-degree relative.

Statistical analyses

Descriptive statistics (mean±standard deviation, frequency [%]) were used to describe baseline characteristics based on CKD-EPI and MDRD equations. Comparing baseline characteristics among respondents (study participants) versus non-respondents (including those with missing data of covariates at baseline or those without any follow-up) was done using Student's *t*-test and chi-square tests, as appropriate. The mean difference (95% confidence interval [CI]) of continuous variables and the difference in the prevalence (95% CI) of each category of categorical variables were estimated to compare respondents with non-respondents.

Survival time was defined as the time of censoring or date of incident CKD, whichever firstly occurred. The event date for the incident CKD cases was defined as mid-time between the date of follow-up visit in which the CKD was diagnosed for the first time, and the most recent follow-up visit prior to the diagnosis. The follow-up time was drawn from the difference between the calculated mid-time date and the date at which the subjects entered the study. For censored subjects, the survival time was the interval between the first and last observation dates. Study participants were censored due to death, loss to follow-up, or the end of observation period. Follow-up duration and incidence rates were calculated using the measured survival time.

Incidence density rate of CKD per 1,000 person-years and respective 95% CIs were calculated for each gender and the total population across age groups by dividing the number of events to person-years at risk.

Univariate Cox regression was performed for each categorical potential risk factor including sex (men as reference), age groups (21 to 40 years as reference), BMI (normal as reference), central obesity, BP categories (normal as reference), FPG baseline categories (FPG <7.22 mmol/L as reference), glucose-lowering medications, low HDL-C, hypertriglyceridemia, hypercholesterolemia, lipid-lowering medications, positive history of CVD, physical activity, education level (greater than 12 years as reference), smoking status (never smokers as reference), family history of CVD, family history of DM, and eGFR baseline tertiles (top tertile as reference). Covariates with *P* values <0.20 in univariable analysis were then selected to enter the multivariable Cox proportional hazard regression analysis, to assess the association of selected categorical potential risk factors with incident CKD. Three models were defined: Model 1 was adjusted for age and sex; Model 2 was further adjusted for clinical variables including education level, history of CVD, BP categories, lipid-lowering medications (only for CKD-EPI analysis), and glucose-lowering medications; Model 3, further adjusted for laboratory data including FPG baseline categories and eGFR baseline tertiles.

To be sure about the event classification ability of the suggested variables, Harrell's C-index was calculated, and using bootstrap resampling with 1,000 replications, optimism-corrected C-index (95% CI) was reported to consider optimization. A C-index equal to 1.0 indicates perfect discrimination. Moreover, the Akaike information criterion (AIC) was calculated for the measurement of the model fit. By adding a new factor to the base model, a drop of >10 in AIC is considered as a significant improvement in risk prediction [26].

The proportional hazards assumption in the Cox model was assessed with the Schoenfild residual test and all proportionality assumptions were appropriate. Statistical analyses were performed using SPSS for Windows version 20 (IBM Co., Armonk, NY, USA) and STATA version 14 (StataCorp., College Station, TX, USA); *P* values ≤0.05 were statistically considered significant.

RESULTS

The study population consisted of 797 participants (350 men) with a mean age of 51.6 years in CKD-EPI analysis. The baseline characteristics of respondents and non-respondents are shown in Table 1 for CKD-EPI analysis. Compared to non-respondents, respondents were about 4 years younger and had 0.7 unit higher BMI. Moreover, hypertriglyceridemia and family history of DM were more prevalent among respondents; however, non-respondents had higher prevalence of history of CVD and glucose-lowering medications usage. Other characteristics were similar between respondents and non-respondents. Additionally, for MDRD analysis, the baseline characteristics of the respondents and non-respondents are shown in

Table 1. Baseline characteristics of the respondents (study participants) and non-respondents in CKD-EPI analysis: Tehran Lipid and Glucose Study

