Insulin resistance in chronic kidney disease: its clinical characteristics and prognostic significance

F. Caravaca, I. Cerezo, R. Macías, E. García de Vinuesa, C. Martínez del Viejo, J. Villa, R. Martínez Gallardo, F. Ferreira, R. Hernández-Gallego

Nephrology Department. Infanta Cristina Hospital. Badajoz, Spain

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ABSTRACT

Introduction: Insulin resistance (IR) increases significantly the risk for cardiovascular disease (CV) in the general population. IR is a common metabolic disorder in patients with chronic kidney disease (CKD). However, the influence of IR on the evolution of CKD patients has scarcely been studied. **Objective:** This study aims to determine whether IR is associated with the progression of CKD, the development of new CV events, or all-cause mortality of non-diabetic patients with CKD stage 4 or 5 not yet on dialysis. **Material and methods:** The study group consisted of 365 non-diabetic patients (63 ± 16 year, 169 females) with GFR <30 ml/min. The degree of IR was estimated by the Homeostasis Model Assessment parameter (HOMA). The outcome measures were: progression of CKD (composite of initiation of dialysis or doubling of baseline serum creatinine level), new cardiovascular events, and all-cause mortality. Unadjusted and multivariable-adjusted relative risks were calculated for HOMA either as a continuous or qualitative variable (tertiles), using Cox proportional hazards models. **Results:** Mean HOMA value (± SD) was 4.28 ± 2.07. HOMA values correlated significantly with body mass index (beta = 0.37; p <.0001), plasma triglycerides (beta = 0.22; p <.0001), plasma albumin (beta = 0.19; p = .007), and serum phosphate (beta = 0.17; p = .031). Progression of CKD was observed in 234 patients (64%) with a median follow-up of 542 days. Patients with HOMA values in the lower tertile (<3.13) showed a slower progression of CKD than that of the rest of study patients (log rank 4.16, p <.05). In adjusted models for age, sex, baseline GFR, body mass index, and proteinuria, HOMA values in the lower tertile entered as an independent variable in the best predictive equation for progression of CKD (HR 0.72, p <.03). Fifty-one patients developed a new CV event and 103 patients died during the study period (median follow-up of 1,103 days). HOMA did not relate to the development of new CV events or all-cause mortality in unadjusted or adjusted models for age, sex, comorbid index, plasma albumin, and C-reactive protein. **Conclusions:** In conclusion, progression of renal disease was slower in those non-diabetic CKD patients with low HOMA values; however, HOMA values did not relate to the development of new CV events or all-cause mortality.

Key words: Chronic kidney disease. Mortality. Progression renal insufficiency. Insulin resistance. Cardiovascular risk.

Resistencia a la insulina en la enfermedad renal crónica: características clínicas asociadas y significado pronóstico

RESUMEN

Introducción: *La resistencia a la insulina (RI) es una alteración prevalente en los pacientes con enfermedad renal crónica (ERC). Su relación con la morbilidad cardiovascular (CV) y la mortalidad en la ERC ha sido poco estudiada.* ***Objetivos:*** *Los objetivos de este estudio fueron determinar la relación de la RI con la progresión de la ERC, el desarrollo de nuevos eventos CV y la mortalidad por cualquier causa en pacientes con ERC prediálisis.* ***Material y métodos:*** *Estudio de cohorte prospectivo observacional en el que se incluyeron 365 pacientes no diabéticos (63 ± 16 años, 169 mujeres) con un filtrado glomerular <30 ml/min. El grado de RI fue estimado mediante el parámetro «Homeostasis Model Assessment» (HOMA). Los sucesos evolutivos analizados fueron: progresión de ERC (entrada en diálisis o duplicar creatinina sérica inicial), desarrollo de nuevos procesos CV, o la mortalidad por cualquier causa.* ***Resultados:*** *Los pacientes con valores HOMA en el tercil inferior (<3,13) mostraron una progresión más lenta de la ERC en un modelo de regresión de Cox ajustado a edad, sexo, filtrado glomerular basal, índice de masa corporal y proteinuria, (razón de riesgo = 0,72; p = 0,03). Durante el período total de seguimiento 51 pacientes desarrollaron nuevos eventos CV y 103 fallecieron. Los valores HOMA no se relacionaron con el desarrollo de nuevos eventos CV ni con la mortalidad en modelos no ajustados o ajustados a*

