www.nefrologialatinoamericana.com
ISSN: 2444-9032

Nefrología Latinoamericana

Volume 21 • Number 1 • January-April 2024

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EDITORIAL

World Kidney Day 2024: promoting equitable access to health care and optimal medication

Día Mundial del Riñón 2024: promover un acceso equitativo a la atención en salud y a la medicación óptima

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The problem of chronic kidney disease

Chronic kidney disease (CKD) is a pandemic. With regional variations, it affects 1 in 10 adults (9.1% to 13.4%) worldwide (850 million people)[1], with an incremental prevalence when analyzed by decades. This is attributed to an increase in life expectancy and the rise of conditions that elevate the risk of CKD, mainly hypertension, diabetes, and obesity, among others[2]. Most patients will not need dialysis, partly because the development of CKD determines a higher likelihood of dying from cardiovascular disease (myocardial infarction, stroke, and peripheral vascular disease) than entering chronic dialysis[3]. This mortality imposed by CKD is globally recognized. Since 1990, it has been the leading cause of death from non-communicable diseases with the highest increase in incidence, ranking at the top of the table[4]. It also leads to high disability. In the estimation of disability-adjusted life years (DALYs), which represents the number of years lost due to ill health, disability, or premature death, for the Americas in 2019, CKD ranked among the top causes, with a DALY rate of 686.1/100 000 population, not including the burden of DALYs from cardiovascular disease attributable to CKD[1].

Chronic kidney disease affects vulnerable populations

Poverty is a recognized risk factor[5] in the development and progression of CKD, with a greater impact among the lower-income quintiles of the population. This situation is particularly significant in Latin America due to reduced access to health care and a higher prevalence of diseases that increase the risk of CKD, such as obesity and diabetes[6]. There is an association between the development of CKD and low birth weight, being small for gestational age, and premature birth[7]. These conditions result in fewer functional nephrons and lead to the future development of CKD[8], occurring more frequently in vulnerable populations[9]. The prevalence of pre-eclampsia and gestational diabetes is higher in lower socioeconomic strata[10] and is also associated with future CKD development, both in the mother and her child[11].

There are racial differences[12], with a higher prevalence of CKD in the Black and Hispanic populations[13], attributable to biological factors (genetic profiles more associated with CKD, more aggressive hypertension) and socioeconomic factors (these groups are more frequently found in the lowest income quintiles)[6]. Lower

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Date of reception: 01-12-2023
Date of acceptance: 26-01-2024
DOI: 10.24875/NEFRO.M24000034

Available online: 17-05-2024
Nefro Latinoam. 2024;21:1-4
www.nefrologialatinoamericana.com

educational attainment is another factor associated with CKD development and progression[13]. An extreme scenario is people experiencing homelessness; this group has a very high prevalence of CKD, with increasing figures worldwide[14]. An emerging problem is the link between CKD and exposure to environmental pollution[15], as well as occupational exposure to agrochemicals and adverse environments[16], which are more common in vulnerable populations. There is a bidirectional relationship between economic development and CKD. Low-income groups, with a higher prevalence, and a higher DALY rate[1], and this burden of disability limits the economic advancement of the patient and their household.

Chronic kidney disease is preventable

Prevention of CKD begins before birth, by ensuring maternal health before and during pregnancy, and continues by ensuring healthy growth in early childhood for children born with low birth weight or prematurely[17]. Healthy mothers start with healthy girls, with good nutrition in childhood and growing up in environments with adequate resources. These policies, promoted in the United Nations' Sustainable Development Goals, require health to be included in all development policies[18]. Preventive strategies should be integrated into a broad approach to preventing non-communicable diseases, where correcting lifestyle factors is the most important and effective thing, supported by regulations and legislation[19]. Some successful approaches include economic incentives to reduce the price of healthy foods, increased taxes on unhealthy products, regulation of food composition (salt, fats, and sugar), support for education and physical activity programs, provision of public recreational facilities, and campaigns to limit the advertising and sale of harmful products[20]. Other primary prevention strategies include controlling risk factors for CKD, such as hypertension, diabetes, and obesity[21,22]. In addition to minimizing "classic" risk factors, efforts should be made to mitigate "non-traditional" factors, such as acute kidney injury events (10-20% of hospitalized patients)[23], exposure to nephrotoxic agents (anti-inflammatories, antibiotics, and antacids), and use of contrast media in radiological studies[24]. Awareness and regulation of alternative drugs that can cause acute kidney injury and subsequently CKD should be emphasized[25]. The use of recreational drugs (cocaine, heroin, and methamphetamines) is associated with the development and progression of CKD and should be addressed[26]. Secondary prevention strategies should include early detection for timely intervention. Mass screening in the general population is not cost-effective[27], but screening in high-risk populations (those older than 65 years, with hypertension or diabetes, autoimmune or infectious diseases, and family history of CKD) is cost-effective[28,29]. International guidelines[30] recommend screening in high-risk populations. Once CKD is diagnosed, addressing its progression at the primary care level[31] and with multidisciplinary programs has proven beneficial[32,33].

Diagnosing chronic kidney disease is easy

A consultation with a primary care physician and basic laboratory tests (creatinine and urine examination) or imaging modalities (renal ultrasound) is usually sufficient to diagnose CKD. Adding this evaluation into high-risk populations has been shown to be effective in numerous reports[34].

A set of drugs has changed the natural course of chronic kidney disease

The introduction of drugs capable of slowing the progression of CKD, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor antagonists (ARBs), was followed by 20 years without therapeutic innovations. In the past 5 years, a group of drugs has changed the natural course of CKD and impacted the development of cardiovascular events in these patients[35]. Sodium-glucose cotransporter 2 (SGLT2) receptor inhibitors (gliflozins) attenuate the progression of CKD and the development of major cardiovascular events and also decrease the development of newly diagnosed diabetes in CKD patients[36]. Non-steroidal mineralocorticoid receptor antagonists (finerenone) reduce progression and death from cardiovascular events in patients with diabetic kidney disease[37]. Glucagon-like peptide-1 (GLP1) receptor antagonists (semaglutide) are effective in slowing the progression of CKD in both diabetic and non-diabetic patients[38], and they also maintain weight loss in obese patients[39], providing an additional strategy in controlling risk factors for developing CKD. The combined administration of these drugs (associated with ACEIs or ARBs) enhances the individual beneficial outcomes of each group[40].

Equitable access to health care and optimal drugs is a necessity

The World Kidney Day celebrated every second Thursday of March (https://www.worldkidneyday.org/2024-campaign/) aims to raise awareness of the CKD pandemic

by encouraging educational and outreach activities. It seeks to generate collective awareness by developing and enhancing health policies related to kidney care and global cardiovascular prevention. The emphasis of the international community for 2024 is on the need for equitable access to kidney care and drugs that have proven useful in changing the natural course of this pandemic.

Many countries in Latin America have all the tools available to make an early diagnosis of CKD, identify its causes, address progression factors, and, where necessary, offer a program for chronic dialysis and kidney transplantation. There are inconsistencies that, at the very least, need to be understood. A significant portion of health investment in kidney care is directed (with variations among countries) toward funding chronic dialysis and kidney transplantation. From the perspective that CKD is a preventable disease or one whose natural course can be changed, predominantly focusing resources on interventions in the most advanced stage of the disease (dialysis and kidney transplantation), benefiting a small number of patients, while necessary, is an inefficient policy if established in isolation. This investment for the management of advanced stages of CKD contrasts with minimal assistance (in terms of health policies and economic investment) in the initial stages, where there is an opportunity to make effective changes.

Access to drugs that change the natural course of the disease is highly unequal. New molecules that have proven capable of changing the progression of CKD and mortality from cardiovascular causes (with regional differences) are minimally covered by health-care systems. There is ample evidence that early interventions on CKD reduce overall health-care costs[41]. A recent study evaluated the economic benefit of introducing some of these drugs (SGLT2 receptor inhibitors) in Germany, Spain, and the United Kingdom, and concluded that their addition determines the efficiency of renal health spending linked to a decrease in cardiovascular events and progression of CKD requiring dialysis[42]. The lack of rational and efficient policies improve access to kidney care and drugs fuels the cycle of inequality. Vulnerable populations have a higher prevalence of CKD, less access to care, and a total lack of access to drugs. Only those who manage to reach it have coverage for dialysis and kidney transplantation procedures regarding kidney health.

It is necessary to raise awareness about CKD, its high frequency, and the impact of CKD on quality of life and mortality. An intelligent and efficient care system needs to be developed, considering especially the most vulnerable populations.

Funding

The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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ORIGINAL ARTICLE

Incidence, clinical presentation, and mortality of SARS-CoV-2 infection in patients on chronic dialysis during the first stage of the pandemic in Uruguay

Incidencia, presentación clínica y mortalidad de la infección por SARS-CoV-2 en pacientes en diálisis crónica durante la primera etapa de la pandemia en Uruguay

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Abstract

Objective: *In March 2020, a health emergency was declared due to COVID-19 in Uruguay. Patients undergoing chronic dialysis (CD) were particularly affected by the disease. The objective is to describe the incidence, clinical presentation, and mortality of patients in CD with COVID-19 at the beginning of the pandemic.* **Material and methods:** *All patients in CD in Uruguay were included in the period from 03-01-2020 to 03-31-2021. Clinical, analytical, and morbidity/mortality data were collected for those who had COVID-19 and compared with the general population for the same period.* **Results:** *232 patients in CD (97.8% hemodialysis) had COVID-19 (infection rate: 8045.58/100,000), doubling the infection rate of the general population (4653.51/100,000), with a similar profile of new cases in both groups. Most presented symptoms (73.7%), 36.6% requiring hospitalization (15.5% in critical care) and 10.3% requiring invasive ventilation. Mortality was 22.4%, significantly higher than the general population for all age groups. Patients in CD who died from COVID-19 were older (69.5 vs. 59.5 years) and had more cardiovascular morbidity (80.8 vs. 61.7%) than those who survived. Presence of cardiovascular disease (HR: 2.996; p = 0.082), need for hospitalization (HR: 2.563; p = 0.097), and requirement for invasive ventilation (HR: 2.149; p = 0.037) increased mortality.* **Conclusions:** *COVID-19 had a high infection rate, high morbidity, and high mortality in patients in CD in the early stage of the pandemic.*

Keywords: *Coronavirus disease 19. Chronic dialysis. Hemodialysis. Peritoneal dialysis.*

Resumen

Objetivo: *En marzo de 2020 se declaró emergencia sanitaria por COVID-19 en Uruguay. Los pacientes bajo diálisis crónica (DC) fueron un grupo particularmente afectado por la enfermedad. El objetivo es describir la incidencia, presentación clínica y mortalidad de pacientes en DC con COVID-19 al inicio de la pandemia.* **Material y métodos:** *Se incluyeron todos los pacientes en DC en Uruguay en el periodo del 1-03-2020 al 31-03-2021. Se recolectaron datos clínicos, analíticos y de morbimortalidad de quienes tuvieron COVID-19 y se compararon con la población general para el mismo periodo.* **Resultados:** *232 pacientes en DC (97.8% hemodiálisis) tuvieron COVID-19 (tasa de infección: 8045.58/100.000), doblando la tasa*

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Date of reception: 17-01-2024
Date of acceptance: 10-03-2024
DOI: 10.24875/NEFRO.M24000036

Disponible en internet: 17-05-2024
Nefro Latinoam. 2024;21:5-12
www.nefrologialatinoamericana.com

de infección de la población general (4653.51/100.000), con perfil de nuevos casos similar en ambos grupos. La mayoría presentaron síntomas (73.7%), requiriendo internación el 36.6% (el 15.5% en cuidados críticos) y ventilación invasiva el 10.3%. La mortalidad fue del 22.4%, significativamente mayor que la población general para todos los grupos de edad. Los pacientes en DC que murieron por COVID-19, tenían mayor edad (69.5 vs. 59.5 años) y más morbilidad cardiovascular (80.8 vs. 61.7%) que quienes sobrevivieron. Incrementaron la mortalidad la presencia de enfermedad cardiovascular (HR: 2.996; p = 0.082), necesidad de internación (HR: 2.563; p = 0.097) y requerimiento de ventilación invasiva (HR: 2.149; p = 0.037). **Conclusiones:** *COVID-19 tuvo alta tasa de infección, elevada morbilidad y alta mortalidad en pacientes en DC en la primera etapa de la pandemia.*

Palabras clave: *COVID-19. Diálisis crónica. Hemodiálisis. Diálisis peritoneal.*

Introduction

On March 11, 2020, the World Health Organization declared the coronavirus disease 19 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 21 (SARS-CoV-2),[1] and 2 days later, the health emergency was declared in Uruguay after the first four cases of COVID-19 were confirmed[2]. Based on the temporal dynamics in the number of cases, different "waves" of the disease were defined, considering in Uruguay a first wave starting from December 06, 2020, a second wave starting from March 17, 2021, and a third wave starting from June 26, 2021; a fourth wave did not occur, as in other countries in the region[3]. As of December 31, 2021, and having already surpassed the third wave of the disease, Uruguay had registered 413,404 confirmed cases, with an incidence of 11,901 cases/100,000 inhabitants, and 6170 deaths due to COVID-19[3]. During this period, multiple measures were established to mitigate the spread of the disease and its complications: public health interventions (national testing policy, information campaigns, mandatory use of face masks, closure of schools and workplaces, restriction of internal movement, and international travel), social support (support programs for isolation, access to protective devices, food security support programs), and economic support, among others[4].

Patients undergoing chronic dialysis treatment were a particularly affected group by the disease, with an increased risk of acquiring it, developing severe complications, and dying from COVID-19[5]. Most of the analyzed cohorts showed an increase in mortality among those receiving chronic dialysis, 4 times higher than the general population[6,7]. In Uruguay, a series of interventions were established to minimize contagion, provide early diagnosis, and optimize isolation in hemodialysis units[8]. These measures were complemented by prioritizing the vaccination of this at-risk group when vaccines became available[9].

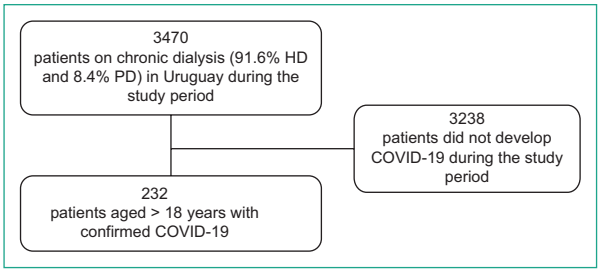

Figure 1. Study population. PD: peritoneal dialysis; HD: hemodialysis.

The aim of this study is to describe the incidence of COVID-19, its clinical presentation, and mortality in all patients undergoing chronic dialysis treatment in Uruguay during the first stage of the COVID-19 pandemic and before vaccination.

