

Original article

Estimation of the variation in glomerular filtration rate based on glycosylated hemoglobin, serum creatinine, and age in type 2 diabetic patients with or without chronic kidney disease

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Abstract

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Context: The methods currently used to calculate glomerular filtration rate (GFR) underestimate this measurement in the population of diabetic patients, therefore, there is a need to develop diabetes-specific methods for estimating glomerular filtration rate in this specific population. Objective: This study aims to evaluate a predictive model based on the use of HbA1c to estimate the variability of glomerular filtration rate in diabetic patients with or without chronic kidney disease (CKD).

Methods: We analyzed data from diabetic patients belonging to a prospective follow-up cohort of a renal health surveillance program at a Peruvian hospital. The following factors were included in the multiple linear regression model: age, sex, diastolic blood pressure (DBP), systolic blood

Keywords: Glycated hemoglobin A, Glomerular filtration rate, Creatinine, Diabetes mellitus, Chronic kidney disease.

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pressure (SBP), body mass index (BMI), cholesterol, triglycerides, HDL, LDL, serum creatinine, urinary creatinine, microalbuminuria, hemoglobin, basal glycemia, and HbA1c.

Results: A total of 122 patients were included in the analysis. The final multivariate model, which included variation of HbA1c, age, and creatinine variation, was highly significant (P < 0.0001), with an adjusted R^2 of 80 %. The other variables analyzed were not significant predictors of glomerular filtration rate variation, despite showing some correlation.

Conclusions: The study shows that HbA1c, age, and creatinine variation significantly predict the variation of glomerular filtration rate in diabetic patients with or without chronic kidney disease and opens the possibility of using this model as a prognostic tool for this specific population.

Estimación de la variación de la tasa de filtración glomerular basada en la hemoglobina glicosilada, la creatinina sérica y la edad, en pacientes diabéticos tipo 2 con o sin enfermedad renal crónica

Resumen

Contexto: los métodos utilizados actualmente para calcular el filtrado glomerular subestiman esta medición en la población de pacientes diabéticos; por ende, existe la necesidad de desarrollar métodos específicos para la diabetes que estimen el filtrado glomerular en esta población.

Objetivo: este estudio tiene como objetivo evaluar un modelo predictivo basado en el uso de la HbA1c para estimar la variabilidad del filtrado glomerular en pacientes diabéticos con o sin enfermedad renal crónica.

Métodos: analizamos datos de pacientes diabéticos pertenecientes a una cohorte de seguimiento prospectivo de un programa de vigilancia de salud renal adscrito a un hospital peruano. Los siguientes factores se incluyeron en el modelo de regresión lineal múltiple: edad, sexo, presión arterial diastólica (PAD), presión arterial sistólica (PAS), índice de masa corporal (IMC), colesterol, triglicéridos, HDL, LDL, creatinina sérica, creatinina urinaria, microalbuminuria, hemoglobina, glucemia basal y HbA1c. **Resultados:** se incluyeron 122 pacientes en el análisis. El modelo multivariado final, que incluía la variación de la HbA1c, la edad y la variación de la creatinina, fue altamente significativo (p <0,0001), con un R2 ajustado del 80 %. Las otras variables analizadas no fueron significativas para predecir la variación del filtrado glomerular, a pesar de mostrar cierta correlación.

Conclusiones: el estudio demuestra que la HbA1c, la edad y la variación de la creatinina predicen significativamente la variación del filtrado glomerular en pacientes diabéticos con o sin enfermedad renal crónica, y abre la posibilidad de su uso como herramienta de pronóstico para esta población específica.

Palabras clave: hemoglobina glicosilada, tasa de filtración glomerular, creatinina, diabetes mellitus, enfermedad renal crónica.



Introduction

Chronic kidney disease (CKD) affects about 50 % of the global diabetes population [1], with rates ranging from 40 % to 83 % in developed countries [2–4]. It is estimated that the prevalence of CKD in patients with diabetes will continue to increase dramatically over the next decade, regardless of their stage [5].