Correspondence: Francisco Caravaca
Servicio de Nefrología. Hospital Infanta Cristina.
Avda. Elvas, s/n. 06080 Badajoz. Spain.
fcaravacam@senefro.org

edad, sexo, índice de comorbilidad, albúmina sérica y proteína C reactiva. ***Conclusiones:*** *En conclusión, la progresión de la ERC fue más lenta en pacientes con los valores HOMA más bajos, aunque este parámetro no fue capaz de predecir el desarrollo de nuevos eventos cardiovasculares o la mortalidad.*

Palabras clave: *Enfermedad renal crónica. Mortalidad. Progresión insuficiencia renal. Resistencia insulina. Riesgo cardiovascular.*

INTRODUCTION

Insulin resistance (IR), which is characterized by a functional deficit in this hormone despite high plasma levels, leads to a series of changes in the composition of plasma lipids, coagulation, endothelial function and vascular resistance, as well as endocrine changes and obesity. In combination, this increases the risk of developing high blood pressure and accelerated atherosclerosis.[1-4] The increase in cardiovascular risk associated with IR has been shown in the general population.[1-4]

The biochemical data of a high proportion of patients with chronic kidney disease (CKD) is compatible with IR,[5-8] even in the earliest stages of renal insufficiency. Although this metabolic disorder, which is associated with uraemia, was first described in the 1980s by DeFronzo and Alvestrand,[9,10] its physiopathological mechanisms are not yet fully understood.

CKD patients have a very high risk of developing cardiovascular (CV) diseases[11,12] and the link between these processes and traditional CV risk factors is specific.[13] The role that IR plays in the development of CV disease and mortality in the CKD population has not been subject of many studies.[7,14-16]

The objectives of this study were to determine the prevalence and clinical and biochemical characteristics associated with IR in a patient population with advanced CKD prior to dialysis, and to establish the prognostic value of IR in the progression of CKD, the development of new CV processes and all-cause mortality.

MATERIAL AND METHODS

Patients

In the study, 365 patients (average age 63 ± 16 years, 169 females) with stage 4-5 chronic kidney disease, who were monitored by a specialist in advanced chronic kidney disease (ACKD) were included. The inclusion criteria were as follows: patients over 18 years of age with no previous diagnosis of diabetes mellitus and baseline (fasting) blood glucose levels below 126 mg/dl, in a stable clinical condition with no acute intercurrent disease at the time of the baseline study and receiving no treatment with corticoids or other drugs with a significant "anti-insulin" action.

The aetiology of renal insufficiency was: undetermined origin (154 patients), primary glomerulonephritis (76 patients), chronic interstitial nephritis (66 patients), polycystic disease (31 patients), ischaemic nephropathy (30 patients) and other etiologies (8 patients).

Although none of the patients included in the study had diabetes mellitus, other comorbid diseases were common: 41 patients had a previous history of ischaemic cardiopathy, 55 of heart failure, 61 of cerebral or peripheral vascular disease, 23 of malignant disease and 40 of chronic obstructive pulmonary disease, and 19 patients had other significant comorbidities.

The drugs which were most frequently prescribed were antihypertensive agents (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, betablockers), diuretics, statins, antiplatelet drugs and phosphate binders.

Clinical Data and Laboratory Analysis

In addition to demographic data, systolic and diastolic blood pressure measurements, and body mass index were included. Comorbidity levels were quantified using the method developed by Davies et al.[17] Because of their potential link to insulin resistance, variables included the regular consumption of drugs such as betablockers, diuretics and angiotensin-converting enzyme inhibitors (ACEI) and/or angiotensin receptor antagonists (ARA).

