Advances in Medicine and Engineering Interdisciplinary Research, 2024, Volume 2, Issue 3
DOI: 10.32629/ameir.v2i3.2599
ISSN Online: 2972-3825
ISSN Print: 2972-3833

Chronic Kidney Disease and Cardiovascular Mortality - An Ignored Risk Factor

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Abstract: Objectives: The aim is to determine hidden chronic kidney disease (CKD) and its relationship with the appearance of cardiovascular events (CVD) and mortality. Furthermore, the aim is to identify cardiovascular risk factors (CVRF) and calculate the control degree of diabetes mellitus (DM) type 2 and dyslipidemia (DLP) prior to CVD. Material and methods: It consists of a retrospective cohort study carried out in the Basic Health Zones (BHZ) of San Agustín, (population of 33.321 users) which consists of the health centers San Agustín, Illes Columbretes, and the auxiliary clinics of Borriol and Raval; and on the other hand, the BHZ of Almassora (25.831 users), calculated in analysis between January 2015 and December 2018. The main variables were CKD, CVD, mortality and CVRFs. Results: The final sample consisted of 243 patients from two cohorts: 135 without CKD and 99 with CKD (including 36.4% of occult CKD cases). The hazard ratio (HR) of developing CVD was 4.28 and mortality was 12.3 in the group with CKD compared to the group without CKD. Regarding the relationship of CVRFs prior to the appearance of CVD, in the cohort with CKD, hypertension (HTN), DLP, and type 2 DM had significant results, compared to the cohort without CKD. Likewise, in the CKD cohort, the percentage of DLP control was less than 50.0%, and greater than 66.66% in type 2 DM. Conclusions: It is observed that a third of patients are not diagnosed with CKD, which has a high probability of developing CVD or death. Given the lack of diagnosis, interventions in the control of DLP and type 2 DM are lower.

Key words: chronic kidney disease (CKD); cardiovascular disease (CVD); mortality; primary health care; disease prevention

1. Introduction

Chronic kidney disease (CKD) is an important public health problem worldwide since different studies have shown that it can affect 10-20% of the adult population according to prevalence estimates made in different countries [1-8]. The presence of CKD is included as an independent risk factor and is a cause of cardiovascular disease morbidity or cardiovascular events and mortality, regardless of CKD stage [1, 6-17].

CKD is defined as the presence of proteinuria (currently the urine albumin-creatinine ratio or CAC is preferred) and/or reduced renal function (eGFR) below 60 ml/min·1.73m^2 maintained over a 3-month interval, which can be confirmed by renal biopsy with or without decreased eGFR or albuminuria [1-6, 11-18]. Based on the above definition, its lack of diagnosis is considered occult CKD.

The underlying pathological state is caused by a complex interaction of traditional (age, sex, diabetes mellitus or type 2 DM, hypertension) and non-traditional (volume overload, bone-mineral metabolism, uremic toxins, anemia, oxidative stress) risk factors. Likewise, as the population ages, the incidence and probability of presenting CKD increases [1, 2, 7, 9, 11, 12, 15-22]. Therefore, these would be individuals with a high or very high cardiovascular risk (CVR) who require blood pressure and lipid control adjusted to their CVR according to the SCORE tables or to their baseline comorbidities [1, 13, 23, 27].

Given the prevalence and the importance of the therapeutic and prognostic implications of detecting CKD at early stages, it is important to determine occult CKD. The earliest stages of CKD are often asymptomatic and are often detected during the evaluation of comorbid conditions that may be reversible. Most CKD progresses for decades and some patients do not progress for many years of follow-up [3, 10, 11, 13, 14, 18, 19, 22-27].

2. Objectives

Primary objective: to objectify occult CKD.

Secondary objectives: to determine the relationship between CKD and the appearance of CVD and mortality in stages G3 and G4 in our area of action, as well as to describe the cardiovascular risk factors (CVRF) and the degree of control of type 2 DM and dyslipidemia (DLP).

3. Material and Methods

Design and setting: Cohort study, i.e. a descriptive, observational, retrospective longitudinal study. The study was conducted on the population assigned to the Basic Health Zones (BHZ) of San Agustín (33.321 users), which consists of the health centers San Agustín, Illes Columbretes and the auxiliary clinics of Borriol and Raval; and on the other hand, the BHZ of Almassora (25.831 users), belonging to the General University Hospital of Castelló (HGUCS). The search for occult CKD was performed by observing the analytical tests performed in the reference laboratory of HGUCS in the period from January 2015 to December 2018.

Inclusion and exclusion criteria: Analyses performed from January 2015 to December 2018 (77.196) of patients over 18 years of age from the BHZ of the study, excluding those who presented end-stage renal disease (ESRD). This allowed us to follow 2 cohorts of 150 patients out of the 77.196 analyses of patients over 18 years of age, performed on patients from the study's BHZ, excluding those with end-stage renal disease (ESRD).

