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Fasting plasma glucose, lipid ratios, and atherogenic coefficient are the risk factors for hypertension in chronic kidney disease patients on hemodialysis: A report from the Regional High Speciality Hospital of Peninsular Yucatan, Mexico

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ABSTRACT: Chronic kidney disease (CKD) is associated with the development of cardivascular disease (CVD). CKD is one of the major public health problems in Mexico. Derived parameters of lipid profile, namely atherogenic index of plasma (AIP), atherogenic coefficient (AC), and Castelli risk index (CRI I and CRI II) are useful for predicting hypertension among CKD patients on hemodialysis that are not widely reported from Mexico. Objective of the present study was to find interrelationships among blood pressure, fasting plasma glucose (FPG), and derived parameters of lipid profile (AIP, AC, CRI-I, and CRI-II) among adult CKD patients on hemodialysis in a hospital in Yucatan, Mexico. Methods: An observational study was performed using the medical records (2016 and 2017) of 47 CKD patients on hemodialysis in the Regional High Speciality Hospital of Yucatan Peninsula (HRAEPY in Spanish acronym). Multiple linear regression models were developed to evaluate the use of FPG level and derived parameters of lipid profile (AC, CRI-I, and CRI-II) as risk factors predicting mean arterial pressure (MAP). Results showed remarkable prevalence of excess weight (55% overweight, 15% obesity) and hypertension (64%) in the sample. Correlation coeffcients and multiple linear regression models showed significant rise of blood pressure in association with elevated FPG level and derived lipid profile parameters. The results confirm the use of FPG, AC, CRI-I and CRI-II as the indicators for an early diagnosis of hypertension and related CVDs among CKD patients on hemodialysis.

KEY WORDS: lipid profile, cholesterol, triglycerides, hypertension

ABBREVIATIONS: AC – Atherogenic coefficient; AIP – Atherogenic index of plasma; BMI – Body mass index; BP – Blood pressure; CKD – Chronic kidney disease; CRI-I – Castelli risk index I; CRI-II – Castelli risk index II; CVD – Cardiovascular disease; DBP – Diastolic blood pressure; ESRD – End-stage renal disease; FPG – Fasting plasma glucose; HDL-C – High density lipoprotein cholesterol; LDL-C – Low density lipoprotein cholesterol; MAP – Mean arterial pressure; MetS – Metabolic syndrome; SBP – Systolic blood pressure; TC – Total cholesterol; TG – Triglycerides; T2DM – Type 2 diabetes mellitus.

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Introduction

Chronic kidney disease (CKD) is a progressive decline of renal function (glomerular filtration rate) that leads to the end stage renal disease (ESRD); dialysis and kidney transplantation are the alternatives to survive. CKD is a global burden that has several causative factors, often considered as a comorbidity of diabetes and cardiovascular disease (CVD) (Luyckx et al. 2018). Increasing prevalence of CKD is one of the major public health concerns in Mexico.

Several studies suggest that obesity, diabetes, and dyslipidemia are the major interrelated risk factors for CVD (Alam and Siddiqui 2014; Bener et al. 2007) that also play critical roles in the development of CKD (Elsayed et al. 2008; Webster et al. 2017; Yusuf et al. 2004). On the other hand, decline in kidney function can also result in the worsening of blood pressure (BP) levels. High prevalence of these chronic diseases are reported in Mexico that are increasing every year (Hernández et al. 2016). Diabetes alters lipid metabolism that leads to induce atherogenic dyslipidemia, an important risk factor for the development of CVD (Ferrannini et al. 1991; Nimmanapalli et al. 2016). Therefore, CVD is reported to be responsible for morbidity and mortality in type 2 diabetes mellitus (T2DM) (Elsayed et al. 2008). On the other hand, arterial vascular diseases namely atherosclerosis and arteriosclerosis are associated with CKD (Benz et al. 2018; Bermudez-Lopez et al. 2019; Moe and Chen 2004; Sarnak et al. 2003; Stenvinkel et al. 2003). Atherosclerosis is an inflammatory response to the endothelial wall damage. Rupture of lipid-rich plaques initiates atherogenesis and leads to the thrombotic occlusion of coronary artery, a type of ischemic heart disease (Moe and Chen 2004).