Blood samples were taken from patients after a prolonged fasting period (at least 8 hours) in order to determine the following parameters: haemogram, glucose, urea, creatinine, uric acid, calcium, phosphate, total cholesterol, triglycerides, albumin (Advia Chemistry Multianalyzer, Siemens Healthcare Diagnostics) and venous bicarbonate (ABL 800 FLEX analyzer). The plasma concentration of highly sensitive C-reactive protein was determined by nephelometry (N High Sensitivity CRP, Behring, Marburg, Germany). The plasma concentrations of PTH were determined by IRMA (1-84 N-tact PTH IRMA Diasorin).

Glomerular filtration was estimated by means of the 4-variable MDRD formula. The protein catabolic rate (NPNA) was calculated by measuring urinary nitrogen excretion using the combined formulas of Cottini et al and Maroni et al, in accordance with the description given by Bergström et al.[18] The NPNA was adjusted to the actual weight of the patient.

Plasma concentrations of insulin were determined by means of two-site, solid-phase chemiluminiscent immunometric assays (Immulite® 2000 Immunoassay System Siemens Healthcare Diagnostics). The intra-assay and total coefficients of variation were 6.1 and 7.1% respectively.

To establish the level of insulin resistance we used the Homeostasis Model Assessment Insulin Resistance (HOMA)[19] parameter, the utility and reliability of which have been validated in patients with chronic kidney failure.[20] This parameter is calculated by means of the following formula: fasting insulin (μU/ml) x fasting glucose (mmol/l)/22.5.

Study Design and Statistical Analysis

This study is divided into two section, a first section consisting of a transversal analysis, in which the clinical and analytical characteristics associated with different levels of insulin resistance are described, and a second section, in which, by means of a prospective analysis, an attempt is made to establish the prognostic value of the HOMA parameter on three outcome events: *a)* CKD progression, defined as the initiation of dialysis or the doubling of baseline serum creatinine; *b)* the development of new severe acute cardiovascular processes (myocardial infarction, unstable angina, the need for coronary intervention, transistory or established cerebrovascular accidents or severe ischaemia of the lower limbs) and *c)* all-cause mortality.

After an initial assessment, patients were monitored by means of regular visits every 1-3 months, while they continued to be seen by a specialist due to ACKD, or by the reporting of any change in the progression of the disease after the initiation of dialysis. Patients were ruled out for study purposes in cases of all-cause mortality, renal transplant, follow-up losses (16 patients) or completion of the study period (1 November 2008). Censoring date considered for patients who were lost was their last consultation.

Median follow-up until the initiation of dialysis was 542 days (interquartile ranges: 221–922 days) and median follow-up until death or censoring date was 1,103 days (interquartile ranges: 643–1,707 days).

The comparison of continuous variables between groups was performed using analysis of variance (ANOVA) or the Kruskal-Wallis test, depending on the distribution characteristics of the variables. The Scheffe test was used for *post hoc* comparisons. For the comparison of two independent continuous variables the Student's t test for unpaired samples was used or the non-parametric Mann-Whitney test, depending on the distribution characteristics of the variables. The Chi-square test was employed to compare discrete variables.

To analyze the variables that showed the best links with the HOMA parameter (continuous variable), multivariate linear regression models were used, covariables being automatically selected by the (backward) conditional elimination process.

To establish whether there was an independent link between the HOMA parameter and study outcomes, multivariate Cox proportional hazard models were used and the relative risks and 95% confidence intervals were determined. The HOMA parameter was analyzed both as a continuous and a discrete entity (terciles).

The models were adjusted by introducing variables or risk factors with a potential influence on the final events which were the subject of the study (age, sex, comorbidity index, plasma albumin, C-reactive protein, residual renal function, proteinuria, etc.). The selection of the variables which best fitted the models was done automatically by the progressive conditional elimination process.

To confirm risk proportionality, in all the survival studies we examined the graphs which were obtained by correlating the logarithm (-survival rate logarithm) with the survival time logarithm, as well as the graphs correlating the partial residues of each covariable against survival time.