In Peru, up to 59.09 % of people with type 2 diabetes are affected by CKD. It is also known that it is the main cause of end-stage kidney disease and that it requires dialysis. The national rate of Peruvian prevalence per million population for renal replacement treatment is 335.3, with hemodialysis, peritoneal dialysis, and functional kidney transplant rates of 230.7, 39.1, and 65.5, respectively. Diabetes accounts for 40 % of hemodialysis patients in a public hospital [6]. This requires an adequate capacity to evaluate and monitor the evolution of CKD in this specific population.

The use of glomerular filtration rate (GFR) is undoubtedly the most commonly used tool for detecting, managing, and predicting the prognosis of CKD in patients with metabolic diseases such as type 2 diabetes mellitus [7]. However, several studies indicate that the methods for its estimation, such as the MDRD (Modification of Diet in Renal Disease) formula or the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula, may be inadequate in diabetic patients due to an underestimation of these values [8,9].

While CKD-EPI and MDRD are standard for GFR estimation, studies highlight their limitations in diabetic populations due to altered muscle mass, creatinine metabolism, and renal hemodynamics [8, 9]. For instance, CKD-EPI tends to underestimate GFR in hyperfiltering diabetic patients, potentially delaying timely interventions [9]. This underscores the need for diabetes-specific models incorporating glycemic markers like glycosylated hemoglobin (HbA1c).

In addition, other studies suggest that the values of HbA1c, an essential test for glycemic monitoring and control in diabetic patients, may be related to the variation in GFR [10,11]. An inverse correlation between the increase in HbA1c and the decrease in GFR [12] was reported, even in the population of non-diabetic patients [13, 14]. Moreover, a study assessing GFR predictive models using new parameters showed that the use of HbA1c has a high percentage of accuracy for predicting GFR [15].

The use of HbA1c to predict the variation of GFR could be very useful, given the need to find new alternatives for estimating GFR in diabetic patients without increasing costs, since these tests are part of the monitoring and control of all diabetic patients.

The aim of this study was to evaluate a predictive model for estimating GFR variability in diabetic patients based on HbA1c variability through a multiple linear regression analysis, incorporating into the analysis other variables that may influence GFR variability, such as age, sex, blood pressure, body mass index (BMI), and routine laboratory tests.

Material and methods

The study is based on a retrospective cohort of patients enrolled in the Adult Surveillance Program for Noncommunicable Chronic Diseases, specifically those participating in the Renal Health Surveillance Program (VISARE) at the Hospital-I Pacasmayo of Essalud, La Libertad, Peru, a program that is implemented nationwide for patients treated in Essalud.

This cohort undergoes regular quarterly controls for the follow-up of patients with a diagnosis of diabetes mellitus type 2, with or without CKD. Patients receive a medical evaluation every 3 months and monthly nursing checkups for taking blood pressure (BP), BMI, and programming of laboratory tests established by the Renal Health Program for diabetic patients under Essalud. These include monthly evaluation of fasting glycemia, semiannual evaluation of HbA1c, and annual evaluation of lipid profile, hemoglobin, microalbuminuria, urine creatinine, and serum creatinine.

Authorization was granted by Hospital I Pacasmayo to use VISARE program data and access patients' medical records. Information was subsequently collected from the hospital database for the period from January 1, 2014, to December 31, 2015.

We included patients who presented continuity in their medical controls within this program. The total number of patients identified according to the database obtained was submitted to the study selection criteria.

Selection criteria

Inclusion criteria: Patients over 18 years of age with a confirmed diagnosis of type 2 diabetes mellitus, enrolled in the Renal Health Surveillance Program with at least one annual control in said program; patients with recorded data on age, sex, and laboratory tests at the time of periodic control in the program, including serum creatinine, urine creatinine,



microalbuminuria, hemoglobin, basal glycemia, and HbA1c; diastolic blood pressure (DBP), systolic blood pressure (SBP), BMI, GFR, use of nephroprotective drugs, and comorbidities.

Exclusion criteria: Patients with missing or poorly recorded data in any of the annual controls considered for the study.