Materials and methods

This was an observational and multicenter study, including all patients aged ≥ 18 years on chronic dialysis (hemodialysis and peritoneal dialysis) in Uruguay from March 01, 2020, to March 31, 2021. A total of 3470 patients (3180 [91.6%] hemodialysis and 290 [8.4%] peritoneal dialysis) received chronic dialysis during that period, with a prevalent population as of December 31, 2020, of 2896 patients[10].

An electronic form was developed requesting epidemiological, clinical, and disease progression data from patients who had COVID-19 identified in secretions obtained by nasopharyngeal swab through polymerase chain reaction testing (Fig. 1). This form was sent to the 38 chronic hemodialysis centers and the 7 peritoneal dialysis centers operating throughout the territory. All centers completed the form sent. Data on the general population for the same period, regarding total COVID-19 cases, the epidemiological profile of the infected, hospitalization, and death, were obtained by consulting the Ministry of Public Health.

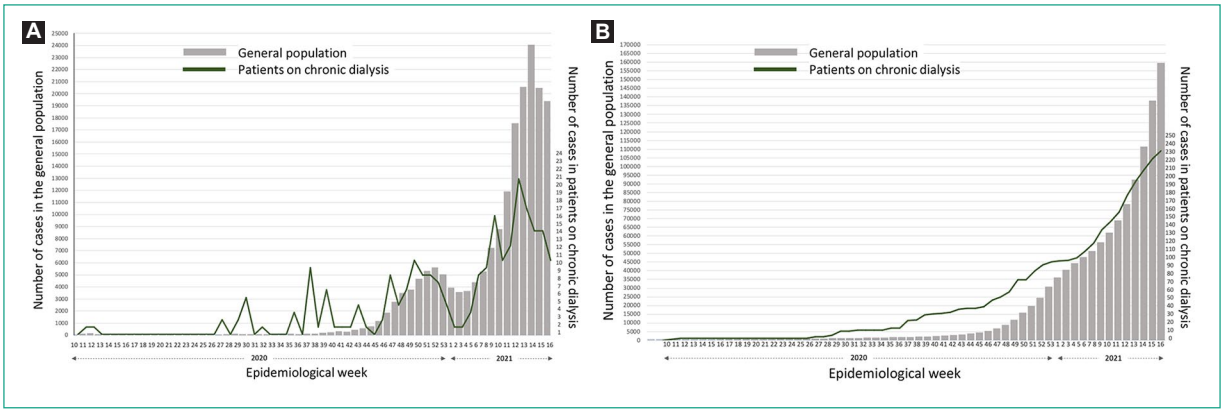

Figure 2. Number of new. **A:** and cumulative. **B:** confirmed coronavirus disease 19 cases in the general population (columns, left axis) and in chronic dialysis patients (line, right axis) for each epidemiological week during the study period.

For the analysis, the Statistical Package for the Social Sciences statistical package was used. Results were expressed as mean and standard deviation for parametric variables and as median (25^{th} percentile-75^{th} percentile) for non-parametric variables. For the analysis of continuous variables, the Student's t-test (parametric variables) and the Mann–Whitney U test (non-parametric variables) were used. Multivariate analysis was performed using Cox multivariate regression with a calculation of the hazard ratio (HR) and 95% confidence interval (CI). To analyze the weight on mortality of different variables, age, sex, presence of cardiovascular disease, diabetes mellitus, or immunosuppressive treatment, and the need for admission to the intensive care unit or invasive ventilation were considered. A statistically significant difference was considered at a value of $p < 0.05$. For the calculation of the infection rate, the number of infected individuals divided by the total exposed population was considered. For the infection rate of the general population, the estimated population as of December 2020 was used, and for the calculation of the infection rate of dialysis patients, the population undergoing dialysis in December 2020 was used. To estimate the mortality rate, the number of deaths divided by the exposed population was considered. The case fatality rate was calculated considering the number of deaths from COVID-19 divided by the number of COVID-19 patients.

Patients signed, at the time of admission to chronic dialysis, an informed consent format agreeing to the use of anonymous data for research purposes. The study was approved by the Hospital de Clínicas Research Ethics Committee.

Results

During the study period, 232 patients had confirmed COVID-19. The population characteristics are shown in Table 1. Patients with COVID-19 had a high morbidity rate due to cardiovascular disease (65.9%) and diabetes mellitus (43%). Almost all infected individuals (97.8%) received hemodialysis as a renal replacement technique, with minimal cases of infection among the peritoneal dialysis population. Of the total infected, only 30% were currently employed, and half (47.3%) had some functional limitation.

The infection rate for SARS-CoV-2 in the general population was 4653.51 for every 100,000 inhabitants, while the infection rate for dialysis patients during the same period was 8045.58 for every 100 000 inhabitants. Fig. 2 depicts the number of new and cumulative COVID-19 cases in the general population and in the hemodialysis patient group by epidemiological week. The number of new cases in chronic dialysis patients describes the same epidemiological profile as in the general population. Regarding the source of infection, among those who could clearly identify it, 35.8% occurred intrafamilial/at home, and 21.5% were infected during transportation to the hemodialysis center, at the center itself, or in a hospital due to reasons other than COVID-19.

Most patients (73.7%) experienced COVID-19 with symptoms, with the most frequent being cough and expectoration (39.6%), fever (27.6%), and dyspnea (25.9%). One-third of patients (36.6%) required hospitalization related to COVID-19, and in 15.5% of total cases, hospitalization occurred in a critical care area. Invasive ventilation was required by 10.3% of those affected.

Table 1. Clinical characteristics of the population

Feature	Total (n = 232)	Died from COVID-19 (n = 52)	Survived (n = 180)	p-value
Sex: female/male, n (%)	82 (35.3)/150 (64.7)	15 (28.8)/37 (71.2)	67 (37.2)/113 (62.8)	0.195
Age, mean ± s	61.76 ± 16.26	69.52 ± 16.92	59.51 ± 16.92	0.004
Hemodialysis/peritoneal dialysis (n, %)	227 (97.8)/5 (2.2)	52 (100)/0	175 (97.2)/5 (2.8)	0.284
Time on RRT (years)	5.01 ± 3.82	4.28 ± 3.70	5.34 ± 3.73	0.109
Kt/V*	1.53 ± 0.41	1.41 ± 0.28	1.55 ± 0.42	0.302
Comorbidity				
Cardiovascular disease†, n (%)	153 (65.9)	42 (80.8)	111 (61.7)	0.002
Diabetes mellitus, n (%)	100 (43.1)	27 (51.9)	73 (40.5)	0.075
Obesity‡, n (%)	51 (21.9)	15 (28.8)	36 (20)	0.115
Active smoking§, n (%)	32 (13.8)	6 (11.5)	26 (14.4)	0.705
Immunosuppressive treatment, n (%)	14 (6.0)	2 (3.8)	12 (6.6)	0.352
Charlson comorbidity index, mean ± SD	5.37 ± 2.70	6.78 ± 2.3	5.01 ± 2.68	0.021
Functional status				
Employed, n (%)	30 (12.9)	3 (5.8)	27 (15)	0.056
Without functional limitations, n (%)	108 (46.5)	14 (26.9)	94 (52.2)	0.003
With functional limitations, n (%)	63 (27.1)	17 (32.6)	46 (25.2)	
Very limited functionally, n (%)	31 (13.3)	8 (15.3)	23 (12.7)	
Unable to take care, n (%)	16 (6.9)	8 (15.3)	8 (4.4)	
Lab test results				
Albumin (g/dL), mean ± SD	3.79 ± 0.51	3.77 ± 0.48	3.80 ± 0.51	0.403
Hemoglobin (g/L), mean ± SD	11.63 ± 9.11	12.88 ± 8.63	11.27 ± 7.35	0.316
Place of COVID-19 contagion				
Unknown, n (%)	75 (32.3)	18 (34.6)	57 (31.6)	0.253
Intra-domiciliary/familial, n (%)	83 (35.8)	18 (34.7)	65 (36.1)	
During transport to HD Center, n (%)	20 (8.6)	2 (3.8)	18 (10)	
At the HD Center, n (%)	14 (6.0)	2 (3.8)	12 (6.6)	
Initial clinical signs of COVID-19				
Asymptomatic, n (%)	61 (26.3)	3 (5.8)	58 (32.2)	0.000
Fever, n (%)	64 (27.6)	23 (44.2)	41 (22.8)	0.004
Dysgeusia or anosmia, n (%)	45 (19.4)	8 (15.3)	37 (20.5)	0.232
Cough or expectoration, n (%)	92 (39.6)	35 (67.3)	57 (31.6)	0.000
Dyspnea, n (%)	60 (25.9)	33 (63.5)	27 (15)	0.000
Digestive symptoms, n (%)	41 (17.7)	9 (17.3)	32 (17.8)	0.518
COVID-19 treatment				
Hospitalization, n (%)	85 (36.6)	43 (82.7)	42 (23.3)	0.000
Length of hospital stay (days), mean ± SD	4.49 ± 3.58	8.35 ± 6.52	3.4 ± 2.92	0.000
Critical care hospitalization, n (%)	36 (15.5)	24 (46.1)	12 (6.6)	0.000
Non-invasive ventilation, n (%)	24 (10.3)	15 (28.8)	9 (5.0)	0.000
Invasive ventilation, n (%)	21 (9.0)	19 (36.5)	2 (1.1)	0.000

HD: hemodialysis; RRT: renal replacement therapy; SD: standard deviation.
*Kt/V, dialysis dose.
†Acute myocardial infarction, stroke, lower limb arteriopathy, heart failure.
‡Body mass index ≥ 30 kg/m^2.
§Persistence of smoking habit in the last 6 months.

During the study period, 52 patients died from COVID-19, resulting in an overall case fatality rate of 22.4% and a mortality rate of 149.85/10 000 patients. Table 2 and Fig. 3 show the COVID-19 case fatality rates in the general population and in chronic dialysis patients, stratified by age groups. The case fatality rate was significantly higher in chronic dialysis patients than in the general population, with significantly higher rates in older patient groups.

When comparing patients who died from COVID-19 with those who survived the disease, the former were older (69.5 vs. 59.5 years; p = 0.004), had a higher Charlson score reflecting increased comorbidity (6.78 vs. 5.01; p = 0.021), higher cardiovascular morbidity (80.8 vs. 61.7%; p = 0.002), and significantly worse pre-disease functional status. For the clinical signs of the disease, those who died from COVID-19 generally presented with more symptoms (94.2 vs. 67.8% symptomatic; p = 0.000),

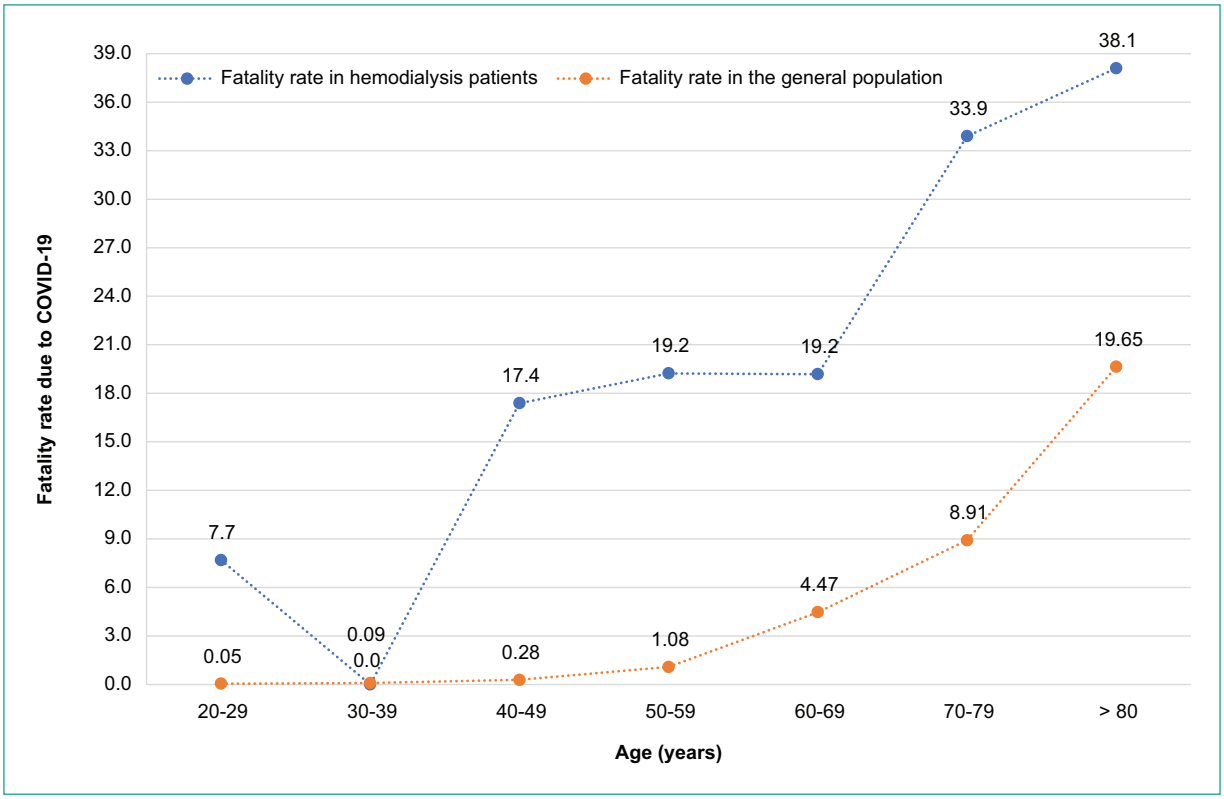

Figure 3. Coronavirus disease 19 case fatality rate in the general population and in chronic dialysis patients, stratified by age groups.

Table 2. Fatality rate of COVID-19 in the general population and chronic dialysis patients, stratified by age groups

Age (years)	Fatality rate*	
	General population	Chronic dialysis
20-29	0.05	7.7
30-39	0.09	0.0
40-49	0.28	17.4
50-59	1.08	19.2
60-69	4.47	19.2
70-79	8.91	33.9
> 80	19.65	38.1

*Fatality rate, deaths from COVID-19 divided by COVID-19 infected × 100.

with a higher prevalence of fever (44.2 vs. 22.8%; p = 0.000), cough with expectoration (67.3 vs. 31.6%; p = 0.000), and dyspnea (63.5 vs. 15%; p = 0.000). Patients who died from COVID-19 more frequently required hospitalization (82.7 vs. 23.3%; p = 0.000) had longer hospital stays (8.35 vs. 4.49 days; p = 0.000), a higher need for admission to the intensive care unit (46.1 vs. 6.6%; p = 0.000), and a higher need for invasive ventilation (36.5 vs. 1.1%; p = 0.000). In multivariate analysis, the presence of cardiovascular disease (HR, 2.996; 95% CI: 0.871-10.309; p = 0.082), need for hospitalization (HR, 2.563; 95% CI: 0.843-7.797; p = 0.097), and need for invasive ventilation (HR, 2.149; 95% CI: 1.046-4.415; p = 0.037) increased the risk of death.