Lipid ratios such as as Castelli risk index I and II (CRI-I and CRI-II respectively), atherogenic index of plasma (AIP), and atherogenic coefficient (AC) can be used to diagnose the risk of hypertension among CKD patients (Koleva et al. 2015). Nevertheless, relatively fewer studies had explored the association between AIP, AC, CRI-I, CRI-II, and hypertension. In Mexico, CKD prevalence among adults is alarming and hemodialysis is the most common way to treat ESRD. In this background, the aim of the present study was to find the interrelationships among blood pressure, fasting plasma glucose (FPG), and derived lipid profile parameters (AIP, AC, CRI-I, CRI-II) among adult CKD patients on hemodialysis.

Participants and methods

The present observational study was approved by the Ethics Committee of the Regional High Speciality Hospital of Yucatan Peninsula (HRAEPY in Spanish acronym); the public institution provides tertiary health care services to the peninsular States of Mexico namely, Campeche, Quintana Roo, and Yucatan. Medical records of height, weight, blood pressure (BP), fasting plasma glucose (FPG), and lipids profile of 86 patients aged 20 years and above who had undergone hemodialysis at least for three times between 2016 and 2017 were available in the HRAEPY; 39 medical records were excluded due to incomplete and/or missing data. The sample size for the present study was 47 adults (12 men and 35 women). Diabetes, urinary lithiasis and hypertension were the most common causes of chronic renal failure (CRF) among the patients of

the present study. Participants had an estimated mean time of 36.67±27 months under treatment with hemodialysis. Erythropoietin, iron, and vitamin D were the common drugs prescribed for the patients on hemodialysis. Additionally, prescription of glucose level controlling drugs namely, insulin and metformin for T2DM and angiotensin inhibitors for hypertension were found to be administrated among patients. However, drug therapy was adapted according to the health status of each participant. Regarding the associated comorbidities, 21 participants had T2DM and 19 were diagnosed with metabolic syndrome (MetS).

Measurements of height (cm) and weight (kg) were recorded following standard protocol (WHO 1995). Height was measured to the nearest tenth of a centimeter using a standard stadiometer with platform (Detecto, USA). Body weight was recorded to the nearest 0.05 kg using an electronic scale (Detecto, USA). Blood pressure (BP) (systolic and diastolic, SBP and DBP respectively) was estimated using the Phoenix X36 Hemodialysis System (Gambro, USA). Clinical biochemistry tests were done following standard protocol to estimate levels of FPG (mg/dL), cholesterol (mg/dL), triglycerides (TG) (mg/dL), high-density lipoprotein cholesterol (HDL-C) (mg/dL), and low-denisty lipoprotein cholesterol (LDL-C) (mg/dL). A pre-validated equipment (autoanalyzer COBAS® Integra 400 Plus, Roche Diagnostics) was used for the clinical biochemistry tests.

Body mass index (BMI) was calculated as weight (kg) divided by height (meter square). BMI-based nutritional status of CKD patients was evaluated as normal weight 18.5–24.9 kg/m^2 , overweight 25–29.9 kg/m^2 and obesity ≥30 kg/m^2 (WHO 1995). Other diagnostic criteria were raised BP or hypertension (SBP/DBP ≥130/85 mmHg), increased FPG (≥100 mg/dL), triglycerides (≥150 mg/dL), and reduced level of HDL-C: (<40 mg/dL in women and <50 mg/dL in men) (González-Chávez et al. 2008). Mean arterial pressure (MAP) was calculated as DBP+ 1/3*(SBP-DBP) (Safar and Boudier 2005). The derived parameters of lipid profile were calculated following standard equations (Bo et al. 2018; Kamoru et al. 2017):

Total Cholesterol (TC) = HDL level + LDL level + 20 percent of TG level

Atherogenic coefficient (AC) = (TC- HDL-C) / HDL-C

Atherogenic index of plasma (AIP) = [$\log_{10}$ (TG / HDL-C]

Castelli Risk Index I (CRI-I) = (TC / HDL-C)

Castelli Risk Index II (CRI-II) = (LDL-C / HDL-C).