Characteristic	Respondents	Non-respondents	Differences (95% CI)[a]
No. of participants (men)	797 (350)	252 (124)	
Continuous variable			
Age, yr	51.6±10.6	55.8±11.6	−4.3 (−5.9 to −2.6)
BMI, kg/m^2	29.0±4.6	28.3±5.3	0.7 (0.0 to 1.5)
WC, cm	96.5±10.9	95.1±11.3	1.4 (−0.3 to 3.0)
SBP, mm Hg	131.4±21.3	134.7±23.7	−3.3 (−6.7 to 0.1)
DBP, mm Hg	82.4±11.2	81.7±12.3	0.8 (−0.9 to 2.5)
eGFR, mL/min/1.73 m^2	76.3±11.2	75.0±11.2	1.2 (−0.3 to 2.8)
FPG, mmol/L	9.0±3.4	9.5±3.6	−0.5 (−1.1 to 0)
2h-PCPG, mmol/L[b]	14.9±4.9	15.6±5.5	−0.8 (−1.8 to 0.3)
TC, mmol/L	5.9±1.3	5.9±1.4	0.1 (−0.1 to 0.3)
HDL-C, mmol/L	1.0±0.3	1.1±0.3	0 (−0.1 to 0.0)
TG, mmol/L	2.8±1.9	2.8±2.6	0.0 (−0.3 to 0.3)
Categorical variable			
Educational level, yr			
<6	458 (57.5)	140 (55.8)	1.7 (−5.3 to 8.7)
6–12	283 (35.5)	92 (36.7)	−1.1 (−8.0 to 5.7)
>12	56 (7.0)	19 (7.6)	−0.6 (−4.3 to 3.2)
Smoking status			
Never	611 (76.6)	170 (73.6)	3.1 (−3.3 to 9.5)
Former	89 (11.2)	25 (10.8)	0.3 (−4.2 to 4.9)
Current	97 (12.2)	36 (15.6)	−3.4 (−8.6 to 1.8)
Low physical activity	560 (70.3)	162 (72.6)	−2.4 (−9.0 to 4.3)
Hypercholesterolemia	581 (72.9)	173 (68.7)	4.2 (−2.3 to 10.8)
Hypertriglyceridemia	615 (77.2)	178 (70.6)	6.5 (0.1 to 12.9)
Low HDL-C	630 (79.0)	185 (74.6)	4.4 (−1.7 to 10.6)
Positive history of CVD	78 (9.8)	43 (17.1)	−7.3 (−12.4 to −2.2)
Family history of premature CVD	158 (19.8)	46 (18.3)	1.6 (−3.9 to 7.1)
Family history of DM	399 (50.1)	104 (41.3)	8.8 (1.8 to 15.8)
Anti-hypertensive medications	126 (15.8)	51 (20.2)	−4.4 (−10.0 to 1.1)
Lipid-lowering medications	78 (9.8)	36 (14.3)	−4.5 (−9.3 to 0.3)
Glucose-lowering medications	276 (34.6)	105 (41.7)	−7.0 (−14.0 to −0.1)

Values are presented as mean±standard deviation or number (%).
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CI, confidence interval; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; 2h-PCPG, 2-hour post-challenge plasma glucose; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; CVD, cardiovascular disease; DM, diabetes mellitus.
[a]Differences between respondents vs. non respondents in mean values of continuous variables and prevalence values of categorical variables, [b]Measurement of 2h-PCPG was done only for participants without history of glucose-lowering medications.

Table 2. Baseline characteristics of the respondents (study participants) and non-respondents in MDRD analysis: Tehran Lipid and Glucose Study

