Clinical Research

Renal evaluation in patients with type 2 diabetes mellitus and its association with diastolic blood pressure

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ABSTRAK

Latar belakang: *HbA1c berkorelasi dengan laju filtrasi glomerulus (LFG) dan tekanan darah diastolik (DBP). Tujuan utama penelitian ini adalah untuk mengevaluasi variabel biokimia dan klinis, dalam kaitannya dengan LFG pada pasien dengan diabetes mellitus tipe 2 (DMT2).*

Metode: *Penelitian ini merupakan studi retrospektif, longitudinal, dan deskriptif, melibatkan pasien DMT2, yang dirawat dari Januari hingga Desember 2014, di Clínica de Diabetes, Rumah Sakit Regional "Gral. Ignacio Zaragoza", ISSSTE, Kota Meksiko, Meksiko. LFG dihitung menggunakan tiga rumus: kolaborasi epidemiologi penyakit ginjal kronik (CKD-EPI), Cockcroft-Gault, dan* modification of diet in renal disease *(MDRD), pada dua periode observasi, 3 dan 6 bulan. Hasilnya dibandingkan dengan uji t atau uji Wilcoxon-Mann-Whitney tergantung pada distribusi variabel. Uji Pearson digunakan untuk menganalisis korelasi antara LFG dengan setiap rumus dan variabel yang digunakan.*

Hasil: *Rerata usia adalah 56,5±11,3 tahun pada kelompok setelah 3 bulan (n=110) dan 57,1±13,8 tahun pada kelompok setelah 6 bulan (n=47). Pada kedua kelompok, formula dengan persentase terendah kasus CKD adalah CKD-EPI dan perbedaan dari formula ini memiliki korelasi positif yang signifikan dengan DBP.*

Kesimpulan: *Rumus CKD-EPI menunjukkan persentase terendah kasus CKD dalam periode tindak lanjut pendek, dan perbedaan yang secara konsisten berkaitan dengan DBP, menegaskan pentingnya mengendalikan DBP untuk mengurangi evolusi menjadi CKD.*

ABSTRACT

Background: HbA1c is correlated with the estimated glomerular filtration rate (eGFR) and diastolic blood pressure (DBP). Our main objective was to evaluate the trend of biochemical and clinical variables, in relation to the eGFR in patients with type 2 diabetes mellitus (T2DM).

Methods: This was a retrospective, longitudinal, and descriptive study, including patients with T2DM, who were cared for from January 2014 until December 2014, at the Clínica de Diabetes, Hospital Regional "Gral. Ignacio Zaragoza", ISSSTE, Mexico City, Mexico. eGFR was calculated using three formulas: the chronic kidney disease – epidemiology collaboration (CKD-EPI), Cockcroft-Gault, and modification of diet in renal disease (MDRD), during two periods of observation, 3 and 6 months. The results were compared by Student t tests or Wilcoxon-Mann-Whitney test depending on the variable distribution. Pearson correlation was employed to determine the relation between the eGFR determined with each formula and the analyzed variables.

Results: The mean age was 56.5±11.3 years in the group of 3 months' follow-up (n=110) and 57.1±13.8 years in the group of 6 months' follow-up (n=47). In both groups, the formula with the lowest percentages of cases of CKD was CKD-EPI and the difference of this formula had a basal and final significant positive correlation with the DBP.

Conclusion: The CKD-EPI formula showed the lowest percentages of cases of CKD in a short follow-up period, and its difference is consistently associated with the DBP, confirming the importance of controlling the later to mitigate the evolution to CKD.

Keywords: CKD-EPI, Cockcroft-Gault, MDRD, type 2 diabetes mellitus

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Lack of adherence to treatment involves large economic expenditures. Worldwide studies claim that one half of patients with type 2 diabetes mellitus (T2DM) do not adequately comply with their treatment and that fewer than 30% of patients change their habits or lifestyles.[1] Compliance with adequate and intensive treatment is related with the delay in disease onset.[2]

Measuring adherence presents difficulties because there is no unique method ascribed for it. The World Health Organization (WHO) defines adherence as the extent to which the behavior of a person corresponds to the recommendations agreed upon between the health professional and the patient, in terms of taking medications, monitoring a dietary treatment, and executing the programmed lifestyle changes.[3] Some authors have demonstrated that the best adherence percentage achieved in chronic patients ranges between 50 and 75%.