Patient Selection: Patients were assigned to two cohorts, each comprising 150 individuals. In the cohort without CKD, patients who had developed CKD at the time of the study were excluded. Similarly, in the cohort with CKD, those who had progressed to end-stage renal disease (ESRD) or had a prior history of cardiovascular disease (CVD) were discarded. Consequently, the final sample size was reduced to 135 patients in the cohort without CKD and 99 patients in the cohort with CKD (Figure 1).

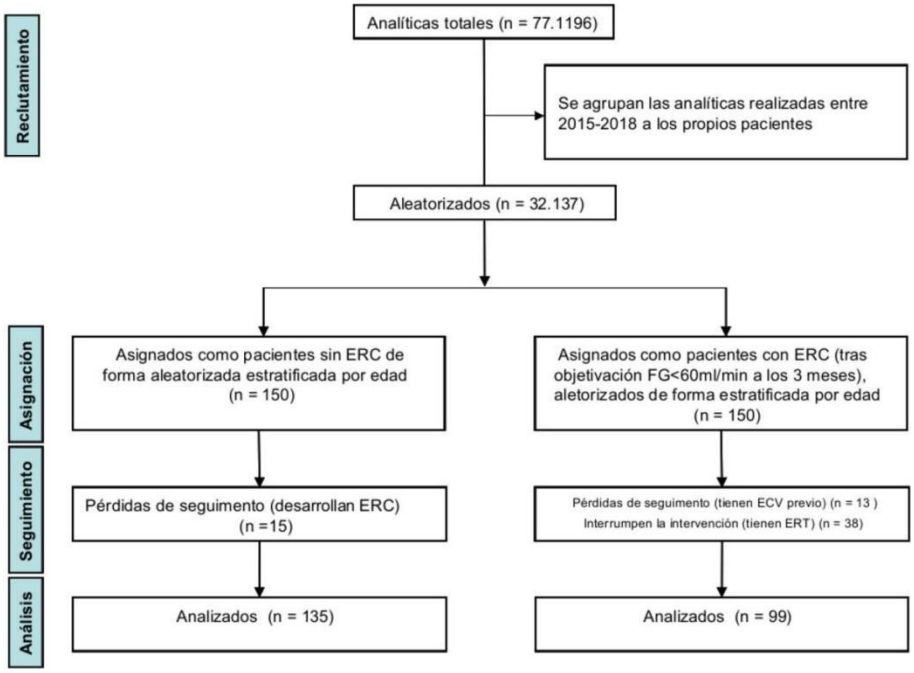

Figure 1. Flow chart of number of cases and their selection.

The patients were stratified according to both BHZ and age, yielding the following distribution: 80 patients from the BHZ of Almassora and 154 patients from the BHZ of San Agustín; furthermore, by age, there were 83 patients between 45 and 64 years, 72 patients between 65 and 79 years, and 79 patients aged 80 years and over.

Analysis strategy: Primary outcomes of interest included all-cause death and CVD until the end of 2019. Study variables were age, sex, excess weight (differentiating between overweight and obesity), alcohol consumption, tobacco use, diagnoses of HTN, LDL and LDL levels, type 2 DM and HbA1c levels, hyperuricemia or gout, CKD, eGFR, CAC, CVD, and type of CVD.

Subject data were pseudoanonymized for analysis. Primary outcomes of interest included death from any cause, cardiovascular events through December 31, 2019. A cardiovascular event was defined as coronary heart disease (CHD), cerebrovascular accident (CVA), or peripheral arterial disease (PAD) according to ICD-9 codes.

Data analysis: The hazard ratio (HR) was calculated with a 95% confidence interval (CI) and a p value < 0.05 to be considered a statistically significant result in the different analyses, for the study of the association between CVRF and CVD in patients with CKD. The analytical results and their periodicity of LDL and HbA1c were also assessed to determine control. In addition, subjects with CKD who presented CVD and/or death underwent a Kaplan-Meyer analysis, since the last determination of eGFR.

For the inclusion of variables related to traditional risk factors, the dates prior to the development of CVD were used, and in some cases laboratory results were reviewed to check whether there was a lack of diagnostic records. In addition, subjects with CKD who presented CVD and/or death from any cause underwent Kaplan-Meyer analysis, after calculating the time elapsed since the last eGFR determination until the occurrence of the event.

Ethical and legal aspects: All procedures were performed under the ethical standards of the Ethics Committee for Research Ethics with Medicines, CEIM 663 (HGUCS) of the department of Castelló, approved in December 2019, and under the Helsinki declaration of 1964 and its subsequent amendments or comparable ethical standards. All names and identifiers were removed before the data were analyzed, in accordance with the procedures approved by the data protection law.

