Artículo Original

Atherogenic index of plasma is the best predictor of metabolic syndrome among Mexican adult patients with chronic kidney disease on hemodialysis
El índice aterogénico del plasma es el mejor predictor de síndrome metabólico en pacientes adultos con enfermedad renal crónica bajo tratamiento de hemodiálisis en México.

Ana Ligia Gutiérrez Solis[1], Ricardo Hernández Cardoza[1], Sudip Datta Banik[2], Rosa María Méndez González[2].
[1] Research Unit of the Regional High Speciality Hospital of Yucatan Peninsula, Merida, Yucatan, Mexico.
[2] Department of Human Ecology, Centro de Investigación y de Estudios Avanzados del IPN (Cinvestav-IPN) Merida, Yucatan, Mexico.

RESUMEN

Introducción: Estudios relacionan al síndrome metabólico (SM) con la enfermedad renal crónica (ERC). La Hemodiálisis es la forma más común de tratar a los pacientes con ERC. En México se encuentra poca información sobre la asociación de estas condiciones y utilidad de los parámetros lipídicos. **Objetivo**: Estimar la utilidad de parámetros lipídicos en el desarrollo de SM en pacientes adultos con ERC bajo tratamiento de hemodiálisis en un hospital de Yucatán, México. **Métodos**: Estudio transversal que utilizó las historias clínicas de pacientes adultos con ERC en hemodiálisis de un hospital público de Yucatán, México. Se analizó la edad, índice de masa corporal (IMC), presión arterial (sistólica y diastólica), niveles de glucosa plasmática en ayunas, triglicéridos y colesterol unido a lipoproteínas de alta densidad (HDL). Los parámetros lipídicos estudiados fueron el índice aterogénico del plasma (AIP) y el índice de riesgo de Castelli (IRC I y II). Se realizó un análisis de regresión logística binomial para comprender la asociación diferencial de los parámetros lipídicos y el SM. **Resultados**: El valor medio de la edad de los pacientes fue de 48 años. 45% de los pacientes tenían SM y su asociación con ERC fue significativa (p <0.05). Las frecuencias de sobrepeso y obesidad (70,31%), hipertensión (67,18%), hiperglucemia (46,87%), hipertrigliceridemia (21,85%) y HDL bajo (50%) fueron notables en la muestra. Los modelos de regresión logística binomial ajustados por edad y sexo mostraron que SM predijo significativamente (p <0,05) por el exceso de peso, presión arterial elevada, hipertrigliceridemia, AIP y HD bajo. **Conclusión**: Se descubrió que la AIP es el mejor predictor de SM en pacientes con ERC.

Palabras clave: síndrome metabólico, enfermedad renal crónica, hemodiálisis, índice aterogénico del plasma.

SUMMARY

Background: Cientific research links Metabolic syndrome (MetS) to chronic kidney disease (CKD). Hemodialysis is the most common way to treat CKD patients. Little information regarding the association of these conditions and the utility of derived parameters are found in Mexico. **Objective**: Our aim was to estimate differential roles of individual and derived parameters to develop MetS among adult CKD patients on hemodialysis in a hospital from Yucatan, Mexico. **Methods:** The crosssectional study used medical records of 64 adult patients above 20 years of age (21men, 43 women) with CKD on hemodialysis who received attention during 2016 – 2017 in a public hospital in Yucatan, Mexico. Data of age, body mass index (BMI), blood pressure (systolic and diastolic), levels of fasting plasma glucose, triglycerides and high-density lipoprotein cholesterol (HDL-C) were analyzed. Derived lipid parameter were atherogenic index of plasma (AIP) and Castelli risk index (CRI I and III). Binomial logistic regression analysis was done to understand the differential association of lipid parameters with the development of MetS. **Results**: Mean value of age of the pateins (pooled sample of men and women) was 48 years. Overall, 45% of the patients had MetS and its association with CKD was significant (p<0.05). Frequencies of BMI-based excess weight (overweight and obesity), (70.31%), hypertension (67.18%), hyperglycemia (46.87%), hypertriglyceridemia (21.85%), and low HDL-C (50%) were remarkable. Age and sex adjusted binomial logistic regression models showed that MetS was significantly predicted (p<0.05) by excess weight, raised blood pressure, hypertriglyceridemia, AIP, and low HDL-C. **Conclusion:** CKD patients had higher risk for MetS with at least 3 components. AIP was found to be the best predictor of MetS.