Based on studies of T2DM, the latter is the leading cause of chronic kidney disease (CKD)[4] even where it is not related with histological diabetic nephropathy.[5] Incipient diabetic nephropathy is classically defined as increasing albuminuria, heralding a decline in the glomerular filtration rate (GFR). In fact, the prevalence of CKD in patients with T2DM is estimated to be 25–40% worldwide.[6]

Monitoring of renal function should be carried out by calculating the estimated GFR (eGFR), with three main techniques currently with widespread use: 1) the chronic kidney disease – epidemiology collaboration (CKD-EPI) equation, which generally results in lower prevalence of CKD and more accurate assessment of prognosis;[7] 2) the Cockcroft-Gault formula, which indicates creatinine clearance, and 3) the modification of diet in renal disease (MDRD) formula, which evidences eGFR.[8]

The formula developed by Cockcroft and Gault possesses a good correlation with the true GFR and is clinically useful in patients aged 20–100 years; however, it has strong limitations in diabetes and should therefore be avoided, in addition its being overestimated in situations of advanced renal insufficiency and especially in obese and edematous patients.[9] On the other hand, the MDRD combines nutrition and sociodemographic variables is recommended by the National Kidney Disease Education Program (NKDEP) to measure GFR in adult population.[10] This formula tends to underestimate eGFR at higher levels, but performs better at lower eGFR (≤60 mL/min per 1.73 m^2). Last, the CKD-EPI equation was developed in an effort to create a more precise formula than the MDRD, especially when the actual GFR is >60 ml/min/1.73 m^2.[11]

HbA1c is correlated with the eGFR and diastolic blood pressure (DBP).[12] In fact, a short term glycemic control can get reductions of blood pressure and GFR.[13] This study aimed to describe the most consistent variables associated with deterioration in eGFR using the CKD-EPI, Cockcroft-Gault, and MDRD equations within a time-frame period of three and six months in patients with T2DM.

METHODS

Patients

This was a retrospective, longitudinal, and descriptive study developed at the Clínica de Diabetes, Hospital Regional “Gral. Ignacio Zaragoza”, ISSSTE, Mexico City, Mexico. Patients with T2DM, of all ages, seen from January until December 2014, irrespective of metabolic control, were included in the study. We excluded patients not willing to participate in the study, and those who missed an appointment during the study were eliminated.

Following a 12 hours fasting, venous blood samples were taken in Vacutainer™ tubes for determination of glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-ch), low-density lipoprotein-cholesterol (LDL-ch), triglycerides, and uric acid (Hitachi 917® Autoanalyzer) and HbA1c. Capillary blood glucose was measured with a Precision® glucose monitor. Serum glucose was measured utilizing the glucose oxidase method, and HbA1c, with the turbidimetric inhibition immuno assay (TINIA) method (Roche).

Clinical assessment

After their blood samples were taken, the patients ate breakfast from 9–10 a.m., and filled in the directed history (only at their first appointment), a survey of ingested kcal in the previous 24 hours, and a questionnaire on diabetes. Two hours postbreakfast glucose was measured, and the patients received education on diet, self-monitoring, exercise, American Diabetes Association (ADA) therapeutic targets, and chronic complications through classes and workshops.

Patients were measured (m) and weighed (kg) (Torino). Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Blood pressure was measured with a mercury sphygmomanometer (Baumanometer, USA) after five min of rest.

A 24-hours dietary recall was used for this purpose. Diet was categorized within three choices: 1) consumption of 80–120% of the indicated kcal; 2) <80% of the indicated kcal, and 3) >120% of the kcal indicated. Diet was classified as dichotomous whether this had or had not a balanced proportion of 50–60% carbohydrates, 10–20% protein, and <30% fat. Calculated kcal were based on ideal weight minus 200 kcal/day if the patient was overweight.