Discussion

We present the clinical and evolutionary characteristics of patients on chronic dialysis who had COVID-19 at the beginning of the epidemic and before vaccination. Table 3 shows the results of similar cohorts for the same period.

The infection rate of dialysis patients was twice that estimated for the general population (8045.58 vs. 4653.51 for every 100, 000 inhabitants). This finding is consistent with other reports[11,12] and can be explained by the difficulty this population had in achieving mobility restrictions. Most infected individuals were part of the

Table 3. Summary of studies on COVID-19 in dialysis patients at the beginning of the pandemic

Author	Country, Region	Study period	Patients RRT (n)	Patients COVID-19 (n)	COVID-19 prevalence (%)	Hospitalization (%)	Invasive ventilation (%)	Mortality (%)	Variables associated with mortality
Torres-Díaz et al.[11]	Chile, Latin America	03-2020 to 12-2020	26 824	HD: 21,021 PD: 1498 KT: 4305	3029	11.29	HD: 12.8 PD: 7 KT: 5.2	HD: 49.8 PD: 50 KT: 50	14.9
Vallejos et al.[12]	Argentina, Latin America	03-2020 to 02-2021	30 300	2496	8.23	NA	NA	24	NA
Bisigniano et al.[14]	Argentina, Latin America	04-2020 to 04-2021	36 918	3709	10	HD: 95.4 PD: 3.6	45.2	ICU: 33	9.13
Quiroga et al.[15]	Spain, Europe	03-2020 to 12-2021	NA	6080	HD: 50% PD: 3% KT: 46% HD domiciliary: 1%	NA	64	ICU: 15	19
Sánchez-Álvarez et al.[13]	Spain, Europe	03-2020 to 04-2020	NA	868	HD: 63% PD: 4% KT: 33%	NA	85	ICU: 8	ICU: 75
Lano et al.[16]	France, Europe	03-2020 to 05-2020	2336	129	HD: 97.5% PD: 2.5%	5.5	81	ICU: 16	NA
Seidel et al.[17]	Germany, Europe	02-2020 to 04-2020	755	56	HD: 100%	7.4	76.8	ICU: 28.6	NA
Jager et al.[18]	Netherlands, Europe	02-2020 to 04-2020	113 594	4298	HD: 96.2% PD: 8.8%	3.8	NA	NA	

HD: hemodialysis; ICU: intensive care unit; KT: kidney transplant; NA: not available; OR: odds ratio; PD: peritoneal dialysis; RRT: renal replacement therapy.

hemodialysis patient group, with significantly lower infection rates among those receiving peritoneal dialysis and home hemodialysis (Table 3). New infection cases in our population followed the epidemiological profile of the general population (Fig. 2), a pattern also observed in another report from the region[12]. Those who contracted the disease were older, had more concomitant diseases, and had diminished functionality, which may partly be explained by the potential impact of these factors on the immunity of an already fragile population. Patients with the disease were more symptomatic, with respiratory symptoms pre-dominating, as in other cohorts[13], and had a higher prevalence of digestive symptoms vs. the general population, as highlighted by other authors[13]. Requirements for hospitalization, admission to the intensive care unit, and the need for mechanical ventilation were clearly higher in the group with more severe disease, a consistent finding in all reported series (Table 3). The mortality rate of our cohort was 22.4%, significantly higher than that of the general population, a condition that persists regardless of age group (Fig. 3). However, it is more prominent among the elderly. When compared with other cohorts, both from the region and other continents, the high mortality rate in the dialysis population is similar. Deceased individuals in our cohort were older, had higher comorbidity burdens, and had lower functional performance (Table 1), suggesting that within the chronic dialysis population, there was a group with greater frailty. Regarding the weight of different factors on mortality, in our group, the presence of cardiovascular disease and the need for hospitalization and invasive ventilation increased the risk of death. Although some of these variables did not reach statistical significance, this may be due to the number of participants in the study. These same variables, along with age, diabetes, and pneumonia, showed increased mortality in other analyzed cohorts (Table 3)[11-18].

One strength of this study is the inclusion of the entire dialysis population of the country. It is a retrospective study, which may result in some data on the course of the disease and its progression being lost, constituting a weakness. The implementation of sanitary measures, both in dialysis units[8] and nationwide[4], may have influenced preventing more unfavorable outcomes.

Conclusion

The SARS-CoV-2 infection was more prevalent in chronic dialysis patients than in the general population, especially among those receiving hemodialysis. COVID-19 in this population was more symptomatic, had a more severe clinical presentation, and resulted in significantly higher mortality than in the general population, across all age groups, but especially in the elderly.

Funding

The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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PERMANYER

ORIGINAL ARTICLE

Acute kidney injury in patients with severe COVID-19: clinical course, risk factors, and outcomes in a referral center in Mexico City

Lesión renal aguda en pacientes con COVID-19 severo: curso clínico, factores de riesgo y desenlaces en un centro de referencia de la Ciudad de México

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Abstract

Objective: *Acute kidney injury (AKI) has been associated with adverse outcomes in patients with COVID-19. However, due to resource limitations across various centers, particularly in Latin America, the clinical course of AKI varies widely. Few data have analyzed modifiable risk factors that can reduce in-hospital stay and mortality. Thus, we aimed to determine the factors associated with extended in-hospital stay and mortality.* **Materials and methods:** *This is a retrospective cohort study that included clinical/biochemical data of 413 patients with COVID-19 and AKI. Multiple linear regression was used to determine which factors were associated with prolonged in-hospital stay and Cox regression was used to evaluate independent factors for mortality.* **Results:** *The mean age of the subjects was 55 ± 15 years, 63.9% were men, 69.7% developed AKI, and mortality was reported by 23.7%. Multiple linear regression showed that older age (β = 0.148, p = 0.002), ferritin (β = 0.13, p = 0.012), and hemoglobin (β = –0.146, p = 0.006) were independently associated with prolonged length of stay. After Cox regression, positive fluid balance (1.029 [1.004-1.054]), mechanical ventilation (5.658 [2.253-5.540]), and dialysis (2.452 [1.436-4.185]) were associated with increased risk for mortality.* **Conclusions:** *Age, hemoglobin, and ferritin were associated with prolonged length of stay, but mechanical ventilation, dialysis, and a fluid balance were associated with mortality in AKI and COVID-19.*

Keywords: *Acute kidney injury. COVID-19. Positive fluid balance. In-hospital stay. Mortality. Renal replacement therapy.*

Resumen

Objetivo: *La lesión renal aguda (LRA) se ha asociado con peores deselances en pacientes con Covid-19. Sin embargo, debido a limitaciones de recursos en diversos centros, especialmente en América Latina, el curso clínico de AKI varía ampliamente. Pocos datos han analizado los factores de riesgo modificables que pueden reducir la estancia hospitalaria y la mortalidad. Por lo tanto, nuestro objetivo fue determinar los factores asociados con una estancia hospitalaria prolongada y la mortalidad.* **Material y métodos:** *Estudio de cohorte retrospectivo que incluyó datos clínico/bioquímicos de 413 pacientes con Covid-19 y LRA. Se utilizó regresión lineal múltiple para determinar qué factores se asociaron con una estancia hospitalaria prolongada y regresión de Cox para evaluar los factores asociados con mortalidad.*

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Date of reception: 26-02-2023
Date of acceptance: 26-09-2023
DOI: 10.24875/NEFRO.23000006

Available online: 16-02-2024
Nefro Latinoam. 2024;21:13-21
www.nefrologialatinoamericana.com

Resultados: *Los pacientes tenían 55 ± 15 años, 63.9% eran hombres, 69.7% tuvieron LRA y la mortalidad fue del 23.7%. La regresión lineal múltiple mostró que la edad (β = 0.148, p = 0.002), la ferritina (β = 0.13, p = 0.012) y la hemoglobina (β = –0.146, p = 0.006) se asoció con una estancia hospitalaria prolongada. Usando la regresión de Cox, el balance de líquidos positivo (1.029 [1.004-1.054]), la ventilación mecánica (5.658 [2.253-5.540]) y la diálisis (2.452 [1.436-4.185]) se asociaron con mayor mortalidad.* **Conclusiones:** *La edad, la hemoglobina y la ferritina se asociaron con mayor estancia hospitalaria, pero la ventilación mecánica, la diálisis y el balance de líquidos se asociaron con mortalidad en LRA y Covid-19.*

***Palabras clave*:** *Lesión renal aguda. Covid-19. Balances hídricos. Estancia intrahospitalaria. Mortalidad. Terapia de reemplazo renal.*

Introduction

Since the beginning of the pandemic, COVID-19 has represented the leading cause of morbimortality around the world[1]. Likewise, acute kidney injury (AKI) as one of the main complications of COVID-19 has been associated with increased mortality and worse outcomes among those with the severe presentation of the infection[1-3]. Some of the factors associated with worse prognosis were older age, unknown diabetes, obesity, and mechanical ventilation, among others[1,3]. However, most of these factors remain non-modifiable during hospitalization, presenting a challenge for health-care professionals across Latin America who have had limited tools at their disposal to manage these patients during the pandemic[4,5].

The mechanism underlying the pathophysiology of COVID-19-induced AKI is complex and heterogenous[6,7]. In fact, COVID-19 can induce acute tubular necrosis, collapsing glomerulopathy, and mitochondrial impairment driven by direct viral damage[7]. Therefore, it is highly possible that patients who had COVID-19-induced AKI and survived may live with reduced renal function and could be at a high risk for requiring dialysis at a younger age after hospital discharge[8,9].

Outside the pandemic context, AKI has been shown to prolong in-hospital stay among both non-critical and critically ill patients. Of note, most hospitalized patients who develop AKI are treated with fluid therapy for intravenous drug infusion or fluid resuscitation before determining the pre-renal or intrinsic cause of AKI[10,11]. Nevertheless, positive fluid balances could prolong hospital length of stay by causing clinical overload, edema, respiratory failure, sepsis, and many other in-hospital complications[10-13]. Although some authors have reported the clinical course and outcomes of AKI and severe COVID-19 infection in Mexico[5], none of them have analyzed the positive fluid balance as a modifiable factor that could reduce in-hospital stay nor complications in these patients. Thus, the aim of the present work was to, first, report the clinical course of AKI and severe COVID-19 infection in patients hospitalized in a single referral center in Mexico City; second, to determine the risk factors associated with longer in-hospital stay and increased mortality, and final, to whether fluid balances during hospitalization could or could not be associated with prolonged hospital length of stay in Mexican patients with severe COVID-19 and AKI.

Material and methods

Subjects

This was a retrospective longitudinal observational study that selected patients from the records of the Internal Medicine Department of the Hospital General Dr. Manuel Gea Gonzalez (HGDMGG) that received attention from April 2020 to December 2021. Patients aged > 18 years old with confirmed COVID-19 infection by positive polymerase chain reaction testing of a nasopharyngeal sample for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) who were admitted were eligible for the study. Severe COVID-19 infection was defined as clinical signs of dyspnea, respiratory frequency over 30/min, oxygen saturation < 93%, arterial oxygen partial pressure/fractional inspired oxygen (PaO_2/FiO_2) ratio < 300, and/or lung infiltrates more than 50% of the lung field within 24-48 h[14]. Likewise, AKI was defined according to kidney disease: improving global outcomes (KDIGO) criteria as follows: Stage 1, as an increase in serum creatinine level by 0.3 mg/dL within 48 h or 1.5-1.9 times increase in serum creatinine level from baseline within 7 days; stage 2, as 2-2.9 times increase in serum creatinine level within 7 days; and stage 3, as 3 or more times increase in serum creatinine level within 7 days or initiation of dialysis[1]. Likewise, community-acquired AKI was defined when patients presented at the emergency department with increased serum creatinine and did not have a history of chronic kidney disease (CKD). Overall, records from 1,058 hospitalized patients were analyzed. Of them, 586 patients were excluded due to

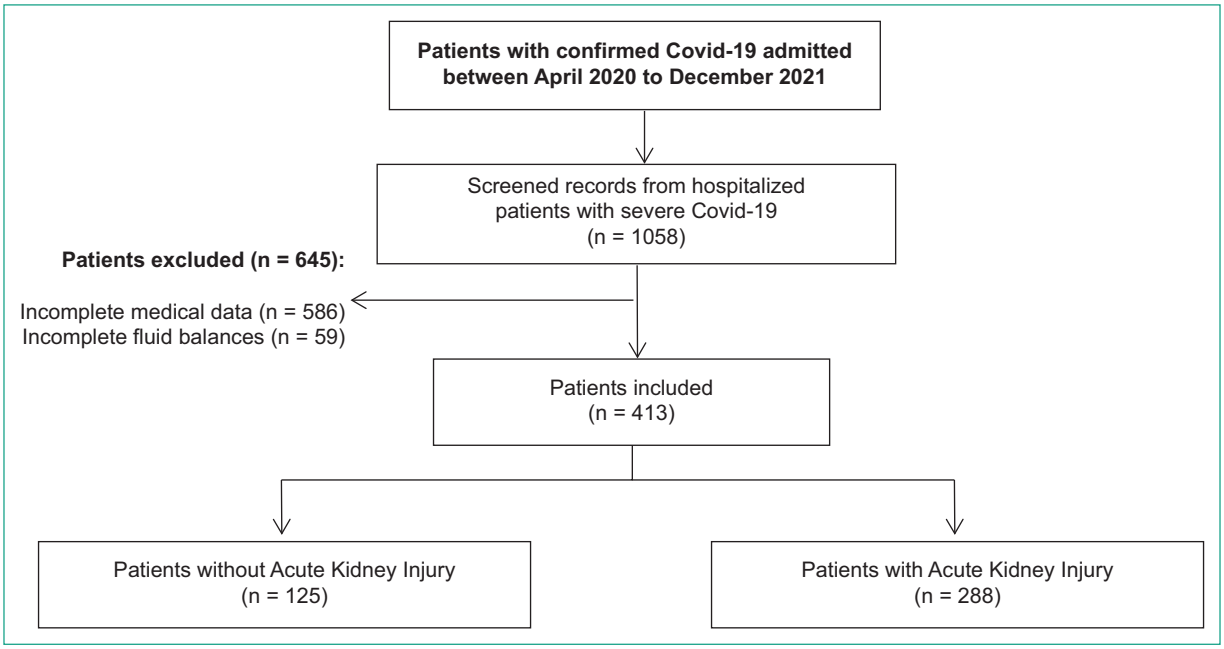

Figure 1. Flowchart of the patients included with severe COVID-19 and acute kidney injury during hospitalization.

incomplete clinical and biochemical data. Afterward, 59 patients who did not have a complete record of fluid balance during hospitalization were excluded from the final analysis (Fig. 1). The present study was approved by the HGDMGG Research Committee and Research Ethics Committee (REF 14-17-2022) and was conducted according to the 1975 declaration of Helsinki. Written informed consent was waived by the Research Committee and Research Ethics Committee given the retrospective nature of the study.