Characteristic	Respondents	Non-respondents	Differences (95% CI)[a]
No. of participants (men)	680 (327)	223 (119)	
Continuous variable			
Age, yr	51.0±11.0	55.8±11.8	−4.8 (−6.5 to −3.1)
BMI, kg/m^2	29.0±4.7	28.0±5.1	1.0 (0.2 to 1.7)
WC, cm	96.5±10.9	94.7±11.1	1.8 (0.1 to3.6)
SBP, mm Hg	131.5±21.5	135.0±24.4	−3.5 (−7.2 to 0.2)
DBP, mm Hg	82.5±11.3	81.4±12.7	1.0 (−0.8 to 2.8)
eGFR, mL/min/1.73 m^2	71.2±8.5	70.6±9.4	0.5 (−0.8 to 1.8)
FPG, mmol/L	8.9±3.2	9.5±3.5	−0.6 (−1.1 to 0)
2h-PCPG, mmol/L[b]	14.8±4.8	15.6±5.6	−0.8 (−2.0 to 0.3)
TC, mmol/L	5.8±1.2	5.8±1.5	0 (−0.2 to 0.2)
HDL-C, mmol/L	1.0±0.3	1.0±0.3	0 (−0.1 to 0.0)
TG mmol/L	2.8±1.9	2.9±2.7	−0.1 (−0.4 to 0.3)
Categorical variable			
Educational level, yr			
<6	374 (55.0)	124 (55.9)	−0.9 (−8.4 to 6.7)
6–12	255 (37.5)	80 (36.0)	1.5 (−5.8 to 8.8)
>12	51 (7.5)	18 (8.1)	−0.6 (−4.7 to 3.5)
Smoking status			
Never	510 (75.0)	146 (71.6)	3.4 (−3.6 to 10.4)
Former	78 (11.5)	23 (11.3)	0.2 (−4.8 to 5.2)
Current	92 (13.5)	35 (17.2)	−3.6 (−9.4 to 2.1)
Low physical activity	474 (69.7)	143 (72.2)	−2.5 (−9.6 to 4.6)
Hypercholesterolemia	481 (70.7)	149 (66.8)	3.9 (−3.1 to 11.0)
Hypertriglyceridemia	522 (76.8)	159 (71.3)	5.5 (−1.3 to 12.2)
Low HDL-C	535 (78.7)	162 (74.0)	4.7 (−1.9 to 11.3)
Positive history of CVD	62 (9.1)	39 (17.5)	−8.4 (−13.8 to 2.9)
Family history of premature CVD	126 (18.5)	40 (17.9)	0.6 (−5.2 to 6.4)
Family history of DM	334 (49.1)	93 (41.7)	7.4 (−0.1 to 14 to9)
Anti-hypertensive medications	98 (14.4)	41 (18.4)	−4.0 (−9.7 to 1.8)
Lipid-lowering medications	64 (9.4)	33 (14.8)	−5.4 (−10.5 to −0.2)
Glucose-lowering medications	228 (33.5)	94 (42.2)	−8.6 (−16.0 to −1.2)

Values are presented as mean±standard deviation or number (%).
MDRD, Modification of Diet in Renal Disease; CI, confidence interval; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; 2h-PCPG, 2-hour post-challenge plasma glucose; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; CVD, cardiovascular disease; DM, diabetes mellitus.
[a]Differences between respondents vs. non respondents in mean values of continuous variables and prevalence values of categorical variables, [b]Measurement of 2h-PCPG was done only for participants without history of glucose-lowering medications.

Table 2, which consisted of 680 eligible respondent individuals (327 men) with a mean age of 51.0 years.

During a median follow-up of 14.40 years (interquartile range [IQR], 10.34 to 16.23 years), 352 incident CKD cases have occurred in CKD-EPI analysis. Considering MDRD equation, 356 incident CKD cases were also found during a median follow-up of 14.37 years (IQR, 10.35 to 16.21 years). The crude incidence rates of CKD across age groups are presented in Table 3. The crude incidence rate of CKD for CKD-EPI and MDRD analyses were 43.84 (95% CI, 39.49 to 48.66) and 55.80 (95% CI, 50.29 to 61.91) per 1,000 person-years in the total population, respectively. In general, women had a higher incidence rate of CKD, which reached a significant level in the total age-group in MDRD analysis (45.76 [95% CI, 38.82 to 53.94] for men and 65.30 [95% CI, 57.11 to 74.66] for women per 1,000 person-years). Moreover, older adults experienced higher incidence rates of CKD.