Exercise (intensive walking, running, or cycling) was reported in days per week of physical activity and min/day. A specific activity was not prescribed due to the heterogeneous work schedule and physical conditions of the patients.

Glomerular filtration rate

The GFR determination was made with the next aforementioned formulas:

CKD-EPI formula

eGFR = 141 × min(SCr/κ,1)$^{\alpha}$ × max(Scr/κ,1)$^{-1.209}$ × 0.993^{Age} × 1.018 [if female] × 1.159 [if black]

Where SCr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

Cockcroft and Gault formula

eGFR (mL/min) = [((140-age) × weight)/(72 × SCr)] × 0.85 if female

Age is expressed in years, weight is expressed in kilograms, and SCr is expressed in mg/dL.

MDRD

eGFR (mL/min/1.73 m^2) = 186 × SCr$^{(-1.154)}$ × Age$^{(-0.203)}$ × 0.742 (woman) × 1.210 (if black)

Where SCr = serum creatinine (mg/dL).

Statistics

Quantitative or continuous variables were described by mean and standard deviation (SD) and, in some cases, by median and range. Qualitative variables were described by absolute frequency and percentage per modality. Quantitative variables were compared between groups by Student t test in case of normal distribution and the Wilcoxon-Mann-Whitney test otherwise. Missing data were not replaced. The analyzed population was defined as all patients who fulfilled all inclusion criteria with no major protocol deviations. Intra- and intergroup differences between baseline and values after three or six months were analyzed with the Student t test. Pearson correlation was employed to determine the relation between the GFR determined with each formula and the variables analyzed. All tests were performed with the SPSS v.20 statistical software program.

Ethics

The Ethical and Research Committees of Ciprés Grupo Médico (CGM), code 2015/03, approved this study. The procedures followed were in accordance with the ethical standards of the General Health Law of Mexico and were subjected to the ethical and moral value judgments of the Declaration of Helsinki, updated in Fortaleza, Brazil.

RESULTS

In the current study, mean age was 56.5±11.3 years in the group of the three-month follow-up (n=110; 71 females and 39 males) and 57.1±13.8 years in the six-month follow-up group (n =47; 28 females and 19 males). Table 1 depicts the general characteristics of the patients. In Table 2, we illustrate the percentages of patients with renal failure by using each formula. In both groups, the formula with lowest percentages of cases of CKD was CKD-EPI.

Among all of the analyzed variables, those that maintained a significant correlation during both periods are presented in Table 3 and Figure 1. As expected, age had a negative correlation with renal function; urea, creatinine, and uric acid all demonstrated all a significant negative correlation with the three formulas. In the lipid profile, there was a constant positive correlation between cholesterol and LDL and cholesterol and