After screening patients according to the selection criteria, information was collected from medical records. This information was encoded for analysis, which was executed using Stata 15.0 statistical software (StataCorp, College Station, TX, USA), performing a multiple linear regression that included the factors previously mentioned as possible predictors of GFR variability.

The outcome variable of the linear model was the change in GFR over a 1-year period, which was calculated according to the values reported from the results for the years 2014 and 2015. Although many patients had quarterly controls, annual GFR variability was taken into consideration to better assess the plausibility of the factors included in this study, since evaluating short periods of these factors would have less influence on GFR variation.

Blood pressure and basal glycemia were defined as the average of at least 3 measurements taken in consecutive months prior to the program's control visit, due to their greater variability by various factors.

Patients with missing or poorly recorded data in any annual control were excluded. Continuous variables were assessed for outliers using Tukey's fences; no extreme outliers required transformation or exclusion.

Statistical analysis

The descriptive analysis was performed for each factor studied by calculating proportions for the categorical variables, as well as the mean, standard deviation, and median for the numerical variables; additionally, the p-value was reported to evaluate the difference between groups in the baseline analysis.

A Pearson correlation analysis was performed for variables with a normal distribution, and the Spearman test was used for variables without normal distribution. The analysis to determine the distribution of normality of the variables was performed using the Shapiro-Wilk test. The inclusion of factors in the multiple linear regression model was performed after evaluating the correlation between each factor studied and the variation of the GFR. The model was adjusted using the factors that showed a significant correlation.

Ethical aspects

The research did not involve the direct participation of human beings (biological samples or interventions); it was conducted using a hospital database authorized for use by the institution's management. The handling of the information collected by the investigators was confidential, and no personal data of any kind will be disclosed.

Results

We identified 234 patients, of whom only 122 diabetic patients met the selection criteria and were included in the multiple linear regression analysis to evaluate the predictive capacity of HbA1c, serum creatinine, and age. Of the study participants, the majority were male (55.7%), with no significant differences compared with females (P=0,20). The mean age was higher for men (67.4 years, C.I.: 65.2 - 69.6) than for women, with significant differences between the two genders (P=0,006). Of all patients, 63 (51.6%) had associated comorbidities, mainly hypertension (HT), with no difference between groups (P=0.72). Additionally, 76 (62.3%) used a nephroprotective drug (ACE inhibitor, ARA inhibitor, or both), which was significantly different from those who did not use nephroprotective drugs (P=0,006).

Regarding the BMI variation, there were no differences between sexes (P=0.16), with males showing a variation of 0.02 (C.I.: -0.31, 0.28) and females a variation of 0.33 (C.I.: -0.67, -0.001) (Table 1). Variables with normal distribution included Hb variation, serum creatinine variation, and annual HbA1c change.

The correlation analysis demonstrated that only HbA1c variation, serum creatinine variation, and microalbuminuria variation showed a significant correlation when evaluated for GFR variability (Table 2).

Multivariate analysis

The final multiple linear regression obtained after selecting the best-adjusted model for predicting GFR variability included HbA1c variation, serum creatinine variation, and age (Figures 1, 2 and 3). The coefficients for the model were -1.94 for HbA1c variation (P = 0.006),



				95 % C.I.	p-value	
Gender, n (%)	M	68	(55.7)		0.20	
	F	54	(44.3)	•••		
	M	67.4	(9.0)	65.2 - 69.6		
Age (years), mean (SD)	F	61.2	(10.6)	58.3 - 64.1	0.006	
	Total	64.6	(1.3)	62.8 - 66.5		
Comorbidities	No	59	48.4			
(hypertension and	Si	63	51.6		0.72	
hyperlipidemia), n (%)	31	03	31.0	•••		
Nephroprotection, n (%)	No	46	37.7		0.006	
	Si	76	62.3			
BMI change, mean	M			-0.31, - 0.28		
		-0.02 -0.33		-0.67, -0.01	0.16	
	F			-0.07, -0.01	0.10	
	Total	-0.16		-0.38, 0.06		

Note. C.I.: Confidence interval; SD: Standard deviation; BMI: Body mass index. **Source:** Own elaboration.