Univariate hazard ratios (HR) and 95% CI of potential categorical risk factors are shown in Supplementary Table 1. Being a woman (only in MDRD analysis), older age groups, prehypertension (only in MDRD analysis), hypertension, using glucose-lowering medications, positive history of CVD, bottom and middle tertiles of eGFR, and having <6 years of formal education were significantly associated with a higher risk of incident CKD. Moreover, compared to the participants with FPG of less than 7.22 mmol/L, having a level of ≥10 and ≥7.22 mmol/L of FPG, were significantly associated with a higher risk of incident CKD in CKD-EPI and MDRD analyses, respectively.

Multivariable HRs and 95% CI of incident CKD among the diabetic population based on CKD-EPI and MDRD equations are presented in Tables 4 and 5, respectively. In model 1, being a woman had age-adjusted HRs of 1.30 (95% CI, 1.04 to 1.61) and 1.54 (95% CI, 1.25 to 1.91) in CKD-EPI and MDRD analyses, respectively. Moreover, compared to the group aged 21 to 40 years, older age groups were at significantly higher risk of incident CKD. Following further adjustment in model 2 (not adjusted with laboratory factors), older age groups, positive history of CVD, hypertension, and using glucose-lowering medications were associated with increased risk of CKD development in both analyses. Moreover, being a woman increased the risk of incident CKD in MDRD analysis. After more ad-

Table 3. The crude incidence rates of CKD per 1,000 person-years among the diabetic population across age groups: Tehran Lipid and Glucose Study

Age groups, yr	CKD-EPI		MDRD	
	E/N	Crude incidence rate (95% CI), /1,000 person-yr	E/N	Crude incidence rate (95% CI), /1,000 person-yr
Men				
21–40	3/52	4.39 (1.42–13.61)	5/52	7.40 (3.08–17.77)
41–60	83/202	37.50 (30.24–46.50)	93/186	50.58 (41.27–61.97)
>60	50/96	83.88 (63.58–110.68)	44/89	74.80 (55.66–100.51)
Total	136/350	38.94 (32.91–46.06)	142/327	45.76 (38.82–53.94)
Women				
21–40	9/72	10.07 (5.24–19.35)	19/66	25.76 (16.43–40.39)
41–60	148/302	47.56 (40.49–55.88)	152/237	68.91 (58.78–80.78)
>60	59/73	110.96 (85.97–143.22)	43/50	128.72 (95.46–173.56)
Total	216/447	47.61 (41.66–54.40)	214/353	65.30 (57.11–74.66)
Total population				
21–40	12/124	7.61 (4.32–13.40)	24/118	16.98 (11.38–25.34)
41–60	231/504	43.38 (38.13–49.35)	245/423	60.58 (53.45–68.66)
>60	109/169	96.65 (80.11–116.61)	87/139	94.33 (76.45–116.39)
Total	352/797	43.84 (39.49–48.66)	356/680	55.80 (50.29–61.91)

CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; E/N, event/number; CI, confidence interval.

Table 4. Multivariable HRs and 95% CIs of incident CKD among the diabetic population in CKD-EPI analysis: Tehran Lipid and Glucose Study