Clinical and biochemical data were obtained at admission. Cumulative fluid balances were measured as the sum of all daily fluid balances during the whole hospitalization. Daily fluid balances were calculated as the difference in all intakes and all outputs, which included diet, free water, and gastrointestinal losses. Insensible losses were not estimated nor included in the final analysis[13]. The body mass index (BMI) was calculated as the basal weight in kilograms (kg) divided by the square of body height in meters (m^2); normal weight was defined as < 25 kg/m^2, overweight as BMI between 25 and 29.9 kg/m^2, and obesity as BMI ≥ 30 kg/m^2,[15]. Hypertension was defined as blood pressure values > 140/90 mmHg or prior documented diagnosis[15]. Type 2 diabetes was defined when fasting plasma glucose values were ≥ 126 mg/dL or when the patient self-reported a previous diagnosis or current hypoglycemic drug use[15]. CKD was defined by the KIDGO guidelines as a glomerular filtration rate < 60 mL/min/1.73 m^2 for more than 3 months, structural renal changes, or when the patient self-reported a previous diagnosis[1]. Estimated glomerular filtration rate (eGFR) was calculated using the 2021 CKD epidemiology collaboration creatinine equation[1].

Biochemical analysis

The central laboratory of the HGDMGG performed all biochemical laboratory measurements. Blood samples from the patients were collected at admission to the emergency department. The measurements were carried out with commercially available standardized methods. Serum creatinine, blood nitrogen urea (BUN), C-reactive protein (C-RP), and lactic dehydrogenase (LDH) were measured using D × C 700 AU Chemistry Analyzer (Beckman Coulter, Fullerton CA). Plasma ferritin concentrations were estimated using enzyme-linked immunosorbent assay (Beckman Coulter D × C 600i, Fullerton CA). D Dimer levels were estimated using an ACL Top 550 CTS (Werfen Company, Spain).

Statistical analysis

Values are expressed as mean ± standard deviation, median (interquartile range), or frequencies (%). Means

and medians were compared using ANOVA or Kruskal–Wallis tests (Mann–Whitney's U test for individual comparison between groups) when needed and frequencies with χ^2 test. The survival rate curves according to the number of AKI stages were plotted through the Kaplan–Meier method, using the log-rank test for statistical significance. Spearman's correlations were calculated to characterize the relationship between the number of days in the hospital and clinical/biochemical characteristics of patients with severe COVID-19. Multiple linear regression analysis was used to evaluate the contribution of clinical and biochemical variables with days of in-hospital stay. Hazard Ratios with 95% confidence intervals (95% CI) were estimated using multivariate Cox regression to evaluate the effect of admission variables on mortality. All variables significantly associated with mortality in the univariate model, as well as those with biological plausibility or scientific evidence, were included in the multiple regression analysis. Analyzes were performed using the SPSS version 25.0 Statistical Package (SPSS Chicago, Il.).

Results

The study included 413 hospitalized patients with severe COVID-19 infection with a median in-hospital stay of 10 (6-17) days (minimum 1 day; maximum 82 days). The mean age of the subjects was 55.2 ± 14.8 years, 63.9% (n = 264) were men, had a mean BMI of 28.2 ± 5.5 kg/m^2 (29.8% had normal weight, 38.4% had overweight, and 31.7% had obesity), 47.2% had type 2 diabetes, 31.2% had hypertension, 4.5% had CKD, and the median cumulative fluid balance of the population was 1442 cc (–456-3700). No patients were reported to previously have heart failure or chronic liver failure. Of note, < 20% (n = 78) of patients received at least one dose of SARS-CoV-2 vaccine. Of the total population, 30.3% did not have AKI (n = 125), 33.9% had AKI stage 1 (n = 140), 13.6% had AKI stage 2 (n = 56), and 22.3% had AKI stage 3 (n = 92). Mortality was reported by 23.7% and 9.4% of patients required renal replacement therapy (RRT). The clinical course and the staging of AKI according to KDIGO are summarized in Fig. 2.

Clinical course of AKI in severe COVID-19

Of the total population with severe COVID-19, 69.7% (n = 288) developed AKI at any stage. Notably, of the 288 patients with AKI, 83.4% (n = 166) had community-acquired AKI. Table 1 shows the clinical and biochemical characteristics of the subjects with and without AKI. Compared with patients without AKI, those with AKI were older, more likely to be men, had lower BMI (including a lower prevalence of patients with obesity), higher rate of hypertension, CKD, higher levels of BUN, D-dimer, LDH, ferritin, but lower hemoglobin at admission. Regarding renal function at admission, serum creatinine was higher and eGFR decreased in those with AKI, as expected. The median cumulative fluid balance tended to be slightly higher in patients without AKI, but not significant.

Among patients with CKD (n = 17), 6 of them developed AKI stage 1 (35.3%), 4 AKI stage 2 (23.5%), and 7 AKI stage 3 (41.2%). Of note, none of these patients were currently undergoing any type of RRT before admission. Overall, 11 patients (64.7%) with AKI in overt CKD required RRT, and only 5 patients (29.4%) died during hospitalization.

In-hospital stay was longer in patients with AKI stage 2 and stage 3 compared with those without AKI (Fig. 3). Likewise, days in hospital were positively correlated with mechanical ventilation ($r = 0.276$, $p < 0.001$), D Dimer ($r = 0.194$, $p = 0.021$), BUN ($r = 0.215$, $p < 0.001$), ferritin ($r = 0.133$, $p = 0.008$), negatively with eGFR ($r = -0.143$, $p = 0.004$), and hemoglobin at admission ($r = -0.43$, $p = 0.003$). Multiple linear regression analysis was used to identify the independent relationship between clinical and biochemical characteristics with prolonged in-hospital stay. After adjustment for AKI at any stage, age, sex, BMI, COVID-19 vaccine, diabetes, hypertension, CKD, D-dimer, C-RP, ferritin, hemoglobin at admission, cumulative fluid balance, eGFR at admission, and RRT, only older age (standardized $\beta = 0.148$, $t = 2.814$, $p = 0.002$), ferritin (standardized $\beta = 0.13$, $t = 2.523$, $p = 0.012$), and hemoglobin at admission (standardized $\beta = -0.146$, $t = -2.772$, $p = 0.006$) were independently associated with prolonged length of stay.

Factors associated with mortality in patients with AKI and severe COVID-19

Mortality was significantly higher among patients with AKI than those without AKI (n = 93 [32.3%] vs. n = 5 [4.0%]; $p < 0.001$). Moreover, the rate of mortality gradually increased along with the staging of AKI: AKI stage 1 17.1% (n = 24), AKI stage 2 19.6% (n = 11), and AKI stage 3 63.0% (n = 58); $p < 0.001$. Among patients with AKI, in the univariate analysis, those who survived were significantly younger, had higher rates of Covid-19 vaccine, lower rate of mechanical ventilation, and RRT. There were no differences in inflammatory biomarkers among those

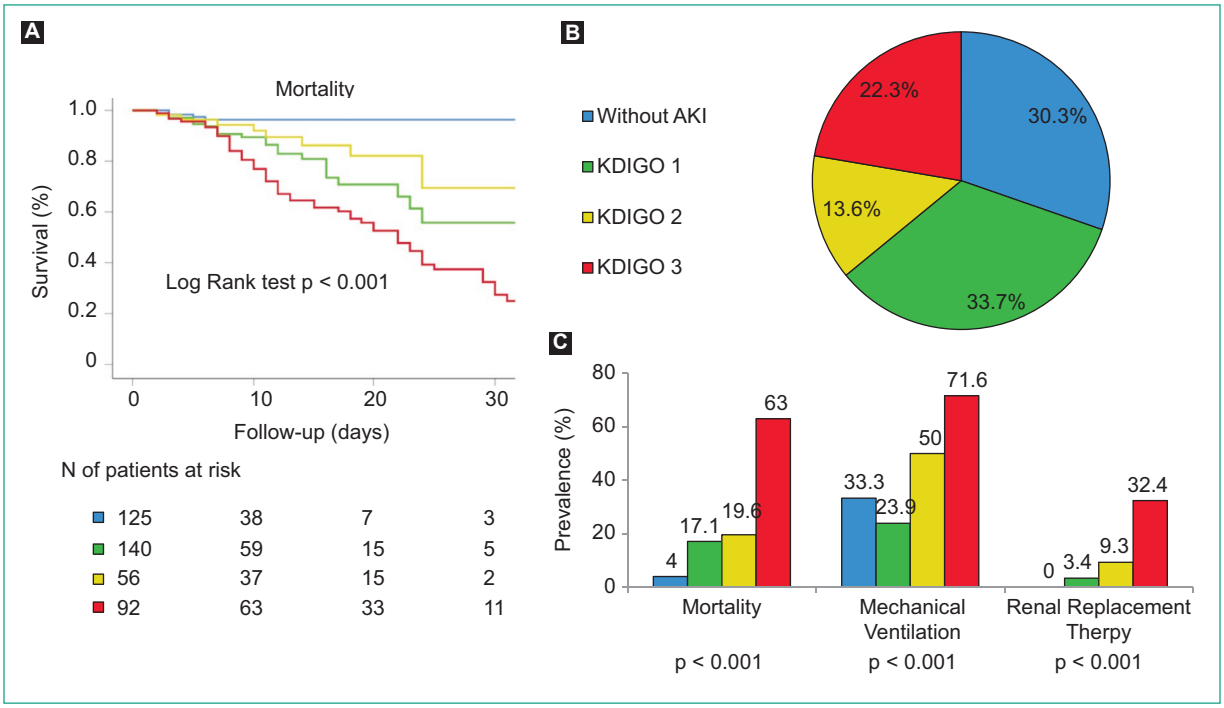

Figure 2. Adverse outcomes among patients with severe COVID-19 and AKI during hospitalization. **A:** cumulative incidence of mortality in patients with severe COVID-19 according to AKI stage; **B:** prevalence of AKI stages in hospitalized patients with COVID-19; **C:** prevalence of mortality, mechanical ventilation, and renal replacement therapy stratified by AKI stage. AKI: Acute kidney injury.

who survived and those who did not. Furthermore, to predict the in-hospital mortality, a multivariate Cox regression analysis was used using a forward conditional method (Fig. 4). The model was adjusted by age, sex, BMI, COVID-19 vaccine, diabetes, hypertension, CKD, mechanical ventilation, RRT, and eGFR at admission. As result, we found that per each 10 years of age older and per each cumulative 1000 cc positive fluid balance, the risk for mortality increased by 32% and 2.9%. In addition, mechanical ventilation and RRT were independently associated with 5.6- and 2.45-fold higher risk for death during hospitalization, respectively.

Discussion

AKI is one of the most common complications of COVID-19 and it has been associated with worse outcomes among those with the severe presentation of the infection[1,3,16]. In this retrospective cohort study of 413 patients with severe COVID-19 admitted to our institution during the pandemic, we found that nearly 70% had AKI and a mortality rate of 23.7%. Several data on COVID-19 across the globe have shown that a prolonged in-hospital length of stay has been associated with increased mortality[6,8,17]. In our cohort taken in a single Mexican referral center, we found that older age, decreased hemoglobin at admission, and ferritin levels were independently associated with prolonged length of stay. Moreover, it has been widely demonstrated that AKI is associated with increased mortality among patients with COVID-19[3,7]. However, the heterogeneous management of the disease during the pandemic, medical inertia of some centers, or effect size of some observational have left different risk factors with a wide range of hazard ratios for death[3]. In the present study and in line with previous reports, older, mechanical ventilation and RRT were associated with increased mortality[1-3,5,17,18]. But interestingly, we found that a cumulative positive fluid balance at the end of hospitalization was independently associated with mortality, which might be a possible modifiable factor that could reduce mortality in severe COVID-19 with AKI.

The prevalence of AKI in COVID-19 ranges from 0.5% in non-hospitalized patients in China to 80% in critically ill subjects in France[3]. Of note, the prevalence of our cohort study was nearly like those reports of AKI and COVID-19

Table 1. Clinical and biochemical characteristics of hospitalized subjects with COVID-19 and AKI

Variables	Without AKI (n = 125)	With AKI (n = 288)	p value
Age (years)	50.3 ± 14.7	57.3 ± 14.3	< 0.001
Female sex (%)	44.0	32.6	0.027
Body mass index (kg/m^2) < 25 kg/m^2 (%) 25-29.9 kg/m^2 (%) ≥ 30 kg/m^2 (%)	29.6 ± 5.3 19.5 41.5 39.0	27.5 ± 5.5 34.9 36.9 28.1	0.001 0.006
COVID-19 vaccine (%)	34.4	12.2	< 0.001
Diabetes (%)	45.6	48.0	0.653
Hypertension (%)	23.2	35.2	0.018
Chronic kidney disease (%)	0.0	6.7	0.003
Days in hospital (day)	7 (5-11)	11 (7-19)	< 0.001
Mechanical ventilation (%)	33.3	44.2	0.707
Vasopressor use (%)	6.4	31.5	< 0.001
Community-acquired AKI (%)	-	83.4	-
Blood urea nitrogen (mg/dL)	15.5 (12.0-21.1)	24.4 (16.4-40.2)	< 0.001
D dimer (μg/mL)	0.30 (0.20-0.60)	0.61 (0.32-1.48)	< 0.001
Lactic dehydrogenase (IU/L)	319 (245-422)	376 (266-509)	0.005
C-reactive protein (mg/dL)	14.6 (6.5-20.6)	16.4 (7.3-23.6)	0.111
Ferritin (ng/mL)	472 (271-750)	686 (345-1193)	0.001
Hemoglobin (g/dL)	14.5 ± 2.4	13.8 ± 3.1	0.049
Serum creatinine at admission (mg/dL)	0.80 (0.60-0.90)	1.11 (0.89-1.61)	< 0.001
Estimated glomerular filtration rate at admission (ml/min)	103 (92-115)	72 (41-96)	< 0.001
Cumulative fluid balance (cc)	1949 (491-3592)	1222 (–1007-3806)	0.064

AKI: acute kidney injury, variables are shown as mean ± SD or median (interquartile range) or percentages; P value: χ^2; T-student test or U-Mann–Whitney tests were used for differences between both groups.

admitted to intensive care units around the world[3,6]. Sabaghian et al. in a recent systematic review questioned the heterogeneity of AKI incidence between studies and suggested that, at the beginning of the pandemic, some of these reports varied in the definition of "severe" COVID-19 disease, with a wide range in admission criteria and hospital care, added to genetic predisposition to kidney involvement[3]. In addition, it could be important to consider that most of these reports were from industrialized Western countries outside Latin America. The pandemic represented a challenge to hospitals with limited resources like Mexico, where RRT was sometimes limited, and patients who may have required admission to intensive care units were managed outside these units due to an overwhelming wave of patients needing hospitalization[5].