-108.81 for serum creatinine variation (P < 0.0001), and -0.04 for age (P = 0.009). The final model was highly significant (P < 0.0001) with the variation in HbA1c explaining 80 % of the GFR variability (adjusted $R^2 = 0.80$). The determination of the best model led to the removal of the constant from the final formula, as it was not significant to the model (Table 3).

Table 2. Correlation of the factors analyzed with respect to the variation of the GFR

	Correlation coefficient	p-value
Age	-0.1363	0.134
Triglyceride variation	0.0318	0.769
Cholesterol variation	0.0327	0.783
LDL variation	0.1507	0.276
HDL variation	0.0772	0.554
Serum creatinine variation	-0.8842	0.000
Creatinuria variation	-0.1331	0.144
Micro albuminuria variation	-0.1973	0.029
Alb/Cr rate variation	-0.1419	0.119

Hemoglobin variation	-0.0831	0.381
BMI variation	0.1707	0.060
Basal glycemia variation	-0.0581	0.525
SBP variation	0.0448	0.624
DBP variation	0.0830	0.363
HbA1c variation	-0.3059	0.000

Note. LDL: Low density lipoprotein; HDL: High density lipoprotein; Alb/Cr : Albumin/Creatinine; BMI: Body mass index, SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HbA1c: Glycated hemoglobin.

Source: Own elaboration.

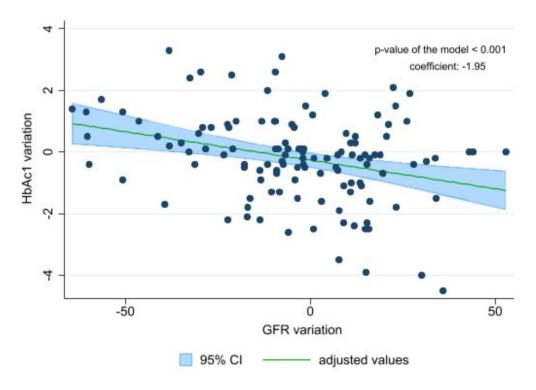


Figure 1. Linear prediction of GFR variation according to HbA1c variation

Source: Own elaboration.

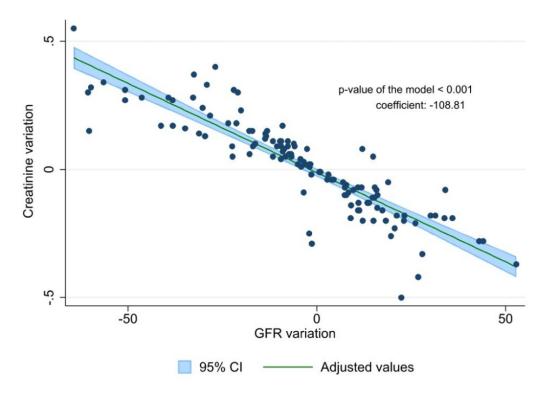


Figure 2. Linear prediction of GFR variation according to creatinine variation

Source: Own elaboration.

Table 3. Multiple linear regression predictive model for GFR variation

	Model coefficient	Standard error	p-value of the model	C.I. 95 %
HbA1c variation	-1.94	0.70	0.006	-3.33 , -0.56
Creatinine variation	-108.81	5.41	0.000	-119.5 , -98.09
Age	-0.04	0.02	0.009	-0.07 , -0.01

Note. Adjusted R²: 0.8003; P <0.0001; HbA1c: Glycated hemoglobin.

Source: Own elaboration.