Variable	Model 1		Model 2		Model 3	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Women (men as reference)	1.30 (1.04–1.61)	0.018	1.22 (0.94–1.58)	0.137	1.17 (0.90–1.51)	0.250
Age groups, yr						
21–40	1		1		1	
41–60	6.14 (3.44–10.98)	<0.001	5.35 (2.96–9.64)	<0.001	4.04 (2.22–7.35)	<0.001
>60	17.18 (9.42–31.32)	<0.001	12.48 (6.65–23.42)	<0.001	7.21 (3.76–13.82)	<0.001
Educational level, yr						
>12			1		1	
6–12			0.87 (0.52–1.46)	0.591	0.82 (0.49–1.38)	0.460
<6			1.08 (0.65–1.80)	0.774	0.88 (0.53–1.48)	0.634
Positive history of CVD			1.82 (1.32–2.52)	<0.001	1.66 (1.20–2.30)	0.002
Smoking status						
Never			1		1	
Former			1.13 (0.77–1.64)	0.533	1.09 (0.75–1.58)	0.657
Current			1.08 (0.73–1.60)	0.689	1.08 (0.73–1.60)	0.707
Blood pressure categories						
Normal			1		1	
Prehypertension			1.15 (0.83–1.59)	0.397	1.22 (0.88–1.69)	0.227
Hypertension			1.46 (1.07–2.00)	0.018	1.39 (1.01–1.90)	0.042
Glucose-lowering medications, yes			1.37 (1.09–1.73)	0.006	1.36 (1.06–1.74)	0.015
Lipid-lowering medications, yes			1.03 (0.73–1.47)	0.860	1.11 (0.78–1.58)	0.549
FPG baseline categories, mmol/L						
<7.22					1	
7.22–10					0.97 (0.74–1.25)	0.793
≥10					1.14 (0.86–1.51)	0.368
eGFR baseline tertiles[a]						
Top tertile					1	
Middle tertile					1.74 (1.26–2.40)	0.001
Bottom tertile					3.43 (2.49–4.73)	<0.001
Harrell's C-index	0.67 (0.65–0.70)		0.71 (0.68–0.73)		0.75 (0.72–0.77)	
Akaike information criterion	4,173.55		4,158.90		4,098.38	

Model 1: adjusted for sex and age; Model 2: adjusted for sex, age, education level, smoking status, history of CVD, blood pressure categories, anti-hypertensive medications, and glucose-lowering medications; Model 3: adjusted for all contents of Model 2+FPG baseline categories and eGFR baseline tertiles.

HR, hazard ratio; CI, confidence interval; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate.

[a]The range of eGFR baseline tertiles: top tertile: eGFR >79.4 mL/min/1.73 m^2; middle tertile: 70.0≤ eGFR ≤79.4 mL/min/1.73 m^2; and bottom tertile: 60≤ eGFR <70.0 mL/min/1.73 m^2 for CKD-EPI analysis.

Table 5. Multivariable HRs and 95% CIs of incident CKD among the diabetic population in MDRD analysis: Tehran Lipid and Glucose Study

Variable	Model 1		Model 2		Model 3	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Women (men as reference)	1.54 (1.25–1.91)	<0.001	1.47 (1.13–1.90)	0.004	1.32 (1.01–1.71)	0.039
Age groups, yr						
21–40	1		1		1	
41–60	3.75 (2.46–5.71)	<0.001	3.42 (2.22–5.27)	<0.001	2.75 (1.77–4.28)	<0.001
>60	7.12 (4.51–11.24)	<0.001	5.88 (3.59–9.64)	<0.001	4.33 (2.59–7.26)	<0.001
Educational level, yr						
>12			1		1	
6–12			0.86 (0.53–1.40)	0.541	0.85 (0.52–1.39)	0.521
<6			1.01 (0.62–1.65)	0.962	0.98 (0.59–1.61)	0.931
Positive history of CVD			1.55 (1.08–2.21)	0.017	1.53 (1.07–2.19)	0.021
Smoking status						
Never			1		1	
Former			0.94 (0.63–1.40)	0.772	0.98 (0.66–1.45)	0.904
Current			1.19 (0.83–1.72)	0.345	1.19 (0.83–1.72)	0.345
Blood pressure categories						
Normal			1		1	
Prehypertension			1.30 (0.94–1.78)	0.111	1.27 (0.92–1.74)	0.145
Hypertension			1.43 (1.05–1.96)	0.025	1.31 (0.96–1.80)	0.090
Glucose-lowering medications, yes			1.31 (1.05–1.63)	0.016	1.19 (0.93–1.51)	0.161
FPG level at baseline, mmol/L						
<7.22					1	
7.22–10					1.10 (0.85–1.42)	0.490
≥10					1.43 (1.07–1.91)	0.015
eGFR baseline tertiles[a]						
Top tertile					1	
Middle tertile					1.62 (1.21–2.17)	0.001
Bottom tertile					2.42 (1.80–3.25)	<0.001
Harrell's C-index	0.64 (0.61–0.67)		0.66 (0.63–0.69)		0.69 (0.66–0.72)	
Akaike information criterion	4,131.41		4,127.72		4,093.60	

Model 1: adjusted for sex and age; Model 2: adjusted for sex, age, education level, smoking status, history of CVD, blood pressure categories, anti-hypertensive medications, and glucose-lowering medications; Model 3: adjusted for all contents of Model 2+FPG baseline categories and eGFR baseline tertiles.