The percentage of missing data was below 1% for all the variables. The quantitative variables which were lost were made up by adding the arithmetic mean value for the rest of the present data.

The data for this study are presented as the mean plus standard deviation (± SD) or as the median and interquartile ranges or minimum-maximum value. A p value of $<.05$ was regarded as statistically significant. The SPSS software version 15.0 (SPSS, Chicago, USA) was used for the statistical analysis and graphs.

RESULTS

Clinical Characteristics Associated with Insulin Resistance

The average insulin and HOMA parameter values were: 17.31 ± 7.54 mU/ml and 4.28 ± 2.07 mU/ml x mmol/l respectively.

The clinical and biochemical characteristics of the patients grouped into terciles according to the distribution frequency of the HOMA parameter are shown in Table 1. Significant differences were not observed for age, sex, comorbidity index, percentage of patients with ischaemic cardiopathy and proteinuria. In patients in the upper tercile, glomerular filtration was significantly lower than in patients in the lower

Table 1. Clinical and biochemical characteristics of patients grouped into HOMA parameter terciles

	Lower Tercile	Middle Tercile	Upper Tercile
Age (years)	60 ± 19	66 ± 14	62 ± 15
Sex (M/F)	72/50	61/61	63/58
Comorbidity			
- Absent	74	61	74
- Mild-Moderate	37	52	40
- Severe	11	9	7
History of ischaemic cardiopathy (% of patients)	12	12	11
History of other vascular processes (% of patients)	18	17	15
Body mass index , kg/m^2	26.3 ± 4.7	28.1 ± 4.9[a]	30.2 ± 5.6[b]
SBP, mmHg	147 ± 25	153 ± 23	149 ± 25
DBP, mmHg	86 ± 13	85 ± 11	87 ± 13
Glomerular filtration (ml/min/1,73 m^2	15.58 ± 5.89	14,64 ± 4,71	13.12 ± 4.08[c]
Proteinuria (mg/24 h)	2,000 ± 2,458	1.819 ± 2.223	1,723 ± 1,732
Serum uric acid (mg/dl)	7.4 ± 1.9	7.7 ± 1.9	7.6 ± 2.3
Plasma albumin (g/dl)	3.84 ± 0.54	3.81 ± 0.50	3.98 ± 0.40e
Total plasma cholesterol (mg/dl)	193 ± 56	203 ± 45	194 ± 49
Plasma triglycerides (mg/dl)	115 ± 51	126 ± 61	171 ± 111[b]
Total serum calcium (mg/dl)	9.19 ± 0.81	9.25 ± 0.84	9.42 ± 0.90
Serum phosphate (mg/dl)	4.65 ± 0.98	4.62 ± 0.97	5.00 ± 1.12[d]
Serum bicarbonate (mmol/l)	21.2 ± 3.4	21.9 ± 4.1	20.6 ± 3.7[e]
Protein catabolic rate (g/kg/24 h)	1.03 ± 0.32	1.08 ± 0.28	1.07 ± 0.27
C-reactive protein (mg/l)	8.86 ± 13.99	9.58 ± 17.82	9.14 ± 14.54
PTH (pg/ml)	217 ± 185	244 ± 164	301 ± 274[c]
Ferritin (ng/ml)	216 ± 248	115 ± 129[a]	148 ± 175
HOMA (mU/ml x mmol/l)	2,26	3.92	6,67
(min.-max.)	(0.73-3.13)	(3.14-4.90)	(4.93-11.88)
ACEI/ARA (% patients)	66	69	67
Betablocker (% patients)	19	17	16
Diuretics (% patients)	48	57	52

[a] p <.05 middle tercile compared to lower tercile; [b] p <.0001 upper tercile compared to other terciles; [c] p <.01 upper tercile compared to lower tercile; [d] p <.05 upper tercile compared to other terciles; [e] p <.05 upper tercile compared to middle tercile.

tercile. Patients in the upper HOMA terciles had a higher body mass index than patients in the lower tercile. Although differences were not observed in total plasma cholesterol concentrations, upper HOMA tercile patients showed significantly higher triglyceride levels than those in the other terciles. Serum phosphate levels were also higher in upper tercile patients than in the remaining terciles.