Previous studies of AKI and COVID-19 have been reported in Mexico City at the Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran[19-21]. Martínez-Rueda et al. demonstrated that community-acquired AKI was linked to a greater disease burden, yet there were no significant differences in mortality rates when compared to hospital-acquired AKI. Although our study reported a higher prevalence of community-acquired AKI (23 vs. 19%), we did not find differences in mortality, AKI 3, nor RRT among our patients with or without community-acquired AKI. Ramirez-Sandoval et al. conducted an analysis of the feasibility of prolonged intermittent RRT in critically ill patients with COVID-19. While this resource may not be widely accessible at every medical center in Mexico, their study reported a mortality rate

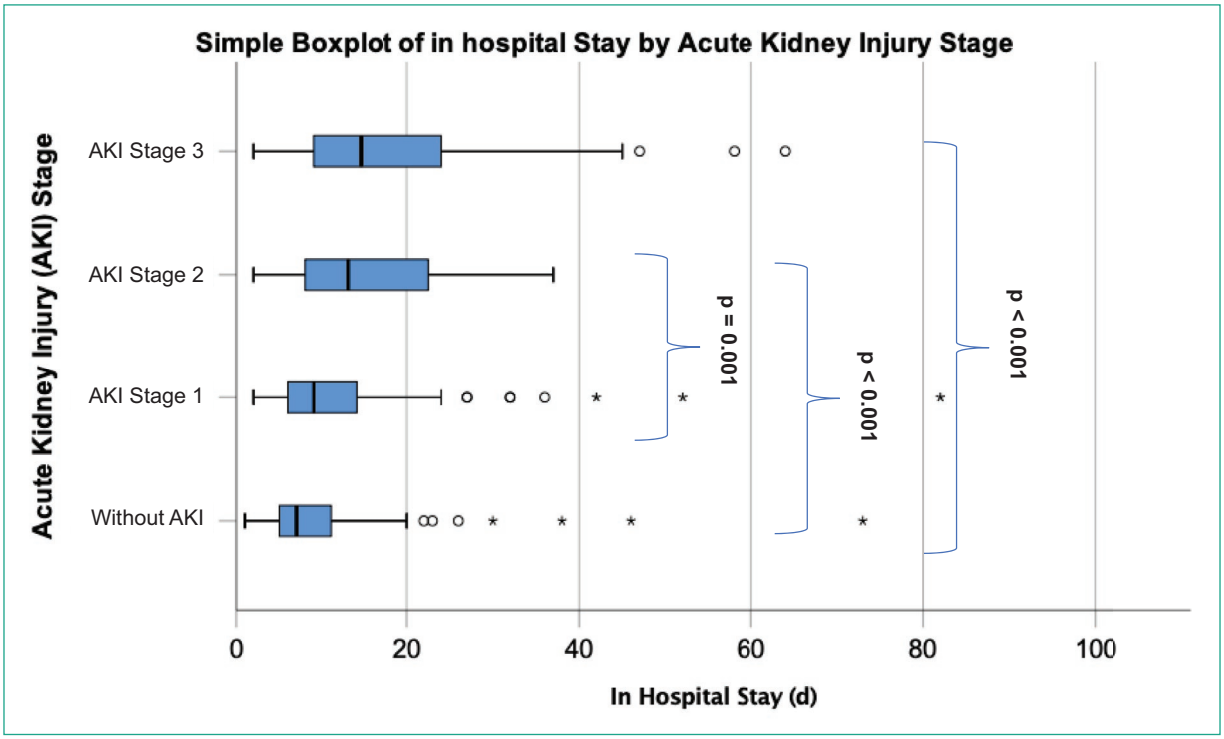

Figure 3. Simple boxplot of in hospital stay by acute kidney injury stage. Boxplot of numerical and skewness distribution of in-hospital stay in days stratified by acute kidney injury stage, p value: Kruskal–Wallis' test for all groups and U-Mann–Whitney test for differences between two groups.

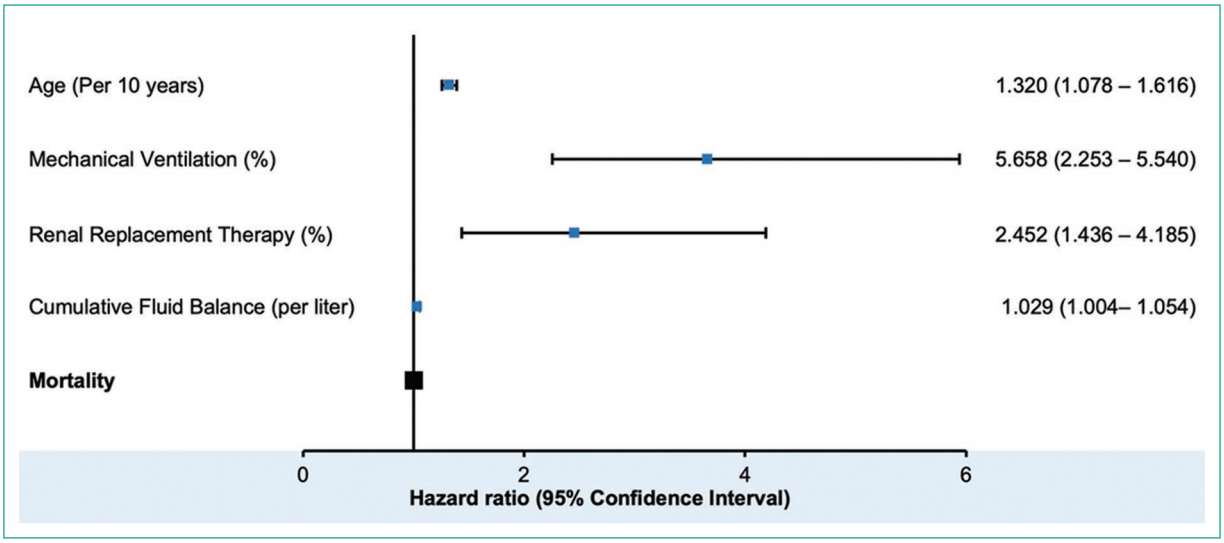

Figure 4. Variables associated with mortality among hospitalized patients with acute kidney injury and severe COVID-19. Age, sex, body mass index, COVID-19 vaccine, diabetes, hypertension, chronic kidney disease, mechanical ventilation, acute kidney injury stage, renal replacement therapy, cumulative fluid balance, and estimated glomerular filtration rate were included in the model.

of 43%, which is lower than that observed in other cohorts utilizing this resource[21]. Unfortunately, we cannot directly compare our data since we did not have access to this resource.

The pathogenesis of AKI in COVID-19 is multifactorial and due to direct and indirect viral mechanisms, it can be caused by pre-renal or intrinsic etiology[6]. Dehydration driven by fever, vomiting, diarrhea was common initial pivotal symptom of COVID-19 infection and has been suggested to induce community-acquired AKI[6,7]. However, intrinsic etiology of AKI has many suggested pathways[7]. Some of the COVID-specific mechanisms are direct viral entry to tubular cells, an imbalanced renin-angiotensin-aldosterone system activation, pro-inflammatory cytokines storm, and an increased prothrombotic state[7]. Unfortunately, due to the retrospective nature of the present study, data were limited to appropriately identify the cause of AKI and were not possible to fully describe it in the present study.

The present study has several strengths. To the best of our knowledge, this was the first study to describe the independent factors associated with prolonged in-hospital stay in severe COVID-19 and AKI. Although we failed to associate cumulative fluid balance with prolonged length of stay, we added positive fluid balance as a modifiable risk factor for mortality in COVID-19 and AKI. Another strength is that the population included were exclusively patients with severe COVID-19, which allowed us to analyze the course of the disease in the setting of severe inflammation. On the other hand, our study has important limitations. As a single-center retrospective study in Mexico, the results may be difficult to generalize, and further studies are needed to confirm our findings. Second, only the weight at admission was reported, and changes in weight during hospitalization that could be useful to correctly define the percentage of weight gain were not measured. However, the full description and association of positive fluid balance and volume overload are going to be reviewed elsewhere. Third, we did not determine the etiology of the AKI, nor the pre-renal or intrinsic source of the injury, which generally requires urinary electrolytes. Fourth, fluid balance is not equal to volume overload, which may imply clinical factors such as pulmonary edema by imaging, edema, among others. We did not report these clinical characteristics, only fluid balances. Finally, it is worth noting that certain scales that could potentially predict mortality in critically ill patients, such as SOFA, the Charlson comorbidity index, and the PaO_2/FiO_2 ratio, were not included in the analysis. These scales could potentially serve as confounding variables for the primary outcomes.

Conclusions

In conclusion, in this retrospective cohort study of hospitalized patients with AKI and severe COVID-19, older age, decreased hemoglobin at admission, and ferritin levels were independently associated with prolonged length of stay. In addition, older, mechanical ventilation, RRT, and a cumulative positive fluid balance were associated with increased mortality. Identifying different modifiable factors such as fluid balances could reduce the impact and mortality of AKI in COVID-19. Nevertheless, further research is needed to characterize volume overload and worse outcomes in AKI and severe COVID-19.

Acknowledgments

The authors sincerely thank the Department of Internal Medicine of the HGDMGG. Partial results were part of the internal medicine thesis of Dr. Héctor R. González-Sánchez.

Funding

The authors declare that they have not received any type of funding for the preparation of this manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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REVIEW ARTICLE

Oral analogues of GLP-1: perspectives on glycemic control and cardiorenal risk in patients with type 2 diabetes mellitus

Análogos orales del GLP-1: perspectivas en el control glicémico y riesgo cardiorenal en pacientes con diabetes mellitus tipo 2

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Abstract

At present, type 2 diabetes mellitus (T2DM) is the leading cause of end-stage kidney disease. The management of T2DM in recent years has moved from a glucocentric approach to a global approach with the priority of introducing treatments that offer renal and cardiovascular protection. In this article, we review in depth the pharmacokinetics and pharmacodynamics of the first oral analog of glucagon-like peptide-1 (oral semaglutide) in comparison with its subcutaneous formulation. The knowledge and implementation of these drugs will be very useful in daily clinical practice.

Keywords: *Diabetes mellitus. Glucagon-like peptide 1 receptor analogs. Semaglutide.*

Resumen

La diabetes mellitus tipo 2 (DM2) es la primera causa de inicio de terapia renal sustitutiva en la actualidad. El manejo de la DM2 en los últimos años ha pasado de un enfoque glucocéntrico a un enfoque global con la prioridad de la introducción de los tratamientos que ofrecen protección renal y cardiovascular. En este artículo revisamos en profundidad la farmacocinética y farmacodinamia del primer análogo oral del péptido similar al glucagón-1 (semaglutide oral) en comparación con su formulación subcutánea. El conocimiento e implementación de dichos fármacos nos serán de gran utilidad en la práctica clínica habitual.

Palabras clave: *Diabetes Mellitus. Análogos del receptor del péptido similar al glucagón tipo 1. Semaglutida.*

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Date of reception: 18-11-2023
Date of acceptance: 10-12-2023
DOI: 10.24875/NEFRO.M24000021

Disponible en internet: 12-03-2024
Nefro Latinoam. 2024;21:22-27
www.nefrologialatinoamericana.com

Introduction

The therapeutic approach to type 2 diabetes mellitus (T2DM) has traditionally focused on glycemic control. However, in recent years, a holistic view of the disease has emerged that has changed the glucose-centric approach and directed therapy toward a new global approach with the introduction of drugs with cardiovascular (CV) and renal benefits. When choosing treatment, each patient is considered individually, whereas considering glycemic control, weight reduction, and the management of CV and renal risk associated with comorbidities such as dyslipidemia and arterial hypertension[1,2].

In recent years, the development of new molecules beyond the standard therapy with metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, and insulin, SGLT2 inhibitors has led to the emergence of glucagon-like peptide-1 receptor analogs (GLP-1-RAs) as an appealing and promising alternative for the management of patients with T2DM[3,4]. GLP-1-RAs are drugs that have provided additional benefits in the management of T2DM that goes beyond glycemic control, which makes them an effective therapeutic option for patients with a high CV risk and those who need weight control. However, due to their pharmacokinetics, they were only available in parenteral presentations, therefore, limiting their use as first-line therapy[5]. Recently, the development of changes in their molecular structure has allowed the possibility of oral administration, being an alternative to improve drug accessibility. In this manuscript, we reviewed the pharmacokinetics and pharmacodynamics of GLP-1-RAs, with a focus on semaglutide, as well as a comparison of the most significant characteristics regarding the oral versus the subcutaneous administration of this drug in light of the most relevant clinical evidence in recent years.

Pharmacokinetics of GLP-1 receptor analogs: oral versus subcutaneous administration

GLP-1, a product derived from the glucagon gene, is an endogenous peptide consisting of 20 amino acids, which is released into circulation 3-5 min after food intake[6]. Added to its effects on the pancreas as an insulin secretagogue and glucagon secretion inhibitor, it stimulates the satiety center in the central nervous system to reduce food and water intake, resulting in weight loss. It also delays gastric emptying and reduces acid secretion in the stomach, regulating post-prandial glucose levels[7]. After its release, it is rapidly degraded by the enzyme DPP-4, resulting in a short half-life of nearly 2 min[8].

GLP-1-RAs are peptide drugs developed with a molecular structure similar to that of endogenous GLP-1 peptide but with changes in their chemical composition to trigger their physiological benefits while having an extended half-life by increasing resistance to inactivation by endogenous DPP-4[9]. At present, six drugs have been approved within this category: exenatide, liraglutide, semaglutide, albiglutide, lixisenatide, and dulaglutide. However, albiglutide is still not on the market[9].

Semaglutide is a 30-amino acid peptide, which is very similar to endogenous GLP-1, with two key changes in its structure that extends its half-life: substitution of alanine at position 8 with α-aminoisobutyric acid, which prevents its degradation by endogenous DPP-4, and the addition of a spacer to conjugate the C18 fatty acid with lysine at position 26, binding it to albumin, increasing its half-life, and delaying renal excretion[10,11]. These changes allow for the subcutaneous administration of semaglutide with a long half-life, favoring once-weekly dosing with a 94% bioavailability and efficacy and safety evaluations in different population groups, including individuals with renal disease[12,13].

Back in 2019, the oral formulation of semaglutide was approved by the FDA, making it the first GLP-1-RA available on the market in this presentation. Oral semaglutide is formulated with sodium N-(8-2 hydroxybenzoyl amino) caprylate (SNAC), which promotes the drug solubility and improves the GI bioavailability[14].

The effects of SNAC on the absorption of semaglutide are complex. First, it reduces drug degradation in the stomach by acting as a buffer, increasing gastric pH, and reducing enzymatic degradation. Second, the binding with SNAC increases the lipophilicity of semaglutide, improving its absorption through the GI lipid membrane and facilitating its entry into circulation. Once in the systemic circulation, both molecules dissociate and semaglutide interacts in the body in the same way as subcutaneous administration[15].