HR, hazard ratio; CI, confidence interval; CKD, chronic kidney disease; MDRD, Modification of Diet in Renal Disease; CVD, cardiovascular disease; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate.

[a]The range of eGFR baseline tertiles: top tertile: eGFR >72.8 mL/min/1.73 m^2; middle tertile: 66.2≤ eGFR ≤72.8 mL/min/1.73 m^2; and bottom tertile: 60≤ eGFR <66.2 mL/min/1.73 m^2.

justment for laboratory factors (model 3), female sex (in MDRD analysis), and older age groups remained at higher risk. Among the different BP categories, in CKD-EPI analysis, the hypertensive group showed a significant higher risk for incident CKD, in comparison with the normal group. Those with an FPG level of ≥10 mmol/L had a higher risk than participants with an FPG level of ≤7.22 mg/dL at baseline in MDRD analysis; however, using glucose-lowering medications was an

independent risk factor in CKD-EPI analysis, only. Furthermore, compared to the top tertile of eGFR, those participants in the bottom and middle tertiles showed an increased risk of CKD development. A positive history of CVD increased the risk of incident CKD with HRs of 1.66 (95% CI, 1.20 to 2.30) and 1.53 (95% CI, 1.07 to 2.19) in CKD-EPI and MDRD analyses, respectively. Finally, there was no significant difference between different education levels and smoking status.

The discrimination power of multivariable prediction models as represented by the optimism-corrected Harrell's C-index was 0.67 (95% CI, 0.65 to 0.70) for model 1, 0.71 (95% CI, 0.68 to 0.73) for model 2, and 0.75 (95% CI, 0.72 to 0.77) for model 3 in CKD-EPI analysis. The corresponding numbers were 0.64 (95% CI, 0.61 to 0.67), 0.66 (95% CI, 0.63 to 0.69), and 0.69 (95% CI, 0.66 to 0.72) in MDRD analysis, respectively.

Focusing on model fitness as presented by AIC, by adding data on significant risk factors including positive history of CVD, BP measurements, and glucose-lowering medications usage to the age and sex adjusted models, in CKD-EPI analysis, AIC value improved from 4,173.55 in model 1 to 4,158.90 in model 2; however, we did not find a similar superiority for model fitness between models 1 and 2 of MDRD analysis. Finally, adding FPG and eGFR levels in models 3 led to lower levels of AIC (4,098.38 in CKD-EPI and 4,093.60 in MDRD) than models 1 and 2 in both analyses.

DISCUSSION

In our cohort study with a median follow-up of more than 14 years, considering CKD-EPI equation, nearly 3.9% of men and 4.8% of women developed CKD, annually. The corresponding rates were 4.6% for men and 6.5% for women in MDRD analysis. Focusing on risk factors, aging, positive history of CVD, using glucose-lowering medications (only for CKD-EPI analysis), hypertension (only for CKD-EPI analysis), and having lower levels of eGFR were found to be significantly associated with higher risk of incident CKD. Furthermore, in MDRD analysis, female sex and FPG level of ≥10 mmol/L were found to be independent CKD risk factors. Generally, CKD-EPI analysis has higher discriminative power than MDRD analysis (C-index: 0.75 vs. 0.69 in the full-adjusted model).