Table 1. General characteristics of the studied groups

	Follow-up period			
	3 months (n=110)		6 months (n=47)	
	Basal	Final	Basal	Final
Albumin (g/dL)	4.1±0.4	4.2±0.3	4.2±0.3	4.2±0.2
BMI (kg/m^2)	28.3±4.2	27.8±3.8	27.6±3.5	27.5±3.4
Ca (mg/dL)	9.2±1.2	9.3±1.2	9.1±0.4	9.2±0.3
Capillary Glucose am (mg/dL)	145.7±62.8	131.6±41.9	144.0±54.9	125.6±52.3
Cholesterol (mg/dL)	168.8±45.5	159.1±45.5	166.4±41.1	161.8±40.5
CKD-EPI (mL/min)	85.5±27.3	87.1±28.6	78.5±29.6	79.1±31.9
Cockcroft-Gault (mL/min)	96.0±53.5	103.1±50.8	84.0±35	82.6±39.7
Creatinine (mg/dL)	0.95±0.71	0.99±0.94	1.12±0.82	1.22±1.1
DBP (mm Hg)	78.1±7.4	76.9±7.5	80.8±9.1	75.4±6.8
Exercise (min/day)		25.2±21.9		27±18.7
Fat (%)	34.3±10	34.6±10.3	33.8±9.8	32.9±9.4
Globulin (g/dL)	3.3±2.8	3.1±1.8	2.9±0.4	2.9±0.3
Glucose (mg/dL)	145.6±62	135.9±45.8	136.1±48.7	132.7±42
HbA1c (%)	8.2±1.9	7.4±1.4	7.7±1.7	7.4±1.5
HDL-ch (mg/dL)	45.7±14.5	48.1±16.8	43.5±11.9	46.8±13.1
LDL-ch (mg/dL)	91.1±35.1	83.6±34.6	87.5±33	88.0±31
MAP (mm Hg)	88.2±20.5	83.2±26	91.9±16.1	86.0±19.4
MDRD (mL/min)	86.1±34.6	97.5±34.7	77.4±31	77.8±36.1
Muscle (%)	28.9±5.5	32.3±22.9	29.2±5	28.9±4.6
P (mg/dL)	3.7±0.8	3.7±0.5	3.5±0.5	3.6±0.5
SBP (mm Hg)	120.9±11.7	117.9±11.9	120±12.8	118.6±10.3
Triglycerides (mg/dL)	171.5±110.9	148.6±116.9	189.3±185.6	144.1±67.1
Urea (mg/dL)	39.7±24	40.5±24.8	44±23.7	44.9±30.5
Uric acid (mg/dL)	5.2±1.3	5.2±1.4	5.9±1.6	5.7±1.4
Visceral Fat (%)	10.6±3.4	10.6±3.3	10.9±3.4	10.5±3.8
Weight (kg)	71.6±13.3	70.7±12.4	69.7±11.5	69.1±11

BMI: Body mass index, Ca: calcium, CKD-EPI: Chronic Kidney Disease-Epidemiology Collaboration, DBP: diastolic blood pressure, HDL-ch: High-density lipoprotein cholesterol, LDL-ch: Low-density lipoprotein cholesterol, MAP: mean arterial pressure, MDRD: Modification of Diet in Renal Disease, P: phosphorus, SBP: systolic blood pressure

triglycerides, and a negative correlation between triglycerides and HDL. Notoriously, there was a negative correlation between urea and albumin. Measurements for blood pressure, as expected, correlated.

The whole population, at baseline, exhibited the following negative Pearson correlation between urea and the three formulas evaluated to calculate eGFR, CKD-EPI (r=–0.876; p≤0.001), MDRD (r=–0.826; p≤0.001), and Cockcroft-Gault (r=–0.742; p≤0.001). When analyzing the same variables for creatinine, the same order was maintained (r=–0.797, p≤0.001), (r=–0.779; p≤0.001), and (r=0.669; p£0.001). For uric acid, the significant negative correlations were only exhibited with two formulas; CKD-EPI (r=–0.511, p=0.001), and MDRD (r=–0.527; p≤0.001).

Table 2. Percentages of patients with renal failure

	Follow-up period (months)			
	3		6	
	Basal	Final	Basal	Final
CKD-EPI	15.45	13.63	10.90	10.00
Cockcroft-Gault	16.36	16.36	12.20	15.45
MDRD	16.36	15.45	13.63	12.72

CKD-EPI: Chronic Kidney Disease-Epidemiology Collaboration, MDRD: Modification of Diet in Renal Disease

In the case of albumin, correlations were positive with MDRD (r=0.386; p=0.020), Cockcroft-Gault (r=0.379, p=0.023), and CKD-EPI (r=0.358; p=0.038). Among the equations, highest positive correlations were between CKD-EPI and MDRD (r=0.959; p≤0.001), second, between CKD-EPI and Cockcroft-Gault (r=0.883, p≤0.001), and last, between Cockcroft-Gault and MDRD (r=0.853; p≤0.001).

Through the multivariate lineal regression analysis in the group of three months follow-up, the variables with a significant prognosis for a final eGFR were age (p≤0.001 for both formulas), serum glucose (p=0.026 for MDRD and 0.015 for CKD-EPI) and urea (p=0.002 for MDRD and ≤0.001 for CKD-EPI). The same analysis in the group of six months showed that the initial value of urea was the only variable positively associated with the final eGFR calculated with CKD-EPI (p=0.008) and MDRD (p=0.005).