Unlike most orally administered drugs, semaglutide is absorbed entirely in the stomach and depends directly on the amount of SNAC with which it is co-formulated; studies have shown that 300 mg of SNAC produces the highest circulating plasma levels[16]. Its degradation primarily occurs through DPP-4, other endopeptidases, and the products are eliminated in urine and feces, which are similar to subcutaneous administration.16 It should be taken on an empty stomach, ideally 30 min before the intake of foods[16]. The drug bioavailability with oral administration is lower than that of subcutaneous administration; however, to compensate for this, higher doses are

Table 1. Pharmacokinetics of semaglutide

Characteristics	Semaglutide (Subcutaneous)	Semaglutide (Oral)
Absorption		
Absolute bioavailability	89%	0.4-1%
Plateau plasma concentration	65 ng/mL (0,5 mg; once a week) 123 ng/mL (1 mg; once a week)	6.7 nmol/L (7 mg; once a day) 14.6 nmol/L (14 mg; once a day)
Time to reach plasma concentration in steady state	4-5 weeks	4-5 weeks
Time to reach maximum concentration	1-3 days	1 h
Distribution		
Distribution volume	12.5 l	8 l
Protein binding	> 99%	> 99%
Metabolization pathways	Proteolytic degradation followed by fatty acid oxidation.	Proteolytic degradation followed by fatty acid oxidation.
Washout profile		
Elimination half-life	1 week	1 week
Elimination speed	0.05 l/h	0.04 l/h

Table adapted from Mahapatra et al.[1]

administered to achieve the same clinical results[17]. Table 1 illustrates the main pharmacokinetic characteristics of oral versus subcutaneous semaglutide.

Oral semaglutide and glycemic control

The initial work supporting the evidence for the use of oral semaglutide as a GLP-1-RA is a preliminary report of a 26-week, randomized, parallel-group, and dose-finding phase 2 clinical trial. With a population of 632 participants, this report demonstrated better glycemic control in patients with uncontrolled diabetes at 26 weeks, supporting the development of more robust subsequent clinical trials that we will discuss in the following sections[18].

The PIONEER 2 trial compared the use of oral GLP-1-RAs versus SGLT-2 inhibitors in patients with uncontrolled T2DM, with both groups receiving basal therapy with metformin. Patients were randomized to open-label treatment with once-daily 14 mg of oral semaglutide (n = 412) or 25 mg empagliflozin (n = 410) with a 52-week follow-up. Oral semaglutide achieved a superior reduction of glycated hemoglobin (HbA1c) compared to empagliflozin on a 26-week course of treatment (–1.3% vs. –0.9%), for an estimated difference of –0.4% favorable to semaglutide (95%CI, –0.6-–0.3; p < 0.0001); however, no superiority was demonstrated regarding weight reduction[19].

Similarly, the PIONEER 3, a phase 3, randomized, double-blind, parallel-group clinical trial, evaluated the efficacy and safety profile of oral semaglutide versus sitagliptin in patients with type 2 diabetes treated with metformin with or without sulfonylurea. Patients were randomized to once-daily oral semaglutide 3 mg (n = 466), 7 mg (n = 466), or 14 mg (n = 465), or sitagliptin 100 mg (n = 467). A total of 1864 participants with HbA1c mean values of 8.3% (SD, 0.9%) and a BMI of 32.5 (SD, 6.4) were included. A reduction in HbA1c levels was identified with semaglutide 7 mg/day and 14 mg/day versus sitagliptin, with a difference of –0.3% (95%CI, –0.4-–0.1%) for the 7 mg/day dose and a difference of –0.5% (95%CI, –0.6-–0.4%) for the 14 mg/day dose, with p ≤ 0.001. In addition, it showed a favorable weight reduction when semaglutide 7 mg and 14 mg was compared to sitagliptin, with a difference of –1.6 kg (95%CI, –2.0-–1.1 kg) and –2.5 kg (95%CI, –3.0-–2.0 kg), respectively, and p < 0.001 for both[20].

Oral semaglutide and weight reduction

Overall, in the PIONEER program, patients with T2DM on various therapeutic options to reduce glucose achieved a weight reduction of, at least, 5%, directly dependent on the dose. This benefit is maintained throughout the clinical trials in both groups with active comparators and even in those compared to placebo. A meta-analysis that included nine clinical trials for the overall analysis of oral semaglutide use in patients with T2DM demonstrated a decrease in body weight of 2.9 kg favorable to semaglutide versus placebo (95%CI, –3.69-–2.30). These results are consistent in all the doses, with a greater reduction reported at the 14 mg dose (–3.28 kg, 95%CI, –3.85-–2.71)[21]. Based on these clinical trials and their subgroup analyses, the weight reduction benefits with orally administered GLP-1-RAs appear to be relatively effective compared to other drugs used to treat T2DM, including subcutaneous semaglutide.

Table 2. Description of the PIONEER clinical trials

Clinical trial	Comparator	Intervention	Participants	Follow-up	Primary endpoint
PIONEER 1[32]	Compared to placebo	Oral semaglutide 3 mg Oral semaglutide 7 mg Oral semaglutide 14 mg Placebo	703 patients T2DM	26 weeks	Glucose control. Change in HbA1% on week 26 compared to baseline.
PIONEER 2[19]	Active comparator	Oral semaglutide 14 mg Empagliflozin 25 mg	822 patients T2DM	52 weeks	Glucose control. Change in HbA1% on week 26 compared to baseline.
PIONEER 3[20]	Active comparator	Oral semaglutide 3 mg Oral semaglutide 7 mg Oral semaglutide 14 mg Sitagliptin 100 mg	1864 patients T2DM	7 8 weeks	Glucose control. Change in HbA1% on week 26 compared to baseline.
PIONEER 4[33]	Active comparator and placebo	Oral semaglutide 14 mg Subcutaneous liraglutide 1.8 mg Placebo	711 patients T2DM	52 weeks	Glucose control. Change in HbA1% on week 26 compared to baseline.
PIONEER 5[31]	Compared to placebo	Oral semaglutide 14 mg Placebo	324 patients T2DM + moderate CKD	26 weeks	Glucose control. Change in HbA1% on week 26 compared to baseline.
PIONEER 6[26]	Compared to placebo	Oral semaglutide 14 mg Placebo	3183 patients T2DM + high CVR	Time elapsed until the index cardiovascular event	Time to MACE
PIONEER 7[34]	Active comparator	Oral semaglutide with a flexible dose Sitagliptin 100 mg	504 patients T2DM	52 weeks	HbA1% target < 7% on week 52
PIONEER 8[35]	Compared to placebo	Oral semaglutide 3 mg Oral semaglutide 7 mg Oral semaglutide 14 mg Placebo	731 patients T2DM	52 weeks	Glucose control. Change in HbA1% on week 26 compared to baseline.
PIONEER 9[36]	Active comparator and placebo	Oral semaglutide 3 mg Oral semaglutide 7 mg Oral semaglutide 14 mg Subcutaneous liraglutide 0.9 mg Placebo	243 patients T2DM	52 weeks	Glucose control. Change in HbA1% on week 26 compared to baseline.
PIONEER 10[37]	Active comparator	Oral semaglutide 3 mg Oral semaglutide 7 mg Oral semaglutide 14 mg Dulaglutide 0.75 mg	458 patients T2DM	52 weeks	No. of emerging adverse events on week 57

CKD: chronic kidney disease; CVR: cardiovascular risk; HbA1%: glycosylated hemoglobin; T2DM: type 2 diabetes mellitus.

Oral semaglutide and CV risk

In patients with high and very high CV risk, GLP-1-RAs can reduce the primary CV outcome. These RCTs include the LEADER clinical trial on liraglutide[22], the HARMONY trial on albiglutide[23], the REWIND on dulaglutide[24], and the SUSTAIN-6 trial on subcutaneous semaglutide[25]. Consistently, these studies proved the occurrence of fewer adverse CV events.

Regarding oral semaglutide, the PIONEER 6 clinical trial was designed to assess the CV safety profile of this drug versus placebo in a non-inferiority approach. This was a phase 3, randomized, double-blind, placebo-controlled trial of patients with T2DM and high CV risk, including an overall population of 3183 patients (1591 from the oral semaglutide group vs. 1952 from the placebo group). The primary outcome, a composite of major

adverse CV events, including CV death, non-fatal myocardial infarction, and non-fatal stroke, was reported in 61 out of the 1591 patients randomized to oral semaglutide (3.8%) versus 76 events reported in the 1592 participants randomized to placebo (4.8%), with a HR of 0.79 (95% CI, 0.57-1.11; p < 0.001), which demonstrates the non-inferiority of the drug versus placebo, which ruled out an excess of CV risk by 80%, and suggested a safety profile similar to subcutaneous semaglutide[26].

This RCT provides preliminary information on the non-inferiority of semaglutide to treat patients with T2DM and high CV risk. However, further clinical trials are needed to assess the drug's superiority. The ongoing, randomized, double-blind, placebo-controlled SOUL clinical trial is evaluating the CV safety outcomes of individuals with T2DM on oral semaglutide, with results expected by 2024 (Clinical Trials NCT03914326)[27].

Oral semaglutide and renal safety

Chronic kidney disease (CKD) is a common comorbidity in patients with T2DM[28,29]. The first clinical trial that assessed the use of oral semaglutide in patients with mild, moderate, and severe CKD versus patients with normal renal function was conducted back in 2018. This trial included 71 patients on oral semaglutide: 24 with normal renal function, 12 with mild impairment, 12 with moderate impairment, 12 with severe impairment, and 11 on renal replacement therapy. This clinical trial concluded that the pharmacokinetics of oral semaglutide did not seem to be affected by CKD, even in subjects on hemodialysis[30].

The RCT PIONEER 5 trial evaluated the efficacy and safety profile of semaglutide in patients with CKD and an estimated glomerular filtration rate (eGFR) of 30 to 59 mL/min/1.73m^2. This trial included a total of 324 patients randomized to the semaglutide group (163 patients) versus placebo (161 patients). On week 26, oral semaglutide reduced HbA1c levels by nearly –1% in the semaglutide group versus –0.2% in the placebo group, with an estimated treatment difference of –0.8% (95% CI, –1%-–0.6%). In addition, differences in body weight were reported, with a reduction of –3.7 kg in the semaglutide group versus –1.1 kg in the placebo group[30].

The studies mentioned earlier demonstrate that oral semaglutide was effective in patients with T2DM and moderate CKD, thus providing an alternative treatment option for this population. The ongoing SOUL clinical trial will present CV safety results in individuals with CKD (Clinical Trials NCT03914326)[27]. Table 2 illustrates the key characteristics of the PIONEER series of studies with oral semaglutide[31-37].

Conclusions

Oral semaglutide is a highly innovative drug and, at present, the only oral drug available within this group of drugs. Oral semaglutide can be considered an option as a pharmacological therapy for individuals with T2DM, primarily due to its significant metabolic effect and CV and renal safety profile. Clinical trials and current evidence demonstrate a good safety and efficacy profile for glycemic control and weight loss, as well as effectiveness in patients with CKD and CV safety. We are awaiting further clinical trials to demonstrate CV protection benefits of this oral drug, same as other drugs of the GLP-1-RAs family in subcutaneous presentation already have. The future appears promising for this therapeutic class, specifically in its different forms of presentation (oral vs. injectable).

Acknowledgments

The authors wish to thank all those who collaborated in the drafting of this manuscript.

Funding

The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

J.R.F declared lecture and consultancy fees from AstraZeneca, Novo Nordisk, Boehringer Ingelheim, Sanofi, Lillie, Bayer, and MSD; R.D.A declared lecture and consultancy fees from AstraZeneca, Novo Nordisk, Boehringer Ingelheim, and Bayer; J.M.H also undeclared lecture and consultancy fees from AstraZeneca, Novo Nordisk, Boehringer Ingelheim, Sanofi, and Bayer; M.J.S. declared lecture and consultancy fees from AstraZeneca, Novo Nordisk, Esteve, Vifor, Bayer, Mundipharma, Ingelheim Lilly, Jansen, Travere, ICU Medical, and Boehringer. The remaining authors declared no conflicts of interest whatsoever.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations

as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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CASE REPORT

Pregnancy and preterm delivery in a peritoneal dialysis patient in a public hospital in Peru. Case report

Embarazo y parto pretérmino en paciente de diálisis peritoneal en un hospital público de Perú. Reporte de caso

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Abstract

Chronic kidney disease (CKD) is associated with a low conception and success rates. There are reports of pregnant women on hemodialysis and peritoneal dialysis (PD), with premature births. The case of an elderly patient with a pregnancy on PD and preterm delivery is reported. A 43-year-old female patient, hypertensive and with CKD 5 on PD. While on PD, she discovered pregnancy. She was maintained on manual PD. At 31 weeks of gestation, she presented premature rupture of membranes. She was born vaginally. PD is a safe therapy during pregnancy.

Keywords: *Peritoneal dialysis. Pregnancy. Preterm labor.*

Resumen

La enfermedad renal crónica (ERC) se asocia a una tasa de concepción y porcentaje de éxito bajo. Existen reportes de gestantes en hemodiálisis y diálisis peritoneal (DP) con nacimiento de niños prematuros. Se reporta el caso de paciente añosa con embarazo en DP y parto pretérmino. Paciente mujer de 43 años, hipertensa y con ERC 5 en DP. Estando en DP descubrió gestación, continúo en DP manual. A las 31 semanas de gestación, presentó ruptura prematura de membranas, tuvo parto vaginal. La DP es una terapia segura durante la gestación.

Palabras clave: *Diálisis peritoneal. Gestación. Parto pretérmino.*

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Date of reception: 09-06-2023
Date of acceptance: 27-08-2023
DOI: 10.24875/NEFRO.M24000018

Available online: 12-03-2024
Nefro Latinoam. 2024;21:28-31
www.nefrologialatinoamericana.com

Introduction

Advanced chronic kidney disease (CKD) affects fertility; however, there are reports of an increasing number of pregnancies in women on dialysis[1]. The conception rate in this group of patients is one in 100 of the overall population, with reported annual incidences ranging from 0.3% to 2.7%[2].

Women with stage 5 CKD who become pregnant experience complications such as a higher risk of preeclampsia, intrauterine growth retardation, polyhydramnios, and an increased rate of premature births, which are associated with increased maternal and fetal morbidity[3].

Peritoneal dialysis (PD) offers benefits during pregnancy, such as in ultrafiltration, avoiding significant hemodynamic changes, and the absence of need for anticoagulation during childbirth. However, the progressive increase in uterine size may require reduced dialysate volumes and impact the position of the catheter, with the potential to impact the efficiency of dialysis[4].

Successful pregnancies in patients on PD have been reported. For example, Batarse et al.[5] reported the results of 47 women on PD during pregnancy in 2015, with a fetal survival rate of 77%, a mean gestational age of 33 weeks, and a mean birth weight of 1755 g.

In Brazil, Calice et al.[6] described the case of a 37-year-old woman who became pregnant 7 months after having started PD and had a successful full-term delivery (39 weeks) with a newborn weight of 2600 g, without complications.

Lim et al.[7] presented the case of a multigravida woman, advanced in age (42 years), on PD, who remained stable during her pregnancy, underwent elective C-section at 36 weeks, and received postpartum hemodialysis (HD) sessions until the surgical wound healed.