4. Results

The mean age of the total number of members (n = 234) was 68.72 (z = ± 15.10), the majority of whom were female (65%). In addition, Table 1 shows the data relating to the cohort with CKD and the cohort without CKD. Occult CKD was found in 36.4% of patients.

Table 1. General description of the cohorts

Variable	Cohort with CKD	Cohort without CKD	Total	Losses[a]
Sample	99	135	234	-
Occult CKD, n (%)	36 (36.4)	-	-	-
Sex (female), n (%)	67 (67.7)	85 (63.0)	152 (65.0)	-
Average age	82.1 (z = ±10.2)	60.0 (z = ±11.8)	68.7 (z = ±15.1)	-
Age ≧ 65, n (%)	93 (94.0)	49 (36.3)	142 (60.7)	
CVD, n (%)	14 (14.1)	9 (6.7)	19 (8.1)	-
Mortality, n (%)	27 (26.7)	4 (3.0)	31 (13.2)	-
HTN, n (%)	83 (83.8)	57 (42.2)	140 (59.8)	-
DLP, n (%)	73 (73.7)	76 (56.3)	149 (63.7)	-
Type 2 DM, n (%)	31 (31.3)	30 (22.2)	61 (26.1)	-
Microalbuminuria or CAC, n (%)	17 (17.1)	5 (6.8)	22 (9.4)	212 (90.6)
Microalbuminuria or CAC in type 2 DM	11	2	13	48 (78.69%)
Hyperuricemia or gout, n (%)	58 (58.9)	21 (15.6)	79 (33.8)	155 (66.2)
Overweight, n (%)	29 (29.3)	29 (21.5)	58 (24.8)	59 (25.2)
Obesity, n (%)	28 (28.3)	30 (22.2)	58 (24.8)	59 (25.2)
Tobacco use (registry), n (%)	36 (36.4)	46 (34.1)	82 (35.0)	152 (65.0)
Active smoker, n (%)	-	20 (14.8)	20 (8.5)	-
Alcoholism (recorded), n (%)	17 (17.2)	18 (13.3)	35 (15.0)	199 (85.0)
Excess alcohol, n (%)	1 (1.0)	2 (1.5)	3 (0.3)	-

Note: CKD: chronic kidney disease, CVD: cardiovascular disease, DM: diabetes mellitus, HTN: hypertension, DLP: dyslipidemia, [a]: Lack of registration in computerized medical records.

The mean eGFR of the patients with CKD was 45.4 (z = ±11.2) and those with CVD was 46.0 (z = ±12.4), that is, a G3A classification. The CVD were a total of 19 cases: 10 CVA, 6 CAD and 3 PAD. The resulting HR between the cohort with CKD that developed CVD with respect to the cohort without CKD was 4.3. In the CKD cohort there were 14 cases of CVD: 6 G3A, 7 G3B and 1 G4. In addition, 4 cases were in the occult CKD group, 3 cases were G3A and 1 cases with G3B. The mean time to onset of CVD in the CKD cohort was 492.1 days (95% CI 305.4-678.8). In detail, the mean number of days in G3A was 587.2 (95% CI 208.3-966) and in G3B was 412.0 (95% CI 213.4-610.7). Looking at mortality, the mean time for patients with CKD was 697.6 days (95% CI 528.7-866.5).

Regarding mortality, the HR between the cohort with CKD and the cohort without CKD was 12.3. Among all 31 patients, 11 patients belonged to the occult CKD group.

Regarding the relationship between the CVRF evaluated and their influence on the development of CVD in the CKD cohort, it was observed that HTN, PLD and type 2 DM had a significant relationship (Table 2). However, the association of these CVRFs did not yield significant results.

Table 2. Comparison of cohorts and hazard ratio in the development of cardiovascular disease

Empty cell	Variable	CKD	No CKD	HTN	CI al 95%	p-value
Mortality	Number	27	4	12.3	4.1-36.5	< 0.05
CVD	Number	14	5	4.3	1.5-12.3	< 0.05
	Age ≥ 65a	13	3	2.5	0.7-9.3	0.3
	Gender (female)	9	1	13.0	1.6-105.7	< 0.05
	HTP[a]	12	4	4.5	1.4-14.5	< 0.05
	DLP[a]	10	2	7.5	1.6-34.9	< 0.05
	Type 2 DM[a]	6	1	8.6	1.0-73.0	< 0.05
	Hyperuricemia or gout[a]	7	3	3.3	0.8-13.2	0.1

Note: CKD: chronic kidney disease; CVD: cardiovascular disease; DM: diabetes mellitus; HTP: high blood pressure; DLP: dyslipidemia, CI: confidence interval, [a]: Considering diagnoses with dates prior to CVD.