Keywords: metabolic syndrome, chronic kidney disease, hemodialysis, atherogenic index of plasma.

Autor de correspondencia: Ana Ligia Gutiérrez Solis, PhD correo electrónico: ana.gutierrez@salud.gob.mx
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Introduction

High prevalence of BMI-based obesity, hypertension, dyslipidemia, metabolic syndrome (MetS) and their association with chronic kidney Disease (CKD) in adults are important public health problems in Mexico (1). Hypertension, diabetes mellitus (DM) and dyslipidemia have differential roles in the development of MetS that are also the principal risk factors for CKD (2). High prevalence of these chronic diseases (Hypertension 25.5% and DM 9.4%) are reported in Mexico (3). Derived lipid parameters, namely atherogenic index of plasma (AIP) and Castelli Risk Indexes I and II (CRI-I and CRI-II) are often used as the indicators of cardiovascular disease (CVD) that are also associated with CKD.The AIP is defined as the log of triglycerides (TG) and high density lipoprotein cholesterol (HDL-C) [log10 (TG/HDL-c)] and is one of the strongest markers for predicting high CVD risk and cardiovascular mortality (4). In fact, AIP has been showed to be a better prognostic marker than other lipid parameters (5). Other lipid ratios include Castelli risk index I (CRI-I) and Castelli risk index II (CRI-II) that are calculated as:TC/HDL-C and LDL-C/HDL-C, respectively. Few reports are available on the association between MetS and derived lipid parameters (AIP, CRI II and II) among CKD patients who were undergoing hemodialysis (6, 7). The derived lipid parameters have shown to be more accurate than total cholesterol (TC), serum triglycerides, and HDL-C in the evaluation of cardiovascular risk (8).

It is known that MetS can affect kidney function negatively. Therefore, it seems that MetS can be considered to be a risk factor for CKD progression. In addition, AIP, CRI-I and CRI-II can be used as the predictive markers for risk and mortality of CVD (4). In Mexico, MetS prevalence among adults is high and expected to increase in future. Data have reported that overall prevalence of MetS can reach up to 70% of the CKD patients on hemodialysis (9). The MetS prevalence among CKD patients on hemodialysis is unknown in Mexico; studies describing the relative strength of association between MetS and AIP or other lipids ratios in CKD patients under hemodialysis, are also not available. In this background, the aim of the present study was to estimate differential roles of MetS components and derived parameters to develop MetS among adult CKD patients on hemodialysis in a hospital from Yucatan, Mexico.

Material and Methods

This crosssectional study was based of medical records of CKD patients available in the Regional High Speciality Hospital of Yucatan Peninsula (HRAEPY) that also issued ethical clearnce. The HRAEPY is located in Merida, Yucatán, Mexico.

Data on age, height, weight, blood pressure (systolic and diastolic) and lipids profile charateristics were collected from the records of 64 adult patients above 20 years of age (21 men, 43 women) who had undergone hemodialysis at least for three times between 2016 and 2017 in the HRAEPY. Body mass index (BMI) was calculated (body weight in kg divided by height in meter square) and excess weight (BMI≥ 25 kg/m2) was estimated following criterion (10). Amongst the clinical criteria for the diagnosis of MetS, the present study used a minimally modified definition of the Third Report of the National Cholesterol Education Program Adult Treatment Panel (NCEP/ATP III), in which BMI was used instead of waist circumference to fulfil MetS criteria among CKD patients that included the following components.

1. BMI ≥ 25 kg/m^2, as indicator of excess weight (overweight and obesity).(11)
2. Elevated blood pressure (BP): (Systolic/ Diastolic or SBP/DBP≥130/85 mmHg.
3. Raised fasting plasma glucose: ≥100 mg/dL
4. High triglycerides: ≥150 mg/dL.
5. Reduced HDL-C: <40 mg/dL in women and <50 mg/dL in men.