The outcomes for AIP were further classified as low risk: AIP < 0.11, intermediate risk: AIP = 0.11–0.21 and high risk: AIP > 0.21. Due to the smallness of sample size, AIP has been categorized in two groups: low and intermediate risk (n = 11) and high risk (n = 36).

Data analysis was done using SPSS statistical software (version 15.00). Descriptive statistics (mean values and standard deviation) of age, anthropometric characteristics (height, weight, and BMI), BP, FPG level, and lipid profile were computed and differences of mean values of the parameters between hypertensive and normotensive individuals were estimated using Student's t-test.

Parametric and non-parametric correlation coefficients (Pearson's r and Spearman's rho respectively) were computed to observe association between parameters. Multiple linear regression models predicting mean arterial pressure (MAP) from FPG, AC, CRI I and CRI II were developed to explain the interrelationships between the parameters. Models were adjusted for age and sex. Confidence interval levels (CI) were set at 95%, and $p< 0.05$ was considered to be significant.

Results

Available data of 47 adult CKD patients (12 men, 35 women) who regularly attended hemodialysis were analyzed. Mean values of age (ranging between 21 and 67 years) did not show significant sex difference (men 48.92 ± 9.89 years, women 48.74 ± 16.98 years). Men were taller than women and showed significant sex difference in the mean values of height (men 157.08 ± 4.36 cm, women 147.03 ± 9.28 cm; t = 5.00, p-value <0.0001). However, mean values of weight (men 65.32 ± 9.89 kg, women 59.80 ± 19.25 kg) and BMI (men 26.48 ± 4.04 kg/m^2, women 27.49 ± 7.70 kg/m^2) were not significantly different in men and women. Blood pressure and lipid profile parameters also did not show significant sex difference except SBP (men 148.25 ± 15.89 mmHg, women 136.09 ± 22.15 mmHg; t = 2.05, p-value <0.05), triglycerides (men 82.92 ± 31.25 mm/dL, women 126.89 ± 56.04 cm; t = 3.36, p = 0.002), and AIP (men 0.23 ± 0.18, women 0.41 ± 0.26 cm; t = 2.67, p = 0.01). The results of sex difference in parameters are not presented in a separate table. Therefore, other results are presented in a pooled sample of 47 adult participants and derived lipid parameters were AC, CRI I, CRI II.

Table 1. Characteristics of CKD patients with normal blood pressure and hypertension

Characteristics	Total (n=47) Mean (SD)	Normotensive (n=17) Mean (SD)	Hypertensive (n=30) Mean (SD)	t	*p*-value
Age (years)	49.04 (15.39)	48.47 (14.61)	49.37 (17.13)	0.18	0.857
BMI (kg/m^2)	27.23 (6.93)	27.65 (8.24)	26.99 (6.20)	0.78	0.998
SBP (mmHg)	139.19 (21.25)	117.41 (7.82)	151.53 (15.72)	9.92	<0.001*
DBP (mmHg)	81.64 (13.67)	68.76 (9.88)	88.93 (9.50)	6.82	<0.001*
MAP (mmHg)	100.63 (14.98)	84.82 (7.94)	109.59 (9.58)	9.52	<0.001*
FPG (mg/dL)	120.57 (49.07)	101.32 (13.13)	131.48 (58.17)	2.72	0.010*
Cholesterol (mg/dL)	144.21 (30.25)	145.94 (28.44)	143.23 (31.66)	0.30	0.765
Triglycerides (mg/dL)	115.66 (54.13)	116.59 (43.32)	115.13 (60.09)	0.09	0.954
HDL-C (mg/dL)	46.64 (13.12)	53.46 (13.57)	42.78 (11.36)	2.75	0.010*
LDL-C (mg/dL)	79.27 (22.01)	74.40 (16.42)	82.03 (24.45)	1.28	0.209
TC (mg/dL)	149.04 (29.84)	151.17 (27.29)	147.83 (31.58)	0.38	0.706
AIP	0.37 (0.25)	0.32 (0.28)	0.39 (0.28)	0.97	0.337
AC	2.40 (1.09)	1.92 (0.53)	2.67 (1.22)	2.93	0.005*
CRI-I	3.40 (1.09)	2.92 (0.53)	3.67 (1.22)	2.93	0.002*
CRI-II	1.85 (0.82)	1.45 (0.38)	2.07 (0.92)	3.25	0.002*

BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; MAP – Mean arterial pressure; FPG – Fasting plasma glucose; HDL-C – high-density lipoprotein-cholesterol; LDL-C – low-density lipoprotein-cholesterol; TC – total cholesterol; AIP – atherogenic index of plasma; AC – atherogenic coefficient; CRI-I – Castelli risk index I; CRI-II – Castelli risk index II. SD – standard deviation; *($p < 0.05$).

In the pooled sample (n = 47), mean values of parameters showed that patients were overweight (BMI = 27.23 kg/m^2), hypertensive (SBP/DBP = 139.19/81.64 mmHg), and diabetic (FPG 120.57 mg/dL) (Table 1). Test for significant differences of mean values between normotensive (n=17) and hypertensive (n=30) CKD patients on hemodialysis showed blood pressure (SBP, DBP, MAP), FPG, HDL-C levels, and derived parameters like AC, CRI I and II were significantly different in two groups (Table 1). No significant differences of mean values between groups were observed for BMI, cholesterol, TG, LDL-C, TC, and AIP. Student's t-test estimating significant differences of mean values of SBP, DBP, and MAP at the levels of AIP (low and intermediate risk versus high risk) and non-parametric correlation between hypertension (binary) and AIP (continuous and categorical) were not significant ($p > 0.05$). Correlation between FPG and AIP was also not significant ($p > 0.05$). Therefore, AIP was not used as an independent variable in the regression analysis for MAP.

Prevalence of excess weight (overweight + obesity) (70.21%) was remarkably high in the sample. Hypertension and hyperglycemia were found in 30 patients (63.83%). Regarding the altered levels of lipid parameters, 12 patients had high triglycerides (25.53%) and 17 individuals had low HDL-C level (36.17%) (Table 2).

Multiple linear regression models adjusted for age and sex were build to examine the influences of FPG, AC, CRI-I, and CRI-II on MAP. Model 1 (age, sex, FPG), model 2 (age, sex, FPG, AC), model 3 (age, sex, FPG, CRI-I), and model 4 (age, sex, FPG, CRI-II) were significant and ANOVA p-values were < 0.05, indicating statistically significant interrelationships between variables at the 95.0% confidence level. MAP showed significant correlation ($p < 0.05$) with FPG ($r = 0.39$), AC, CRII, and CRI-II ($r = 0.30$). It may be mentioned herewith that non-parametric correlation (Spearman's rho) between hypertension (binary, yes or no) and derived parameters of lipid profiles also showed similar results.

Parameter estimates of the response variable (MAP) included 95% confidence interval for the coefficient. The regression models accounted for 16% and 26% of total variability explained by adjusted R^2 in model 1 (FPG level as predictor) and other models (FPG levels and derived variables of lipid profile as the predictors) respectively. MAP as a response variable showed variability around the mean in the fitted models that were explained by the R-squared statistic as 22.0% (FPG) and 33% (FPG and AC, CRI I, CRI II) among CKD patients on hemodialysis.

Table 2. Frequency of variables among CKD patients (n= 47)

Variables	Categories	Frequency	Percent (%)
BMI	Normal	14	29.79
	Overweight	26	55.32
	Obesity	7	14.89
Blood pressure	Hypertension	30	63.83
FPG	Diabetes	30	63.83
Triglycerides	Hypertriglyceridemia	12	25.53
HDL-C	Low HDL-C	17	36.17

BMI – body mass index; FPG – Fasting plasma glucose; HDL-C – high-density lipoprotein-cholesterol.