During the follow-up period, nearly 4.4%/year and 5.6%/year of our diabetic population developed CKD based on CKD-EPI and MDRD equations, respectively. It is important to note that comparing our results with other studies is somewhat difficult due to different equations applied for GFR estimation, duration of follow-up, baseline characteristics of participants, approaches to present incidence rate and some other aspects of the methodology. Using Cockcroft-Gault equation, the incidence rate of eGFR <60 mL/min/1.73 m^2 was reported to be 1.9%/year among a diabetic population in UK [8]. Considering MDRD equation, some previous studies conducted in Western countries showed that the incidence rates of eGFR <60 mL/min/1.73 m^2 among the diabetic populations to be about 2.5%/year in Spain [27], 2.2%/year in Sweden [28], 2.5%/years in Italy [29], and 1.5%/year in the USA [30]. Among East Asian countries, the rates were also found to be about 3.0%/year in Hong Kong [31], 4.3%/year in South Korea [32], and 2.4%/year in Japan [33]. Generally, it seems that among our Tehranian diabetic population, the estimated incidence rates of CKD are alarmingly higher than the corresponding figures in UK [8], Spain [27], Sweden [28], Italy [29], USA [30], Hong Kong [31], South Korea [32], and Japan [33]. There are several possible explanations for the higher incidence rate of CKD among our Iranian diabetic population compared to previous studies on this issue. Firstly, nearly 50% and 30% of the Iranian diabetic population had achieved treatment targets for hyperglycemia and hypertension, respectively [34]. Indeed, many patients with DM are in a poor-controlled state which may contribute to increased diabetic complications such as CKD. Secondly, an unhealthy diet [35], especially higher consumption of salt [36], is prevalent among the Iranian population, which may be considered a risk factor for CKD development [37]. Thirdly, it is reported that urbanization factors had an association with CKD [38]. Therefore, since our study population is limited to Tehran city, the higher incidence in our study can be explained to some degree. Moreover, high exposure to air pollution among Tehranian residents [39] can exacerbate this condition [40].

Aging has been well-known as an independent risk factor for CKD [41]. In agreement with previous studies [8,27], older age groups had higher CKD incidence rates in the current study. We previously reported a similar pattern of incident CKD among a general population in Tehran, in which the effect of aging was more prominent among men. However, in that study, women had a 3-fold higher risk of CKD development [3]. Similarly, we have now illustrated a higher incidence rate of CKD among our female diabetic population. Additionally, women had a 30% and 54% age-adjusted higher risk of CKD development in CKD-EPI and MDRD analyses, respec-

tively. In MDRD analysis, female sex was significantly associated with a higher risk of CKD development, even in the full-adjusted model. Similarly, some previous cohort studies on diabetic populations have also reported a significant association of being female with eGFR decline [8,19,28,29]. These sex differences could be related to sex hormones and sex-specific genetic variants [42].

Positive history of CVD was associated with a 66% and 53% higher risk of incident CKD in full-adjusted models of CKD-EPI and MDRD analyses, respectively. This finding is in line with a previous cohort study on a Spanish diabetic population, indicated that having a previous history of myocardial infarction was associated with approximately 72% higher incidence of CKD [27]. Moreover, based on data analysis of 34 multinational cohorts from the CKD Prognosis Consortium including more than 5 million individuals from 28 countries, positive history of CVD was associated with about 20% higher risk of incident CKD in both diabetic and non-diabetic populations [19]. These findings may be explained by the fact that participants with CVD at baseline had greater duration and severity of shared CVD and CKD risk factors. Another possible explanation is that arteriosclerosis and arteriolosclerosis may contribute to renal dysfunction. The pathogenic mechanisms involved in this process are common for both CKD and CVD development, including endothelial dysfunction, oxidative stress, inflammation, hyperhomocysteinemia, and thrombogenic factors [43,44].

In our results for different BP categories, hypertensive participants (having BP ≥140/90 mm Hg or using anti-hypertensive medications) were at higher risk of CKD development, generally; the issue was probably attributable to the drug-treated cases of hypertension. Hypertension has a two-way causal relationship with renal impairment [45], and it was found to be an independent predictor for CKD development in some previous cohort studies on diabetic populations [19,27,42]. Renal impairment usually occurred in patients with experience of at least 10 years of sustained hypertension [45]. Moreover, it was shown that taking anti-hypertensive medications, especially agents affecting the angiotensin-renin system, is associated with a delay in the time needed to double SCr concentrations and a decline in GFR among diabetic hypertensive with albuminuria [45,46]; however, the effect of using anti-hypertensive medications on increasing risk of CKD development may be explained by the fact that participants who had used anti-hypertensive medications had been previously diagnosed as known hypertensive-diabetic patients. They had been exposed to higher BPs before they were treated and therefore developed renal impairment sooner. Similarly, among the Iranian hypertensive population, treated participants had higher rates of total and CVD mortality, compared to non-treated hypertensive participants with equivalent levels of SBP and DBP [47]. Moreover, despite the high incidence rate of hypertension among the Iranian population [48], awareness is low, and only about 30% of those using anti-hypertensive medication reach BP targets [49].