Other significant differences between terciles were detected for plasma albumin, bicarbonate and PTH (table 1).

C-reactive protein levels were similar and there were no significant differences in the drugs prescribed in the three subgroups (table 1).

In the multiple linear regression models, the variables included in the best predictive equation for HOMA values were: body mass index, triglycerides, plasma albumin and serum phosphate levels (table 2).

Insulin Resistance and CKD Progression

During the follow-up period 234 patients (64%) met the criteria for CKD progression (6 patients doubled their initial serum creatinine levels and 228 started dialysis). Using Kaplan-Meier survival analysis (Figure 1), it was noted that only patients in the lower HOMA tercile showed more prolonged survival without meeting CKD progression criteria

Table 2. Variables associated with the HOMA parameter according to multiple linear regression models

Variable	B Coefficient	95% CI B Coefficient	Beta	p
Body mass index (kg/m²)	0.138	0.102 ; 0.174	0.357	<0.0001
Triglycerides (mg/dl)	0.005	0.003 ; 0.008	0.217	<0.0001
Albumin (g/dl)	0.807	0.414 ; 1.199	0.189	<0.0001
Serum phosphate (mg/dl)	0.311	0.130 ; 0.493	0.157	0.0001
Constant	–4.976	–7.133 ; –2.819		

R^2 = 0.233.

(lower tercile compared to the rest of the patients: log rank=4.19; p=.04).

In the Cox regression analysis, adjusted for variables which are potentially related to the progression of CKD (age, sex, body mass index, systolic and diastolic blood pressure, baseline glomerular filtration rate, proteinuria, haemoglobin, albumin, phosphate, bicarbonate, diabetes and anti-angiotensin treatment, calcium antagonists and diuretics), a HOMA value in the lower tercile continued to correlate significantly with a slower progression of CKD (table 3 and figure 2).

Insulin Resistance and the Development of New Cardiovascular Disease Episodes or Mortality

During the follow-up period 51 patients presented a new cardiovascular episode and 104 died as a result of any cause. Using Kaplan-Meier survival curves, we failed to detect a significant correlation between HOMA terciles and the development of new CV episodes (log rank=0.117; NS) or with all-cause mortality (log rank=2.64; p=0.267).

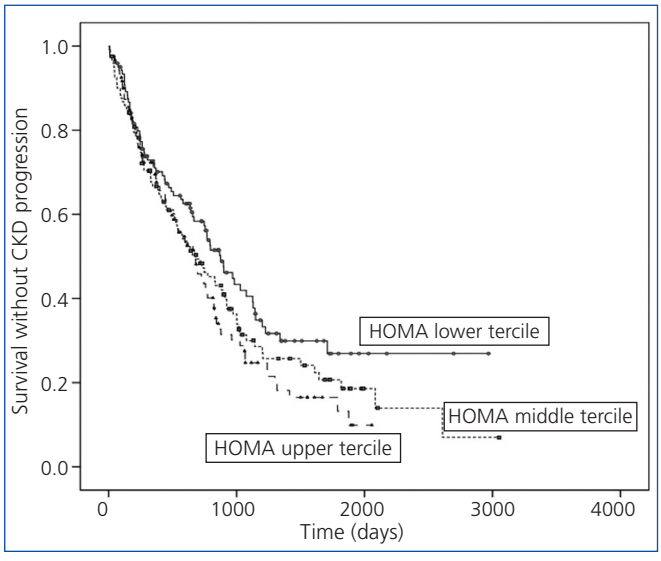

Figure 1. Kaplan-Meier survival curves without CKD progression criteria according to HOMA terciles

In Cox regression models adjusted for age, sex, body mass index, comorbidity index, plasma albumin, C-reactive protein, baseline glomerular filtration rate, proteinuria, serum phosphate and antihypertensive medication, HOMA measured both as a continuous entity and in terciles showed no link either with the development of new CV processes (hazard ratio for the continuous variable=1.106; 95% CI, 0.901–1.358; p=0.337) or with all-cause mortality (HR continuous variable=1.091; 95% CI, 0.991–1.200; p=.076).