Results demonstrated that FPG (t = 2.85) could significantly predict MAP (p = 0.01), after asjusting for age and sex in the regression analysis (model 1). Predictors like AC, CRI-I (t = 2.63), and CRI-II (t = 2.64) also had significant interrelationsips with hypertension (p = 0.01) when other independent variables were constant in the models (Table 3). It was observed that for one unit rise of AC or CRI I, there was a chance of 4.68 mmHg increase in the MAP holding other predictors constant in the model (2 and 3). Among CKD patients on hemodialysis, it was 6.14 mmHg rise in MAP due to one unit higher value of CRI II when other varaibles (age, sex, and FBG) were adjusted in the model 4.

Results indicated no first order linear autocorrelation in the data of multiple linear regression models (value 2.1). Relatively high tolerance (>0.1.2) and low variance inflation factor (<1.02) for the independent variables meant the models exhibited no multicollinearity between independent vatriables. Residuals were normally distributed and showed no patterns (Figures are available from corresponding author on request).

Table 3. Multiple regression-model predicting mean arterial pressure (MAP) among CKD patients (n= 47)

							95% CI for B				
Models	Predictors	B	SEE	Beta	t	p-value	Lower	Upper	AdjR²	F change	p-value
1	Constant	104.85	11.76		8.92	<0.001	81.13	128.56	0.16	3.97	0.01
	Age (years)	−0.20	0.13	−0.21	−1.53	0.13	−0.46	0.06			
	Sex	−5.36	4.56	−0.16	−1.18	0.25	−14.54	3.83			
	FPG (mg/dL)	0.12	0.04	0.39	2.85	0.01	0.03	0.20			
2	Constant	98.65	11.44		8.23	<0.001	75.56	121.74	0.26	5.12	0.002
	Age (years)	−0.20	0.12	−0.21	−1.68	0.10	−0.46	0.04			
	Sex	−7.58	4.39	−0.22	−1.73	0.09	−16.43	1.28			
	FPG (mg/dL)	0.12	0.04	0.38	3.03	0.004	0.04	0.19			
	AC	4.68	1.78	0.34	2.63	0.01	1.08	8.27			
3	Constant	93.95	11.98		7.84	<0.001	69.78	118.15	0.26	5.12	0.002
	Age (years)	−0.20	0.12	−0.21	−1.67	0.10	−0.45	0.04			
	Sex	−7.53	4.35	−0.22	−1.73	0.09	−16.31	1.28			
	FPG (mg/dL)	0.12	0.04	0.38	3.03	0.004	0.04	0.19			
	CRI-I	4.68	1.78	0.34	2.63	0.01	1.09	8.27			
4	Constant	97.56	11.54		8.46	<0.001	74.28	120.85	0.26	5.12	0.002
	Age (years)	−0.21	0.12	−0.21	−1.69	0.10	−0.45	0.04			
	Sex	−6.73	4.34	−0.20	−1.56	0.13	−15.49	2.02			
	FPG (mg/dL)	0.11	0.04	0.37	2.94	0.005	0.04	0.19			
	CRI-II	6.14	2.33	0.34	2.64	0.01	1.44	10.83			

Response variable – mean arterial pressure (MAP).
FPG – fasting plasma glucose; Sex – men=1, women = 2; AC – atherogenic coefficient; CRI-I – Castelli risk index-I; CRI-II – Castelli risk index-II; B – unstandardized regression coefficient; SEE – standard error of estimate; CI – confidence interval; AdjR² – adjusted R square.

Discussion

The prevalence of CKD is increasing worldwide (Luyckx et al. 2018). However, sufficient epidemiological data of CKD are not available from Mexico, not even of the patients who are undergoing renal theraphy (Amato et al. 2005). In the present study among CKD patients undergoing hemodialysis, high prevalence of hypertension and type 2 diabetes mellitus (T2DM) (both 63.83%) were recorded. Reports on the frequency of hypertension range between 70% and 80% globally among patients undergoing regular dialysis (Bucharles et al. 2019). Higher mean values of FPG, AC, CRI-I, CRI-II and lower HDL-C were observed among hypertensive CKD patients in comparison with the patients with normal BP in the present study. The results conform to the earlier reports from other countries (Ene-Iordache et al. 2016; Luyckx et al. 2018; Ninomiya et al. 2005). CVD still remains as the principal cause of morbidity and mortality in CKD albeit availability of some renal replacement therapies that are not only expensive but also involve complications like lack of compatibility, contraindications for patients with cardiac and pulmonary insufficiencies, etc. (Fleming 2011, Carracedo et al. 2020). Obesity also plays an important role in the mortality of patients under hemodialysis; high prevalence of excess weight (overweight + obesity) (70.21%) was remarkably observed in our sample. A cohort study among CKD patients on dialysis showed that obesity (BMI ≥30 kg/m^2) compared with normal weight was associated with an almost 2-fold increased mortality rate (Hoogeveen et al. 2012).