MetS was diagnosed when at least three of the five conditions were found. Derived lipid parameters were calculated as follows: Total cholesterol (TC) = HDL-C + LDL-C + 20% of triglycerides; AIP = [log10 (TG/HDL-C]; CRI-I = (TC/HDL-C) and CRI-II = (LDL-C/HDL-C).

Prevalence of MetS and its components results were estimated separately for men and women (Table 1). Patients were divided into 2 groups:

without MetS (-) and with MetS (+). Baseline characteristics of the variables are expressed in mean and standard deviation (SD) values. Based on the normality of distribution of variables that fulfilled the criteria for Shapiro-Wilk test (p> 0.05), appropriate tests (Student's t-test or Mann-Whitney U) for significant differences were done. Binary logistic regression analysis adjusted for age and sex was performed to identify factors predicting MetS among patients with CKD. Data analysis was done using the Statistical Package for Jamovi (Version 0.9). Confidence interval levels (CI) were set at 95%, and p< 0.05 was considered to be significant.

Results

Mean values of age were 48.33 and 48.58 years among men and women respectively. Women had higher levels of AIP, triglycerides, TC (p=0.03) and CRI-I (p=0.01) in comparison with men. However, men showed higher mean values of SBP with significant sex difference (p=0.03). No significant sex differences were observed with respect to age, BMI, fasting plasma glucose, HDL-C, LDL-C and CRI-II (Table 1).

MetS frequency in the sample was 45.31%. Majority of the patients were excess weight (70.31%). Only one woman was underweight (1.56%). Frequencies of hypertension (67.18%), hyperglycemia (46.87%), hypertriglyceridemia (21.85%) and low HDL-C (50%) were remarkable in the pooled sample of men and women. Frequencies were higher among men in comparison with women peers with respect to excess weight (men 76.19%, women 67.44%) and hypertension (men 80.95%, women 60.46%) (Table 2).

A breakdown of the number of MetS components showed that 31.30% individuals had the presence of at least three components to fulfill MetS criteria. Patients with four and five components to develop MetS were 10.94% and 3.13%, respectively in the sample (Table 3).

In a pooled sample (n = 64) of men and women, patients with MetS and without MetS were compared and significant differences in mean values were were found with respect to BMI (p=0.03), SBP (p=<0.01), DBP (p=<0.01), levels of TG (p=0.02), HDL-C (p=<0.01), AIP (p=<0.01), CRI-I (p=0.01) and CRI-II (p=0.03) with higher mean values in patients with MetS. No significant differences between groups were observed for glucose, TC and LDL-C (Table 4).

Logistic regression analysis was done to predict MetS from different parameters after asjusting for age and sex. The models were significant. Highest odds ratio to predict MetS was obtained for AIP, followed by CRI-II and CRI-I to predict MetS. The area under receiver operating characteric curve (ROC) results revealed that the BMI, SBP, DBP, TG, HDL-C, AIP, CRI-I and CRI-II significantly predicted MetS (+) [all area under the ROC curves (AUCs)>0.6, p<0.05]. SBP showed the highest AUC=0.82 (OR 1.05; 95% CI 1.01-1.08), followed by DBP showing an AUC=0.81 (OR 1.09; 95% CI 1.03-1.15). AIP and CRI-I showed an AUC=0.76. There was no signifcant diference between MetS (with and without) in the AUC (0.59) value for fasting plasma glucose (OR 1.01; 95% CI 0.99-1.03) (Figures are available from the corresponding author on request).

Discussion

In the present study, high prevalence of MetS (45.31%) was observed among CKD patients undergoing hemodialysis that was much higher than the frequency reported (36%) from healthy individuals (without CKD) in Mexico (12). Moreover, significant differences of mean values were observed with respect to BMI, SBP, DBP, TG, HDL-C, AIP, CRI-I and CRI-II between with and without MetS among CKD patients. The results were in agreement with Gomez-Diaz, et al. (13) who carried out a study among children with CKD and MetS, from a hospital in Mexico City; the study noted significant differences in SBP, DBP, and TG, between groups with MetS and without MetS. Reports from different populations have documented that hypertension and raised plasma glucose levels are the MetS components with stronger association for an increased risk for CKD (14). In the present study, it appeared that hypertension, raised TG and low levels of HDL-C were the components that showed significant associations in CKD patients with MetS on