The stratification of the models, based on a body mass index higher or lower than 30 kg/m², failed to substantially modify the results, although the correlation between HOMA and mortality occurred at the limit of statistical significance (HR HOMA terciles=1.28; p=.060).

DISCUSSION

The results of this study show that the degree of severity of insulin resistance in ACKD is linked to obesity and plasma triglyceride, albumin and phosphate levels. Other parameters which show univariate correlation with HOMA values include glomerular filtration rate, serum bicarbonate and PTH. However, neither blood pressure values nor C-reactive protein levels or proteinuria magnitude correlate significantly with HOMA values.

Although there are no standard values for normalized HOMA parameter measurement (in theory a young healthy subject should have a value equivalent to one[19]), the figures presented by the patients included in this study were very high (two thirds of the patients showed a value of >3), which confirms the high prevalence of this metabolic disorder in non-diabetic CKD.

Obesity is very prevalent in CKD.[21] IR and obesity-linked hyperinsulinaemia have been implicated in the development of kidney disease and accelerated atherosclerosis.[22,23] Obesity was very prevalent in the patients included in this study and was a significant factor in determining the degree of severity of IR, suggesting a pathogenic link in the development of

Table 3. Parameters included in the best predictive equation for CKD progression estimated by Cox regression models

Variable	Risk ratio[a]	95% CI Risk Ratio	p
Age (years)	0.98	0.97 ; 0.99	<0.0001
Sex (1 = male)	1.52	1.15 ; 2.00	<0.004
Body mass index (kg/m^2)	0.97	0.94 ; 0.99	0.023
Plasma albumin (g/dl)	0.57	0.42 ; 0.79	<0.0001
Proteinuria (g/24 h)	1.09	1.03 ; 1.15	0.005
Baseline glomerular filtration (ml/min/1.73 m^2)	0.87	0.84 ; 0.91	<0.0001
Serum phosphate (mg/dl)	1.32	1.14 ; 1.53	<0.0001
Lower Tercile HOMA (0.1)	0.72	0.54 ; 0.97	0.032

The following were not included in the best predictive equation: diabetes, systolic and diastolic blood pressure, haemoglobin, bicarbonate, triglycerides, anti-angiotensin drugs, calcium antagonists and diuretics.

[a] Hazard ratio.

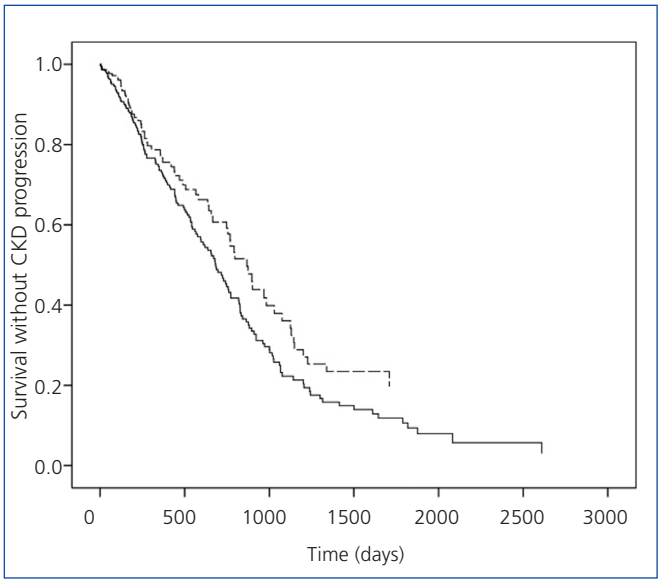

Figure 2. Survival curves in patients with HOMA in the lower tercile (discontinuous line) and the rest of study patients (continuous line). The model is estimation after adjustment for age, sex, body mass index, albumin, proteinuria and phosphate

this metabolic disorder, irrespective of any association which can be attributed to uraemia.