It has been shown that diabetic participants with higher HbA1c levels are more susceptible to CKD development due to uncontrolled diabetes [30]. Similarly, in our results, using FPG levels as a surrogate for HbA1c, those with FPG level of ≥10 mmol/L were at higher risk of incident CKD than those who had FPG level of <7.22 mmol/L in MDRD analysis. Moreover, only 34% of our study population used glucose-lowering medications, mainly biguanide and sulfonylureas agents at recruitment time, which had a higher risk for CKD development, especially in CKD-EPI analysis. We suggested that these participants were known-diabetic patients with longer duration of disease that were more susceptible to diabetic complications.

Regarding the discrimination index, in comparison with MDRD equation, CKD-EPI analysis showed higher range of C-index for the predicted probability of incident CKD in all our models. In the current study, the Harrell's C-index was found to be in an acceptable range for the full-adjusted model (model 3) in CKD-EPI analysis [50]. For CKD-EPI analysis, the index also remained in an acceptable range for model 2 (C-index, 0.71), which included only clinical factors (i.e., age, history of CVD, hypertension, and using glucose-lowering medications). It means that CKD-EPI equation can acceptably predict the risk of CKD development without using laboratory data. Nelson et al. [19] conducted a meta-analysis study on about 800,000 diabetic patients to develop the assessment tools to identify individuals at increased risk of reduced eGFR (i.e., eGFR lower than 60 mL/min/1.73 m^2), using CKD-EPI equation; their prediction model, which included sociodemographic factors, smoking status, CVD, hypertension, BMI, eGFR, albuminuria, type of glucose-lowering medications, and HbA1c levels, showed a C-index for the predicted probability of 0.80 in an excellent range. In another meta-analysis study, a model was established for prediction of early DKD (i.e., eGFR <60 mL/min/1.73 m^2 and/or a urinary albumin-to-creatinine ratio

[UACR] ≥30 mg/g) which included age, BMI, smoking, diabetic retinopathy, HbA1c levels, SBP, HDL-C, TG, and UACR as input factors. In their model validation, the area under the curve (AUC) was found to be 0.765, which was comparable to our results (AUC, 0.75 in model 3 of CKD-EPI analysis), although we used fewer input factors [10].

The strength of this study consists in its long duration of follow-up, standardized measurement techniques, and use of a wide range of possible risk factors. There are several important limitations of this study to be considered. First, we did not have any access to valid data on the duration of DM, HbA1c level, and urine analyses of our participants, especially data on proteinuria. Second, our population study was limited to residents of a metropolitan city, and our results can't be generalized to rural populations. Third, potential risk factors were considered at the time of baseline phases, and possible changes in risk factors were not taken into account during the follow-up period. Fourth, we couldn't standardize the creatinine measurement to isotope dilution mass spectrometry.

To sum up, we found an alarmingly high range of CKD incidence rates among the Iranian diabetic population. According to the C-index of our models, compared to MDRD equation, it was suggested that CKD-EPI equation can be a better choice to use for the prediction models of incident CKD among the Iranian diabetic populations. Finally, in a model including only clinical factors (i.e., age, history of CVD, BP category, and glucose-lowering medications usage), without using laboratory data, risk prediction for incident CKD can be made by CKD-EPI equation in an acceptable range.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2020.0109.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: F.H.
Acquisition, analysis, or interpretation of data: S.S.M., R.H.A., M.H., F.H.
Drafting the work or revising: S.S.M., R.H.A., F.H.
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