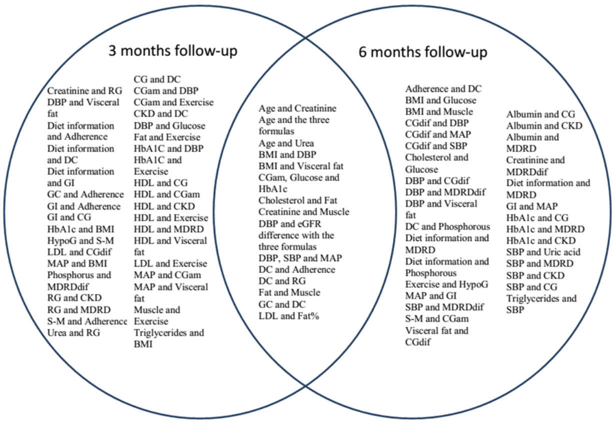

Figure 1. Significant correlations within a three and six month's follow-up. BMI: body mass index, CG: Cockroft-Gault, CGam: Capillary glucose am, CKD-EPI: Chronic Kidney Disease – Epidemiology Collaboration, DBP: diastolic blood pressure, DC: Diet Comprehension, dif: difference (basal-final), eGFR: estimated glomerular filtration rate, GC: Goals in Comprehension, GI: Goals in Information, HDL: High-density lipoprotein, HypoG: Hypoglycemia, LDL: Low-density lipoproteins, MAP: mean arterial pressure, MDRD: Modification of Diet in Renal Disease, RG: Reaching goals, SBP: systolic blood pressure, S-M: Self-monitoring

Table 3. Significant correlations at 3 and 6 months

	Follow-up period (months)			
	3		6	
	r	p	r	p
Age and CKD-EPI	-0.577	≤0.001	-0.512	0.001
Age and Cockcroft-Gault	-0.662	≤0.001	-0.516	≤0.001
Age and MDRD	-0.540	≤0.001	-0.415	0.012
Age and urea	0.351	≤0.001	0.397	0.008
BMI and DBP	0.201	0.041	0.344	0.019
BMI and visceral fat	0.634	≤0.001	0.685	≤0.001
Capillary glucose (am) and serum glucose	0.587	≤0.001	0.546	0.005
Cholesterol and fat	0.304	0.007	0.386	0.016
Comprehension goals and diet adherence	0.375	≤0.001	0.401	0.005
Creatinine and muscle	0.366	0.002	0.410	0.023
DBP and CKD-EPI difference*	0.204	0.041	0.357	0.016
DBP and MBP	0.854	≤0.001	0.893	≤0.001
Diet adherence and diet comprehension	0.565	≤0.001	0.556	≤0.001
Diet comprehension and adherence	0.283	0.003	0.305	0.037
Diet comprehension and reaching goals	0.360	≤0.001	0.330	0.024
Fat and muscle	-0.568	0.048	-0.401	0.015
Glucose and HbA1c	0.652	≤0.001	0.629	0.003
LDL and fat	0.361	0.002	0.367	0.017
SBP and DBP	0.296	0.002	0.398	0.006
SBP and MBP	0.750	≤0.001	0.768	≤0.001

BMI: Body mass index, CKD-EPI: CKD: chronic kidney disease, DBP: diastolic blood pressure, HDL-ch: high-density cholesterol, LDL-ch: low-density cholesterol, MBP: mean blood pressure, MDRD: Modification of Diet in Renal Disease, SBP: systolic blood pressure. *: Basal-final values.

Finally, for the two periods, the only variable associated with an eGFR difference was DBP and CKD-EPI difference (basal–final), (three months: r=0.204, p=0.041; six months: r=0.357, p=0.016). By contrast, the second measure of HbA1C had a negative correlation with the eGFR difference using the Cockcroft-Gault and MDRD (r=-0.245, p=0.011) formulas in the shorter period (three months).