Hypertriglyceridaemia is pathogenically linked to IR.[3,4] This lipid metabolism disorder is also very common in CKD.[24] The results of this study show a significant link between HOMA values and plasma triglyceride levels, which suggests that IR has an important role in the development of this dislipidaemia in CKD.

The positive correlation between HOMA values and plasma albumin concentrations is a prominent finding in this study. Plasma albumin concentration reflects the presence and severity of different processes which have a negative impact on outcomes for CKD patients (e.g. poor nutrition, inflammation, hypervolaemia, etc.) and so this parameter is regarded as a "clinical index of disease",[25] determining mortality in most studies involving CKD patients.

In haemodialysis patients HOMA correlates positively with both the rate of synthesis and breakdown of muscle protein, although there is a tendency towards a negative correlation with net muscle protein balance.[26] While these findings suggest that IR has a negative effect on nutritional status, other studies in pre-dialysis CKD patients show that the amount of protein intake determines hyperinsulinaemia levels and sensitivity to insulin, IR improving in patients on low protein and phosphate diets.[27-29]

A possible explanation for the positive correlation between HOMA and plasma albumin might be differences in protein intake and nutritional status between patients. Although in this study patients in the lower HOMA tercile showed a lower protein catabolic rate (NPNA) than upper tercile patients, the differences were not significant and therefore this hypothesis cannot be accepted.

The plasma phosphate levels also show a positive correlation with HOMA values. In favour of the previous hypothesis, a diet which is inappropriate to the level of kidney failure might help to explain this finding. A reduction of phosphate in the diet has been shown to improve the degree of IR in CKD patients.[28] We should also point out the potential link between insulin and the excretion of phosphate in urine. Insulin has an anti-phosphaturic effect,[30,31] even antagonizing the phosphaturic action of PTH.[32] In the present study estimates

of phosphate were not made and, consequently, this hypothetical link between IR and phosphate cannot be confirmed.

Hyperinsulinaemia and IR predispose to the development or worsening of high blood pressure, and the development and progression of CKD, via mechanisms such as an increase in renal absorption of sodium, increased sympathetic activity, changes in endothelial and podocyte function, dislipidaemia, hyperglycaemia and increased renin-angiotensin activity.[33] In some studies a link has been observed between the HOMA parameter and the rate of CKD progression in patients with glomerulonephritis,[34] and between plasma insulin levels and the rate of progression of age-related renal deterioration.[35]

CKD progression, according to the criteria established in the present study, was slower in patients with a lower degree of IR (lower tercile). Although this finding is statistically significant, even after adjustment for other factors which determine the progression of CKD, and consistent with the potentially negative effects of hyperinsulinaemia, the clinical relevance of this finding does not appear to be very important, if we compare it with the effect of other factors (proteinuria, age, phosphate, etc.) on the progression of CKD.

Although IR is regarded as a cardiovascular and mortality risk factor in the general population,[1-4] the impact of this metabolic disorder in the CKD population is the subject of controversy.[7,14-16] In CKD the link between IR and mortality has only been observed in Japanese patients,[14,16] while in other ethnic groups it has not been possible to demonstrate this relationship.[7,15]

Neither do the results of this study support a link between the magnitude of the HOMA parameter and mortality or the development of new CV events in advanced CKD patients prior to dialysis, findings which once again differ from those observed in the general population.

This study has limitations. The measurement of IR severity is based on a single HOMA parameter sample. The transversal design of the study to identify the determinants of the HOMA parameter limits its ability to adequately explain correlations. The absence of a link between HOMA levels and the development of new CV processes does not rule out a potential connection between IR and the severity and extent of vascular atherosclerotic damage which can be measured by more specific and sensitive procedures. The CKD progression criteria used in this study are not as reliable as the measurement and estimation of changes in glomerular filtration rate during the follow-up period.

In conclusion, insulin resistance, estimated by the HOMA parameter, is prevalent in ACKD, although it does not seem to have a negative influence on the vital prognosis for these patients.

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