Studies reported that metabolic interactions of lipid ratios can reveal important and additional information of patients with chronic diseases. Association of AIP, AC, CRI-I, and CRI-II with CVD have been described through the mechanisms of insulin resistance, dyslipidemia and metabolic syndrome (MetS) (Lee et al. 2017). In 2018, a study carried out among 6,465 adult men aged 30 years and above in China, concluded that AIP was a novel and better biomarker for obesity and T2DM (Zhu et al. 2018). Another study (Onat et al. 2010) among 2,676 middle-aged adults suggested AIP as a surrogate of LDL-C, obesity and hyperinsulinemia in men and high C-reactive protein status in women. AIP independently predicted coronary heart disease, T2DM, hypertension, and MetS among adults. In our study, no significant differences were found in AIP between hypertensive and normotensive CKD patients. Regression coefficient of AIP predicting MAP was not significant and therefore, the results were not presented. Nevertheless, AC, CRI-I, and CRI-II were found to be the significant predictors for MAP, holding age, sex and FPG adjusted in the models. A cross-sectional study among 41 patients with kidney transplantation in South Africa, reported that CRI-II and lipoprotein combine index had higher association with atherosclerotic vascular disease than serum lipid parameters (Oguntola et al. 2018). Results from our study, suggest the relevance of lipids ratios (AC, CRI-I, and CRI-II) over individual lipid parameters among CKD patients under hemodialysis. A cross-sectional study carried out among the patients with and without coronary artery disease in India, reported TC and LDL-C were not different between groups. However, AC, AIP, CRI-I, and CRI-II were significantly different (Bhardwaj et al. 2013).

Limitations

Shortcomings of our study included availability of limited number of medical records of CKD patients on hemodialysis in the hospital. Therefore, comparison between CKD stages was not possible. Longitudinal studies with larger sample size in future will help us to comprehend the synergy between hypertension, CVD, and lipid parameters in CKD patients.

Conclusion

In the present study, correlation coefficients between hypertention and other parameters, namely FPG, AC, CRI-I, and CRI-II were significant. It was evident that AC, CRI-I, and CRI-II can be used as indicators for early diagnosis of CVD in CKD patients. Higher number of women CKD patients on hemodialysis were found in the sample. Differential degrees of glucose and lipid metabolism alterations in men and women and their association with hypertension in CKD have to be investigated in future. The CVD and CKD are chronic and degenerative diseases that are big challenges for the public health systems in Mexico, like other parts of the world. Also it is required to create and improve the database of CKD patients at national level. There is a need to further implement specific and new lines of research for the prevention and treatment of CKD and their complications in order to improve the quality of life of patients and optimize institutional resources that are very limited in Mexico and particularly in the Yucatan Peninsula.

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The Authors' contribution

ALGS: designed the study and performed computations. SDB and RMMG: verified the analysis and outputs. RHC: collected the information from hospital records and supervised the findings of the work. ALGS: wrote the manuscript with support from SDB. The co-authors had equal contributions.

Conflict of interest

The authors declare that there is no conflict of interest.

Availability of data and material

The authors agree to allow the publication and distribution of the materials submitted in all available forms, without limiting territory or language, provided that the material is accepted for publication. Authors confirm that all information are original and free from plagiarism. At the same time the authors declare that the submitted work is not presented and will not be published elsewhere in whatever language and published article will not be shared with anyone without earlier written permission of the publisher, except for academic purposes. Aditonal figures are available from the corresponding author on request through e-mail.

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