Table 1. Sex difference and characteristics of CKD patients (43 women, 21 men). a

Variables	Men Mean±SD (CV)	Women Mean±SD (CV)	p-values
Age (years)	48.33 ±13.53 (0.27)	48.58 ±16.02 (0.32)	0.84
BMI (kg/m^2)	26.18±4.30 (0.16**)	27.43±7.06 (0.25**)	---
SBP (mmHg)	148.52±21.56 (0.14)	135.95±21.23 (0.15)	0.03*
DBP (mmHg)	83.19±11.43 (0.13)	81.67±13.85 (0.15)	0.66
FPG (mg/dL)	121.02±37.82 (0.31)	115.48±47.41 (0.41)	0.39
Triglycerides (mg/dL)	93.57±78.89 (0.84**)	127.00±53.69 (0.42**)	--
HDL-C (mg/dL)	48.02±14.67 (0.30)	46.65±16.22 (0.34)	0.74
TC (mg/dL)	127.24±34.45 (0.27)	145.05±28.94 (0.19)	0.03*
LDL-C (mg/dL)	66.50±27.06 (0.40)	77.61±22.83 (0.29)	0.09
AIP	0.24±0.35 (1.48**)	0.42±0.29 (0.69**)	--
CRI-I	3.07±2.25 (0.73)	4.11±4.17 (1.01)	0.01*
CRI-II	1.58±1.00 (0.63)	1.92±1.02 (0.53)	0.12

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: Fasting plasma glucose; HDL-c: high-density lipoprotein-cholesterol; TC: total cholesterol; LDL-c: low-density lipoprotein-cholesterol; AIP: atherogenic index of plasma [log(TG/HDL-c)]; CRI-I: Castelli risk index I (TC/HDL-c); CRI-II: castelli risk index II (LDL-c/HDL-c). SD: standard deviation; *($p < 0.05$); ** Significant mean difference in the absolute deviation of adjusted coefficient of variation (CV) scores.

hemodialysis. However, raised plasma glucose level was not found to be a significant factor predicting MetS among CKD patients. Many studies have showed a positive association between obesity and CKD (15). The present study also observed a high frequency of obesity (70.3%) among CKD patients. Our findings are in agreement with Kramer et al. (15) who reported prevalence of 60% of obesity among patients on dialysis. Another study from Japan (16) reported that BMI was associated with an increased risk for the development of CKD in men.

The concept of 'MetS' has been postulated for the early identification of individuals who are prone to develop diabetes mellitus (DM) and CVDs. However, it is still unclear if MetS criteria

Table 2. Frequency of MetS components among CKD patients.

Component	Men (n=21) %	Women (n=43) %	Total (n=64) %
BMI ≥25 kg/m^2	76.19	67.44	70.31
High Blood pressure	80.95	60.46	67.18
High Glucose	52.38	44.18	46.87
High Triglycerides	9.50	27.90	21.87
Low HDL-C	28.57	60.46	50.00

BMI: body mass index; HDL-C: high-density lipoprotein-cholesterol.

Table 3. Number of MetS components present among CKD patients (n = 64).

Diagnosis	MetS components	%	95 % CI
MetS (-)	0	1.56	0.1-4.6
	1	18.75	9.-28.3
	2	34.38	22.7-46.0
MetS (+)	3	31.25	19.-42.6
	4	10.94	3.3-18.6
	5	3.13	1.1-7.4

MetS (-): without metabolic syndrome; MetS (+): with metabolic syndrome; CI: confidence interval.

Table 4. Characteristics of CKD patients with and without MetS.