In the case of female, the HR of presenting CVD was 13.0 (95% CI 1.6-105.7) with respect to male in the cohort with CKD. As for age, those aged 65 years or older had 17 cases of CVD, but the p value was not significant. An attempt was made to make an association with the RFs studied in relation to CKD and CVD, but given the scarce data, no significant results in favor of the occurrence of CVD were obtained. Finally, the percentage of control of DLP in all patients who developed CVD was 44.56% according to CVR, of which in the cohort with CKD the value was 29.76%. In the case of type 2 DM, the patients who did not develop CVD had a percentage of adequate control, according to their HbA1c targets of 83.43%, whereas in the cohort with CKD it was 66.66%.

5. Discussion

The conduct of this study reaffirms the notion that CKD poses a significant health problem for various reasons. Firstly, there is a notable underdiagnosis of the disease, with more than one-third of patients in this case going undetected. Secondly, CKD can lead to the development of CVD of any type (14.1%) or even death (26.7%), as evidenced by previous studies [4, 5, 12, 14, 16, 18, 20, 22].

It is important to emphasize that most CVD occurred in patients with high CVR, defined as patients with CKD with G3 [23]. The 11.3% incidence of CVD in the cohort with CKD at stage G3 is a result that has already been observed in other similar studies, although without differentiating between stages G3A and G3B [9, 25].

It is also observed that mortality is higher in G3 stages [9], whereas in other studies, it is more common in G4 [16]. The proportion of subjects who have suffered from CVD is considerable among those with CKD (almost 15%), including stages G3A and G3B, as well as exhibiting a high mortality rate (27%) even in early stages, not just in more advanced stages [12, 16, 18, 19, 20, 25].

Early prevention is possible, but it places greater demands on the objectives to be achieved in controlling CVRFs. When observing the data obtained, it becomes clear that the degree of control is not close to optimal levels, especially in the cohort with CKD at the DLP level (29.76%) [23, 24].

In the data analysis, being female and having CKD increases the risk of CVD [3], contrary to other studies where it is males who are at higher risk [7, 16].

5.1 Strengths and limitations

As a novelty, we started from the analyses performed to analyze whether those patients with altered eGFR were diagnosed or not (therefore, they were classified as having occult CKD, when the maintenance of CKD was observed over time) in the electronic medical record system for their inclusion in the study. In addition, GFR measurement was performed in the same laboratory in a standardized manner with the CKD-EPI formula.

There may be biases in the data analysis derived from the lack of records over a 3-year period, especially with HTN and DM, which can be the cause of both CKD and CVD. In addition, given that the percentage of female is higher, the sample could be biased and not be representative in real life in terms of the results obtained on sex; similarly, the mean age difference between the groups could also account for the higher mortality and CVD rates due to age, which is itself an aggravating factor for renal function.

6. Conclusion

The high prevalence of CKD, its underdiagnosis (approximately 33%) and its progressive and modifiable nature, makes it advisable to design a national program that, on the one hand, facilitates the detection of renal disease in itd very early stages, in order to avoid the development of associated cardiovascular complications, progression of renal disease, and inadequate prescription of drugs; and on the other hand, to allow referral to nephrology consultation at earlier stages that would prevent the patient from entering renal function replacement techniques or renal transplantation programs sufficiently early [9, 11, 18, 19].

With regard to CKD, the development of a renal health program is very important for several reasons: it is a frequent and very harmful disease. However, despite this, it is often unknown, progressive, and very costly to treat in advanced stages. Therefore, it should be diagnosed using two simple and inexpensive tests: renal function (or eGFR) and/or protein excretion analysis (even urine test strips are proposed) [10, 13, 14, 16, 18, 19, 21, 22].

In summary, it has been observed that the decrease in eGFR is an independent risk factor for CVD outcomes and all-cause mortality in the basic health areas of San Agustín, belonging to the HGUCS similar to the studies consulted, but it is noteworthy that most of them are related to incipient stages of CKD G3A and G3B.

Ethical Responsibilities

The work was carried out in accordance with the ethical standards for research and was assessed by the HGUCS CEIm (663). Informed consent was not required because exemption from the Declaration of Helsinki was obtained. Free access by the authors is authorized in case of acceptance.

Acknowledgments

In the year of the start of this work, all staff members of Castro UDMAFYC, especially Angel Mas, Oliver Fores, and Antonio Lorenzo Piquieres, were behavioral consultants at the studio; And colleagues from the Clinical Analysis Services department, Jose Antonio Ferrero Vega and Daniel Garcia Ferrer. We also specifically mentioned our guardian at the residence, hoping to promote research and MBE, as well as an interest in chronic disease care.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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