DISCUSSION

In both groups, there was a predominance of female patients. This is in accordance with several publications that report more assiduous medical consultation from women than from men.[14]

In general, there were more significant correlations among variables within three-months than the six-months period. This means a loss of power in the direct or indirect interactions that, otherwise, allows identification of stronger correlations despite the time involved. This finding is in concordance with a previous study designed to evaluate the effectiveness of a short-term, community-based, individualized lifestyle intervention in patients with mild diabetes or hypertension who exhibited beneficial changes in activity, dietary, and clinical parameters.[15] In a longer follow-up, another group demonstrated that, in order to sustain the impact of a community-based comprehensive intervention for T2DM, improving and repeating the comprehensive strategy is greatly recommended, especially for patients with lower educational levels.[16]

Non-adherence to diabetes medications is associated with higher rates of mortality.[17] In a previous publication of our group, we demonstrated that education programs in T2DM contribute to a decrease in HbA1c within six months, but an intensive program is more effective in reducing cholesterol and LDL.[18] In this new approach within a shorter time period, we verified a positive correlation between diet comprehension and better adherence; this same diet comprehension facilitated reaching metabolic goals of control.

Ekinci et al[19] suggest that aging, perturbations in blood pressure, and the development of intrarenal vascular disease may contribute to decreases in renal function independently of changes in albuminuria.[19] It is likely that these data will remain constant in all countries.

It has been suggested that poor glycemic control may cause the risk of substantially increased blood pressure (BP) variability in subjects with diabetic nephropathy.[20] In our two groups with different follow-up periods, this relationship was not found. The explanation is that this correlation was performed in all patients at each time and in each group, and not only in subjects with CKD.

Classification of subject as CKD or non-CKD patients by different equations implies the assignment of a different risk of end-stage renal disease (ESRD); all-cause mortality, coronary artery disease, and stroke. For example, employing the MDRD equation in patients with T2DM underestimates GFR in patients with normal and high GFR[21] and may be inaccurate in patients with normo-albuminuric patients with diabetes.[22] In agreement with this statement, other authors have found that prevalence of CKD was lower using Cockcroft-Gault or CKD-EPI formulae than MDRD formulae.[23,24] It is critical because being considered as CKD, low eGFR, and higher systolic blood pressure (SBP) are risk factors that are independently associated with peripheral arterial disease.[25] Even more so, in the study of Fabbian et al[24] the authors found that eGFR was <60 ml/min/1.73 m^2 in 15% of patients by MAYO, 26% by Cockcroft-Gault, 27% by MDRD186, 31.5% by MDRD175, and 30% by CKD-EPI. In contrast, in our patients, percentages were lower with the CKD-EPI formula. This difference could be attributed to the fact that the population that we studied was younger by about ten years.

Lifestyle interventions and good diabetes control are also linked with reduction of proteinuria and alleviation of CKD progression.[26-29] In our patients, the exercise had a negative correlation with HbA1c only in the short follow-up period. With deeper analysis, a higher increase is appreciated in creatinine, urea, and uric acid after six months than after three months despite a better control of serum glucose, capillary glucose, HbA1c, lipid profile, and BP.

Therapeutic management of diabetes is more challenging in patients with renal impairment. CKD vs non-CKD patients have less strict glycemic control.[30] Greater emphasis should be placed on the major risk factors, such as hypertension, smoking habits, and hyperlipidemia.[31]

This study has several limitations. First, we were not able to categorize CKD based on the new kidney disease: improving global outcomes (KDIGO) classification recommendations[32] due to missing information about the albuminuria reports. Second, we did not estimate cystatin C, which is constantly produced and excreted by the kidney and has been recommended to be taken into account.[33] Third, the cardiovascular risk score of each patient was not assessed, and subjects who suffered a cardiovascular event could have a lower renal function than those who did not. However, our aim was merely to show how the different formulae work in a clinical setting and their usefulness associated with the variables that show the most important changes and correlations.

We conclude that, in a short evaluation period in patients with T2DM, the CKD-EPI formula shows the lowest percentages of cases of CKD. Besides, the eGFR difference calculated with CKD-EPI had a significant positive correlation with the DBP.

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Conflicts of Interest
The authors affirm no conflict of interest in this study.

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