Characteristics	With MetS (n=29) Mean (SD)	Without MetS (n=35) Mean (SD)	p-values
Age (years)	49.03 (12.93)	48.06 (16.93)	0.79
BMI (kg/m^2)	28.94 (7.73)	25.43 (4.24)	0.03*
SBP (mmHg)	148.21 (16.66)	133.34 (23.74)	<0.01*
DBP (mmHg)	88.03 (9.77)	77.31 (13.50)	<0.01*
Glucose (mg/dl)	124.50 (54.24)	111.33 (33.56)	0.07
Triglycerides (mg/dL)	132.72 (61.13)	102.20 (64.60)	0.02*
HDL-c (mg/dL)	41.40 (13.50)	51.82 (15.85)	<0.01*
TC (mg/dL)	140.45 (33.46)	138.17 (30.65)	0.07
LDL-c (mg/dL)	77.04 (27.07)	71.41 (22.53)	0.36
AIP [log(TG/HDL-C)]	0.48 (0.30)	0.24 (0.35)	<0.01*
CRI-I (TC/HDL-C)	3.77 (1.67)	3.78 (4.75)	0.01*
CRI-II (LDL-c/HDL-c)	2.11 (1.16)	1.56 (0.83)	0.03*

MetS: metabolic syndrome; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL-c: high-density lipoprotein-cholesterol; TC: total cholesterol; LDL-c: low-density lipoprotein-cholesterol; AIP: atherogenic index of plasma; CRI-I: castelli risk index I; CRI-II: castelli risk index II. SD: standard deviation; *($p < 0.05$).

Table 5. Logistic regression analyses of MetS risk among CKD population.

Characteristic	AUC	Sensitivity	Specificity	*p*-value	OR (95%CI)
BMI (kg/m^2)	0.75	0.930	0.238	0.02*	1.15 (1.01-1.32)
SBP (mmHg)	0.82	0.884	0.476	<0.01*	1.05 (1.01-1.08)
DBP (mmHg)	0.81	0.619	0.860	<0.01*	1.09 (1.03-1.15)
Glucose (mg/dL)	0.71	0.190	0.953	0.10	1.01 (0.99-1.03)
Triglycerides (mg/dL)	0.73	0.286	0.953	<0.01*	1.00 (0.99-1.01)
HDL-C (mg/dL)	0.78	0.476	0.860	0.02*	0.94 (0.90-0.98)
AIP [log(TG/HDL-C)]	0.76	0.524	0.907	0.01*	11.73 (1.69-81.04)
CRI-I (TC/HDL-C)	0.76	0.286	0.953	0.04*	1.40 (1.00-1.95)
CRI-II (LDL-C/HDL-C)	0.73	0.333	0.930	0.01*	2.10 (1.16-4.11)

AUC: area under the receiver operating characteristic curve; ; *($p < 0.05$).

can be used as a prognostic tool for CKD diagnosis. To date, some studies showed association between MetS and higher risk for CKD (17, 18). A crosssectional study by Chen, et al. (17) among 6,217 adults in the U.S.A., found a positive and significant association between MetS and risk for CKD and microalbuminuria; the risk increased progressively with a higher number of components of the MetS. Studies have explained how the lipid ratios can reveal important and additional information for

patients with chronic diseases. A study from China (5) reported higher AIP level was positively and strongly associated with obesity. Another study (19) reported that AIP could significantly predict CVD among adults and was associated with DM, high BP, and MetS . In our study, significant differences in AIP, CRI-I and CRI-II were found when groups with MetS and without MetS were compared among CKD patients on hemodialysis.

Previous studies and the present one revealed that individual MetS components and their simultaneous elevated levels, increased the risk for renal damage. However, it was unclear which components can be used to predict the risk for CKD.

Shortcomings of the present study had some influences on the results obtained. Available information of relatively small number of hospital records of CKD patients and lack of records of these patients in their early stages of disease were the principal limitations. However, in absence of information on the association of CKD with MetS and derived lipid parameters, at least from Peninsular Mexican States of Campeche, Quintana Roo and Yucatan, the present study contributes some important results as the first evidence of the usefulness of lipid ratios to predict MetS in CKD patients that are under treatment with hemodyalisis that might be used for public health policies by the Government.

Conclusions

The present study clearly pointed out that AIP, CRI-I and CRI-II had positive and strong associations with CKD and the strength of correlation was higher among the patients who were sufferening from MetS. Therefore, dyslipidemia, high AIP and lipid ratios among CKD patients enhanced risk for CVD. Association of hypertension with AIP, CRI I, and CRIII among CKD patients will be explored in future. Finally, AIP was found to be the best predictor for MetS among CKD patients of hemodialysis.

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