Similarly, Jefferys et al.[8] published cases of five patients on PD. The mean duration of pregnancy was 35 weeks, and PD-related complications included exit site infection, catheter displacement, and peritonitis, which were reported in three out of five pregnancies.

Pregnancy in women on PD is less common, as most published data relate to HD. We present the case of a 28-year-old woman with end-stage renal disease who conceived after 2 years on PD and successfully continued this therapy throughout her pregnancy and postpartum period to this date.

Case presentation

This is the case of a 43-year-old female patient, a native of Chachapoyas, Peru, with a past medical history of hypertension treated with methyldopa. She was diagnosed with stage 5 CKD and started HD with a temporary catheter, later transitioning to PD 3 months later by her own decision. Her gynecological history included a menstrual cycle of 3-4/28 days and six pregnancies with five living children, the last of whom was born 12 years ago with low birth weight (2400 g). All her deliveries were spontaneous.

Six months into PD, she missed her menstrual period. A pregnancy test and medical evaluation confirmed that she was 14 weeks pregnant. She underwent further examinations and received prenatal monitoring in her place of residence, attending monthly check-ups at the Nephrology Service of Hospital Carrión del Callao, Perú. Her medical treatment included subcutaneous erythropoietin 3 times/week, methyldopa, iron, and oral folic acid.

Regarding PD therapy, throughout the pregnancy, the patient remained on manual PD with four exchanges per day (alternating solutions with 1.5% and 2.5% glucose concentration), an initial volume of 2000 cc, which dropped down to 1800 cc starting from the 28th week of gestation. She had a mean ultrafiltration of 600 mL, with residual diuresis starting at 1200 cc at the beginning of the pregnancy and dropping down to 500 cc. Blood pressure levels remained normal, except for 2 weeks before delivery when it increased despite regular antihypertensive management.

On gestation week 31, the patient experienced premature rupture of membranes, initiating labor, which was spontaneous. Obstetric complications included hypertension, requiring adjustment of the antihypertensive dosage, and the need for a postpartum transfusion of 2 units of red blood cells.

Peripartum laboratory tests showed: glucose levels, 76 mg/dL; creatinine levels, 8.22 mg/dL; urea levels, 72 mg/dL; albumin levels 3.1 g/dL; leukocytes 8780 u/L; hemoglobin, 8.5 g/dL; platelets, 229 000; calcium, 7.6 mg/dL; phosphorus, 3.8 mg/dL; uric acid levels, 5.9 mg/dL; normal coagulation profile; negative serology for HIV; syphilis; hepatitis B and C. Urinalysis showed 30-40 leukocytes per field and a negative urine culture. Liver function was normal. Abdominal ultrasound revealed the presence of gallstones.

The birth of a girl weighing 1457 g was reported, measuring 38 cm in length, with Apgar scores of 7 and 8, occurred without visible congenital malformations and normal laboratory test results, except for mild self-limited indirect hyperbilirubinemia.

Four days after delivery, the patient had turbid peritoneal fluid with 120 cells (60% polymorphonuclear leukocytes), which resulted in a diagnosis of secondary peritonitis. She was put on a 14-day course of intraperitoneal ceftazidime and cefazoline, which improved her condition.

Table 1. Published cases over the past 10 years of pregnancies in patients on PD

Reference	Gestational age at delivery (weeks)	Type of delivery	PD-related complications	Mortality associated with renal replacement therapy at the end of gestation
Alhwiesh, 2015 (Saudi Arabia)	37	Vaginal	Not reported	Peritoneal dialysis
Lim et al., 2017 (Malaysia)	36	C-section	Not reported	Peritoneal dialysis (switched to HD postpartum)
Malin et al., 2018 (UK)	34.5	Vaginal	None	Peritoneal dialysis
Choi, 2018 (Korea)	27.4	Cesarean	Not reported	Peritoneal dialysis (switched to HD postpartum)
Shaw, 2018 (Canada)	36	Cesarean	None	Hemodialysis
Veríssimo et al., 2022 (Portugal)	36.6	Vaginal	Exit site infection	Hemodialysis
Cinco et al., 2022 (Mexico)	37	C-section	None	Peritoneal dialysis

The patient was discharged 6 days after delivery, and the newborn 2 weeks after birth.

Discussion

The incidence of pregnancy in women on renal replacement therapy is lower versus that of women on PD versus that of women on HD[9].

Reported cases of successful pregnancies in patients on dialysis are those of young women, rarely over 40 years old[10]. In this case, the patient was 43 years old.

Advanced kidney disease comes with metabolic effects that inhibit ovulation in this patient group, contributing to a low rate of successful pregnancies. In addition to the aforementioned factors, complications specific to CKD are also a concern. Maintaining successful pregnancies has been described in patients who retain residual renal diuresis[11]. In this case, the patient had residual diuresis, which dropped from 1200 cc down to 500 cc during her pregnancy.

Prescribing PD can be challenging, especially in the advanced stages of pregnancy, as it requires reduced infusion volume along with multiple exchanges to maintain adequate clearance[12]. The lack of evidence and experience in the management of PD during pregnancy often leads most physicians to temporarily switch to HD. However, there are reports of three patients only the past 10 years who remained on PD even after childbirth[3,10,13] (Table 1)[3,7,10,12-15]. In this case, the stable clinical parameters of both the patient and the fetus allowed for the continuation of PD without having to change the therapy, even after childbirth.

Piccoli et al.[14] reported a series of cases, including 523 pregnancies on HD and 51 on PD. These data showed that despite comparable rates of premature delivery, PD was associated with a higher rate of newborns (67%) compared to HD (31%).

There are reports suggesting better outcomes with PD, but there are no prospective comparative, randomized studies on HD and PD to determine the best method.3 In this case, the patient had a successful preterm pregnancy while on PD, followed by uncomplicated delivery, which allowed her to continue this type of renal replacement therapy.

Conclusions

PD is a safe therapy during pregnancy, and it can be continued even postpartum.

Acknowledgments

The authors wish to express their gratitude to the dedicated team at the PD Unit of the Nephrology Department at Hospital Nacional Daniel Alcides Carrión, Perú for their commitment and dedication to service.

Funding

The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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CASE REPORT

Fabry's disease in the hemodialysis unit: a case report

Enfermedad de Fabry en la sala de hemodiálisis: a propósito de un caso

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Abstract

Fabry's disease is an X-linked inherited disorder that affects the metabolismo f glycosphingolipids, leading to a deficiency or absence of the lisosomal enzyme alpha-galactosidase A. This deficiency has systemic repercussions, including renal sclerosis and fibrosis. The patient, a 31 year old, was referred due to uremic syndrome and required urgent hemodialysis. In addition, the patient presented symptoms consistent with Fabry's disease (cardiac, ophthalmologic, dermatologic, and neurological), which were subsequently confirmed through genetic testing. At present, the patient receives agalsidase beta every 15 days during hemodialysis. They are under clinical follow-up with limited improvement in symptoms.

Key words: *Fabry's disease. Chronic kidney disease. Hemodialysis. Agalsidase.*

Resumen

La enfermedad de Fabry es una patología hereditaria ligada al cromosoma X que afecta el metabolismo de los glicoesfingolípidos generando déficit o ausencia de la enzima lisosomal alfa galactosidasa A. Este déficit tiene repercusión sistémica, entre ellas esclerosis y fibrosis renal. Es derivado un paciente de 31 años por síndrome uremico con requerimientos de hemodialisis de urgencia, asociado presenta signo sintomatología compatible con enfermedad de Fabry (cardiaca, oftalmológica, dermatológica y neurológica) que se constata posteriormente con estudio genético. Actualmente recibe agalsidasa beta cada 15 días intradialisis. Se encuentra en seguimiento clínico con escasa mejoria de los síntomas

Palabras claves: *Enfermedad de Fabry. Enfermedad renal crónica. Hemodiálisis. Agalsidasa.*

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Date of reception: 22-06-2023
Date of acceptance: 26-09-2023
DOI: 10.24875/NEFRO.M24000019

Available online: 17-05-2024
Nefro Latinoam. 2024;21:32-34
www.nefrologialatinoamericana.com

Introduction

Fabry's disease (FD) is a hereditary X-linked recessive disorder that results in a deficiency in the synthesis of α-galactosidase A, which triggers the intravascular deposition of glycosphingolipids in various tissues and organs.

Clinically, it presents two phenotypes, a classical and a late-onset form. The former starts in childhood, while the latter manifests in adulthood. FD-related nephropathy occurs due to the deposition of glycosphingolipids in podocytes, mesangium, glomerular endothelium, arteries and arterioles, tubular and interstitial cells, leading to glomerular sclerosis, vascular lesions, and ultimately interstitial fibrosis.

Case presentation

This is the case of a 31-year-old man from Bolivia with no confirmed personal medical history who was referred to Hospital Provincial Neuquén, Neuquén, Argentina due to uremic syndrome with criteria for emergency hemodialysis and pancytopenia. The laboratory test results revealed urea levels of 399 mg/dL, creatinine levels of 21 mg/dL, hematocrit of 12%, hemoglobin of 3.9 g/dL, white blood cell count of 3600/uL, platelet count of 51 000/ul, sodium (Na) 132 mEq/L, potassium (K) 4.4 mEq/L, proteinuria in urine, hematuria (7-10/HPF), and no leukocyturia.

During the medical examination, the patient reported experiencing tingling/electric shock-like pain in both hands and feet since childhood. In the 2 months before the consultation, he began experiencing nausea, and vomiting, which hindered the intake of food, unquantified weight loss, and eventually swelling in the lower limbs and face. On physical examination, the patient exhibited hypochromic mucous membranes, pinpoint-sized skin lesions (< 5 mm), hyperpigmented, palpable, and grouped, which did not disappear on pressure and were distributed across the periumbilical, inguinal, and thigh regions, consistent with angiokeratomas. Cardiovascular examination revealed the presence of a grade 3/6 holosystolic murmur with radiation into the ipsilateral neck and axilla.

Additional diagnostic tests included renal ultrasound, which showed a reduced size of both kidneys (right kidney, 9.61 cm; left kidney, 8.08 cm). Similarly, the echocardiogram revealed the presence of mild dilatation of both atria, along with severe concentric LV hypertrophy with an ejection fraction of 76%.

Ophthalmology consultation noted the presence of dry eyes, horizontal nystagmus, verticillate cornea, and tortuosity of deep vessels. During hospitalization, the patient experienced an episode of acute disorientation, which prompted a computed tomography scan that revealed the presence of sequelae of a vascular event in the anterior portion of the left thalamus spreading into the internal capsule, along with an angioma in the right globus pallidus-putamen region. Due to these findings and the colorful clinical presentation, FD was suspected, and enzymatic function was assessed through dried blood spot testing. Emergency hemodialysis was initiated through a temporary catheter due to advanced CKD, and plans were made for the creation of an arteriovenous fistula.

Genetic testing reported α-galactosidase A levels of 0.1 μmol/L/h (normal values ≥ 4.0) and lyso-Gb3 levels of 74.4 nmol/L (normal values ≤ 0.9), which were consistent with FD. Therefore, approval for treatment was requested to the Hospital Pharmacy Committee. At present, the patient is on agalsidase beta (fabrazyme) at a dose of 1 mg/kg every 15 days during hemodialysis sessions. Due to the genetic nature of the disease, the study was extended to the family group, and the presence of the disease was confirmed in the patient's oldest daughter.

Discussion

FD is a hereditary condition caused by mutations in the GLA gene, located on the X chromosome, which lead to a deficiency, or absence of α-galactosidase A. This deficiency results in the accumulation of glycolipids, mainly globotriaosylceramide (Gb3, or GL-3), and globotriaosylsphingosine (lyso-Gb3 or lyso-GL-3) in various tissues and organs, including kidneys, digestive system, nerves, and eyes.

The renal pathophysiology of the disease is still not fully understood. However, it is known that Gb3 deposition in podocytes increases the expression of the cytokine TGF-beta[1], leading to the synthesis of fibronectin and IV collagen in the extracellular matrix. The cytokine-mediated proinflammatory state, along with autophagy activation caused by LC3 protein changes, leads to podocyte dysfunction, manifested by proteinuria, and eventually progresses to glomerulosclerosis[2].

FB is clinically categorized into type 1 (classical) and type 2 (late-onset). Type 1 typically presents in childhood with neuropathic pain in the hands and feet, abdominal pain, diarrhea, angiokeratomas, and hypohidrosis. Other clinical signs may include verticillate

cornea, hearing impairment, and tinnitus[3]. Renal involvement may lead to proteinuria at an early age, with the need for renal replacement therapy after the age of 30. Cardiovascular abnormalities such as arrhythmias, precordial pain, LV hypertrophy, and stroke become apparent during this decade[3].

We should consider the expression of this disease in women, as it is not always asymptomatic. The severity of symptoms can vary depending on X-chromosome inactivation-whether healthy or mutated-known as the "lyonization phenomenon"[3].

The diagnostic process typically involves meeting, at least, three of the four criteria proposed by the Canadian Fabry Disease Treatment Guidelines[4]: (1) Clinical criteria (specifically the presence of verticillate cornea and angiokeratoma); (2) biochemical criteria reduced, or absent α-galactosidase A levels in whole blood, plasma, or leukocytes, as well as the presence of elevated levels of Gb3 and sphingosine-globotriaosylceramide (lyso-Gb3) in blood or urine; (3) molecular criteria (DNA-level modifications); and (4) anatomopathological criteria (detection of deposited material, Gb3, through immunohistochemistry in tissues such as kidney, heart, or skin)[5].

The management of FD requires specific therapy, including enzyme replacement therapy or pharmacological chaperones. The former involves the administration of agalsidase in either its alpha or beta isoform, while the latter (migalastat) has been recently approved. In addition, supportive symptomatic treatment is needed based on individual symptoms[3,6].

Conclusions

FD is a clinically heterogeneous and rare condition that requires a high index of suspicion and specific diagnostic testing for confirmation.

Early diagnosis enables the initiation of enzyme replacement therapy and the evaluation of family members. FD should be considered as a chronic, multisystemic, and progressive disease that significantly impairs a patient's quality of life and reduces his/her overall survival significantly.

In the case of our patient, he remains on renal replacement therapy using the hemodialysis modality. After starting agalsidase treatment, his skin lesions have improved, and he has gained more tolerance to extreme temperatures.

Acknowledgments

The authors wish to express their gratitude to the members of the Nephrology Service at Hospital Provincial Neuquén, the Argentine Society of Nephrology, and the SLANH.

Funding

The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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CLINICAL CASE

Sphingomonas paucimobilis: a rare cause of peritoneal dialysis-associated peritonitis

Sphingomonas paucimobilis: una causa rara de peritonitis asociada a diálisis peritoneal

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Abstract

Sphingomonas paucimobilis is an emerging Gram-negative bacillus that has been reported in both healthy people and immunocompromised hosts. Various infections in humans have been described, including peritoneal dialysis (PD)-associated peritonitis although most have been limited to sporadic case reports. The clinical course and outcomes are variable with a high antibiotic resistance and unpredictable antibiotic sensitivity. Therefore, more data are warranted to clarify its treatment management. Here, we report a rare case of PD-associated peritonitis due to S. paucimobilis in a patient successfully treated with both intraperitoneal and intravenous antibiotics.