Discussion

The prevalence of diabetes is increasing globally, with an estimated 537 million cases in 2021 [16], a significant rise compared to previous decades [17]. Reliable data on the prevalence of diabetes in Peru is scarce, but the few available reports indicate significant percentages [18, 19]. Among these, the percentage of patients with chronic kidney disease is

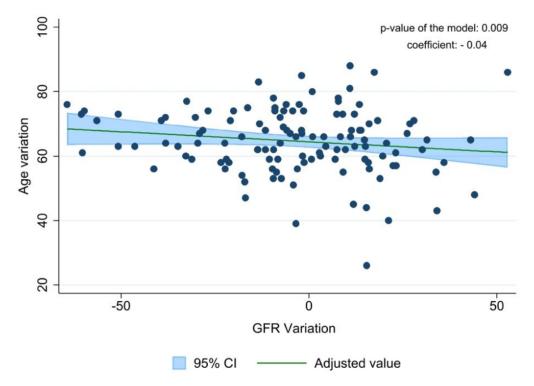


Figure 3. Linear prediction of GFR variation by age

Source: Own elaboration.

also noteworthy [6]. In both developed and some developing countries, diabetes has become the leading cause of CKD. Therefore, it is crucial to accurately evaluate the glomerular filtration rate variation in diabetic patients, regardless of their CKD status.

Our analysis demonstrated that variations in HbA1c, serum creatinine, and age significantly predict GFR variation in diabetic patients, regardless of their CKD condition. Tsuda *et al.* [20] developed a new equation incorporating HbA1c as a variable; however, their sample size was very small (40 cases). In contrast, our study included a much larger sample size, yielding robust performance results.

The inverse correlation between HbA1c and GFR aligns with evidence showing that chronic hyperglycemia drives renal injury via advanced glycation end-products (AGEs), oxidative stress, and endothelial dysfunction [21, 22]. Elevated HbA1c has been associated with faster GFR decline in diabetic populations, as seen in longitudinal cohorts [23, 24], supporting its prognostic relevance. Our model formalizes this relationship, offering a pragmatic tool for settings where direct GFR measurement is not accessible.

The multiple regression model included an adequate number of patients, although the sample corresponded to a single center. It is also important to clarify that creatinine variability and age show collinearity with the Cockcroft-Gault formula, making their inclusion in the model evidently necessary.

The results, showing an explanatory level of 80 % for the final model, are quite satisfactory for this specific population. This highly significant model discusses the need to improve prognostic tools for CKD in these patients; such improvements should consider the underlying disease and aim to incorporate tests that are already part of the periodic control of the disease, such as HbA1c.

One limitation of our study is that the analysis was performed on subjects from a single center under a renal control program. Additionally, the study cohort was not completely uniform in terms of age and nephroprotection variables, with statistical differences observed when analyzed by sex. The average age of male patients was higher than that of female patients, and the proportion of patients receiving nephroprotective drugs was almost double that of those not receiving any drugs. These baseline differences may have influenced the final model, given the known relationship between GFR variation and age [25,26], as well as the impact of nephroprotective drugs (ACE inhibitors and ARBs) on GFR progression. Despite these limitations, a highly significant predictive model was achieved. It is essential to emphasize that studies like ours are necessary in our context, as many GFR estimation formulas are based on foreign populations with different realities regarding commonly used clinical parameters and individual idiosyncrasies.

Despite achieving high predictability (adjusted R^2 = 80 %), our model requires validation in multicenter cohorts with standardized protocols. The single-center retrospective design and heterogeneity in nephroprotective drug use (62.3 % vs. 37.7 %, P = 0,006) may have introduced confounding effects. Future studies should prioritize prospective designs, adjust for drug adherence, and include more diverse populations to improve generalizability.

Conclusion

The optimal model for predicting GFR variation in diabetic patients with or without CKD included HbA1c, serum creatinine variation, and age, demonstrating a high level of predictability. However, it is important to note that the correlation level of HbA1c was low, and factors such as differences in nephroprotective drug use and age disparities between sexes could have affected the results. Future research should consider larger samples and standardized criteria

to eliminate confounding factors that may alter the predictive capacity of HbA1c for GFR variation prognosis. Enhancing the analytical methodology could further strengthen the role of HbA1c as a predictive indicator.

Authors' contribution

WAQ and CAAC did the conception, data collection, design, analysis and interpretation of data, statistical analysis and interpretation of results, critical review of the article and approval of the final version.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Ethical statement

The authors declare that this study involves no ethical issues requiring disclosure.

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