Keywords: *Sphingomonas paucimobilis. Gram-negative. Peritoneal dialysis-associated peritonitis.*

Resumen

Sphingomonas paucimobilis es un bacilo gram negativo emergente que afecta tanto a personas sanas como a huéspedes inmunocomprometidos. Se han descrito varias infecciones, incluida la peritonitis asociada a diálisis peritoneal (DP), aunque la mayoría se ha limitado a casos esporádicos. El curso clínico y los resultados son variables con alta resistencia a los antibióticos y susceptibilidad a los antibióticos impredecible. Por lo tanto, se necesitan más datos para aclarar el manejo del tratamiento. Aquí, informamos un caso raro de peritonitis asociada a la DP debido a Sphingomonas paucimobilis en un paciente tratado con éxito con antibióticos intraperitoneales e intravenosos.

Palabras clave: *Sphingomonas paucimobilis. Gram negativo. Peritonitis asociada a diálisis peritoneal.*

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Date of reception: 13-07-2023
Date of acceptance: 27-12-2023
DOI: 10.24875/NEFRO.23000037

Available online: 19-03-2024
Nefro Latinoam. 2024;21:35-40
www.nefrologialatinoamericana.com

Introduction

Sphingomonas paucimobilis is a yellow-pigmented, non-fermenting, Gram-negative bacillus with a single polar flagellum and slow motility[1]. This bacterium was named and described for the 1st time by Holmes et al. in 1977 and was reported as an agent of human infection in 1979 after isolation from a leg ulcer in a Japanese seaman[2]. It is ubiquitously distributed in the natural environment, especially in water reservoirs and soil, and has also been isolated on hospital devices and equipment such as water systems, distilled water, ventilators, nebulizers, and humidifiers[3]. *S. paucimobilis* is an opportunistic pathogen that has been associated with a great variety of community-acquired and health care-associated infections, including bacteremia, pneumonia, endophthalmitis, meningitis, catheter-related infections, peritoneal dialysis-associated peritonitis, splenic abscesses, biliary tract infections, urinary tract infections, septic arthritis, and osteomyelitis[4-11]. The presence of indwelling devices, an impaired immune system, especially neutropenia and hematopoietic stem cell transplantation, and comorbidities such as malignancy, diabetes mellitus, and alcoholism are significant risk factors for *S. paucimobilis* infection[12]. Although *S. paucimobilis* peritonitis in peritoneal dialysis (PD) patients was reported to occur rarely, it has been encountered with increasing frequency in clinical settings. However, little is known about their clinical course, sensitivity patterns, and outcomes. Here, we report a case of successful treatment of *S. paucimobilis* PD-associated peritonitis, and the first described case from Portugal.

Case presentation

A 43-year-old man with end-stage renal disease of undetermined etiology, performing automated peritoneal dialysis for 2 years, presented to our outpatient clinic with a 2-day history of fever, diffuse abdominal pain, macroscopic hematuria, and pyuria. The patient had a recent medical history of relapsing PD-associated peritonitis caused by *Staphylococcus aureus*, which prompted the removal of the PD catheter and the simultaneous placement of a new one, 2 months before. The patient's medical history also included hypertension, hypertensive heart disease, chronic obstructive pulmonary disease, and glucose-6-phosphate dehydrogenase deficiency. On physical examination, the patient was found to be febrile with a temperature of 39°C, along with diffuse abdominal pain, with no vomiting or intestinal occlusion signs. Murphy's sign was negative. The PD effluent was slightly cloudy but without any inflammatory signs at the PD catheter's exit site or tunnel. Laboratory blood tests revealed a hemoglobin concentration of 8.3 g/dL, a white blood cell count of 15,200/μL with an absolute neutrophil count of 12,200/μL, and an increased C-reactive protein of 47 mg/L. Urinalysis revealed protein 2+, erythrocytes 3+, and leukocytes 3+ with negative nitrites. Urine culture was negative. Dialysis effluent, after a 2 h-dwell, showed numerous white blood cells (469 cells/mm^3), mainly polymorphonuclear (82%). Based on these findings, the patient was diagnosed with PD-related peritonitis and pyelonephritis and was hospitalized at the nephrology department. Empirical intraperitoneal (IP) treatment was initiated with 1 g daily of cefazolin and 1.5 g of ceftazidime on the large dwell for the treatment of PD-related peritonitis, with simultaneous intravenous ceftriaxone (2 g/day), for the treatment of pyelonephritis. On the 3rd day of hospitalization, due to the lack of clinical improvement with a progressive increase in inflammatory parameters with a peak serum C-reactive protein of 249 mg/L and a clinical picture suggestive of sepsis, ceftriaxone was replaced by intravenous meropenem 500 mg/day. It was not clear whether the cause of the worsening was peritonitis or pyelonephritis. On day 7, the white cell count of the effluent decreased to 21 cells/mm^3 with 5% polymorphonuclear. The culture of the peritoneal dialysate was positive after 10 days of incubation and revealed *S. paucimobilis.* Regrettably, the antimicrobial susceptibility testing was not performed. According to the agent isolation, we discontinued IP cefazolin and ceftazidime and started a 250 mg dose of IP amikacin once daily due to a lack of tobramycin in the hospital. Meropenem (IV) and amikacin (IP) were maintained for 21 days with an excellent response, with no relapsing or repeat peritonitis, returning to the previous PD protocol with good ultrafiltration and efficiency.

Discussion

To the extent of our knowledge, we present the 18 cases of *S. paucimobilis* PD-associated peritonitis, successfully treated with IP amikacin and IV meropenem for 21 days, according to the current peritonitis guidelines from the International Society for PD (ISPD), suggesting a 3-week treatment for non-*Pseudomonas* Gram-negative peritonitis[13]. Furthermore, the ISPD guidelines recommend a combined therapy of intraperitoneal and intravenous antibiotics, when PD-related peritonitis is accompanied by other concomitant foci of infection, or when patients present with features of

Table 1. Summary of reported cases in literature

Case no	References	Year	Gender	Age	Susceptible antimicrobials	Antimicrobials	Route of administration	Catheter removal	Outcome
1	15	1984	Female	74	Ampicillin; carbenicillin; gentamicin; tobramycin; erythromycin; tetracycline; sulfamethoxazole-trimethoprim; chloramphenicol	Trimethoprim sulfamethoxazole, IP	IP	No	Cured
2	15	1984	Male	33	Ampicillin; carbenicillin; gentamicin; tobramycin; erythromycin; tetracycline; sulfamethoxazole-trimethoprim; chloramphenicol	Cefazolin IP + tobramycin, IP (duration NR) Ampicillin, IP for 5 days Amoxicillin, PO for 7 days After catheter removal, tobramycin IV (duration NR)	IP, IV, PO	Yes	Catheter removed on day 12 after the start of antibiotic therapy
3	16	1985	Male	61	Cefuroxime; ceftazidime; ticarcillin; amikacin; chloramphenicol	Vancomycin, IP + gentamicin, IP (duration NR)	IP	No	Cured
4	17	1985	Male	50	Not reported	Cephalothin, IP for 4 days Tobramycin, IP for 14 days	IP	No	Cured
5	18	1987	Male	65	Mezlocillin; cefotaxime	Vancomycin, IP for 10 days + tobramycin, IP 12 days + ampicillin for 3 days (route NR) Mezlocillin, IP for 13 days + cefoxitin for 13 days (route NR) Chloramphenicol for 13 days (route NR)	IP	Yes	Catheter removed
6	19	1988	Female	38	Cephalothin; tobramycin	Tobramycin, IP + cephalothin, IP (duration NR)	IP	Yes	Catheter removed on day 7
7	20	1990	Female	64	Aminoglycosides; sulfamethoxazole-trimethoprim	Ciprofloxacin, PO for 5 days Netilmicin IP (duration NR)	PO, IP	No	Cured
8	21	2007	Male	51	Ceftazidime; cefotaxime; cefepime; imipenem; sulbactam/ cefoperazone; tazobactam/ piperacillin; amikacin; ciprofloxacin	Cefazolin + amikacin 14 days Ceftazidime + cefazolin for 4 days	NR	Yes	Catheter removed on day 19
9	22	2008	Male	50	Ampicillin; piperacillin; imipenem; sulbactam/ampicillin; sulbactam/ cefoperazone; tazobactam/ piperacillin; gentamicin; levofloxacin; sulfamethoxazole-trimethoprim	Vancomycin, IP single dose Imipenem IV + gentamicin IP for 18 days After catheter removal, imipenem IV for 7 days	IP, IV	Yes	Catheter removed on day 21 after the start of antibiotic therapy

(Continues)

Table 1. Summary of reported cases in literature *(continued)*

Case no	References	Year	Gender	Age	Susceptible antimicrobials	Antimicrobials	Route of administration	Catheter removal	Outcome
10	23	2011	Male	3.5	Meropenem; amikacin; tetracycline; polymyxin B	Amikacin IP for 4 days Meropenem IV for 7 days	IP, IV	No	Cured
11	24	2013	Male	63	Ceftazidime; cefotaxime; imipenem; meropenem; gentamicin; minocycline; ciprofloxacin	Cefazolin IP (1 g/day) + Ceftazidime IP (1 g/day) 1st relapse: Imipenem IP (1 g)	IP	Yes	Catheter removed. hemodialysis
12	25	2015	Female	50	Cefepime; meropenem; amikacin; clarithromycin; ciprofloxacin	Vancomycin IP + ceftazidime, IP for 1 day Ciprofloxacin, IV for 3 days Tobramycin, IP for 21 days + Meropenem, IV for 21 days	IV, IP	No	Cured
13	26	2016	Female	35	Ceftriaxone; cefepime; imipenem; ciprofloxacin; levofloxacin	Vancomycin + ceftazidime, IP for 3 days Ciprofloxacin, PO + ceftriaxone, IP for 21 days After catheter removal Ciprofloxacin, PO + ceftriaxone, IP for 14 days	PO, IP	Yes	Cured
14	27	2018	Female	63	Ceftazidime; amikacin; gentamicin; ciprofloxacin	Ceftazidime + vancomycin, IP for 3 days Ceftazidime + Amikacin, IP for 21 days	IP	No	Cured
15	28	2020	Male	35	Ciprofloxacin; netilmicin; sulfamethoxazole-trimethoprim;	Ampicillin/Sulbactam + Ceftazidime, IP for 16 days Ciprofloxacin, IV for 35 days + netilmicin, IV for 19 days	IP, IV	Yes	Catheter removed. hemodialysis
16	29	2022	Male	52	Cefepime, ceftazidime, levofloxacin, meropenem	Piperacillin/tazobactam + teicoplanin, IP for 4 days Ciprofloxacin + Meropenem, IP for 21 days	IP	No	Cured
17	30	2021	Female	80	Piperacillin; imipenem/cilastatin; meropenem; tazobactam/ piperacillin; gentamicin; tobramycin; amikacin; minocycline	Ceftazidime, IP for 7 days + Cefazolin, IP for 4 days Meropenem, IV for 14 days Meropenem, IV for 21 days + Tobramycin, IP for 2 days	IP, IV	Yes	Catheter removed. hemodialysis
18	Our study	2023	Male	43	NR	Meropenem IV Amikacin IP	IP, IV	No	Cured

systemic sepsis, which was our case. As shown in Table 1, the clinical course, susceptibility patterns, antimicrobial regimens class, and route of administration of this pathogen are widely heterogeneous across the reported cases and studies, highlighting the need for individualized case-by-case management. Along with that, the few cases reported explain why, to this date, no definitive guidelines exist. In general, this organism is mostly resistant to the common antibiotics empirically used to treat peritonitis, such as penicillins and first-generation cephalosporins, due to the production of chromosomally encoded beta-lactamase production. Conversely, it is usually susceptible to aminoglycosides, carbapenems, trimethoprim-sulfamethoxazole, and ciprofloxacin[14-30]. Based on its multidrug resistance, the use of combination therapy may be beneficial to overcome antibiotic resistance. Considering this data, we decided to add IP amikacin to IV meropenem with excellent response. Moreover, biofilm production by *S. paucimobilis* is a well-known bacterial virulence factor that increases the likelihood of treatment failure, explaining the high frequency of catheter removal and PD withdrawal. Therefore, nephrologists should be aware of the potential virulence of this bacterium. Among potential risk factors associated with S. *paucimobilis* PD-associated peritonitis, our patient underwent surgery 2 months before, which may underly the exposition to indwelling devices, exposing the patient to a hospital-acquired infection.

Conclusion

S. paucimobilis is an emerging pathogen and should be considered an important community-acquired and nosocomial pathogen capable of causing severe infections in humans, especially in immunocompromised hosts. Further studies are necessary to better define host susceptibility factors, antibiotic resistance, and effective therapeutic regimens.

Funding

The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

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Obstructive nephropathy by an ovarian cyst: not that innocent entity

Nefropatía obstructiva por quiste de ovario: una entidad nada inocente

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Introduction

Urinary tract obstruction can lead to chronic kidney disease[1]. The obstructed kidneys displayed increased interstitial fibrosis, tubular atrophy, and inflammation[1]. In these cases, relief of the obstruction is a paramount to avoid irreversible kidney disease[1]. The underlying mechanism for unilateral obstruction is similar, however, the diagnosis is more challenging due to unspecific clinical presentation: no changes in the urinalysis, kidney function can be normal or can slowly decrease over time, and urine output is present[1,2].

The urinary collecting system imaging is essential to detect obstructions and renal recovery may depend on early detection and treatment[1].

Case

We reported the case of non-oliguric chronic urinary obstruction. A 70-year-old woman with a history of autoimmune hemolytic anemia associated with lupus, hypertension, and type 2 diabetes presented with acute kidney injury and normal urine output. Because urine test was positive for leukocyte and hematuria, she was treated for urinary tract infection. Kidney imaging revealed urinary tract occupying lesion, with normal sized kidney and loss of corticomedullary differentiation. Magnetic resonance imaging showed cystic lesion on the left flank, measuring 12 × 8.5 × 7.8 cm, irregular bladder with marked thickening and marked dilation of the urinary system associated with significant parenchymal atrophy (Figure 1). Kidney function slightly improves after bladder catheterization and antibiotic treatment. Considering the cystic lesion palliative kidney support was offered due to poor performance status.

Conclusion

The diagnosis of obstruction due to a growing ovarian cyst was unexpected, in a patient with multiple comorbidities, who maintained urinary output and who presented with symptoms of urinary infection.

Unilateral urinary tract obstruction can slowly cause chronic kidney disease, and it is a paramount to include ultrasound in the study of loss of kidney function. Rarely, the underlying cause is gynecological benignities an underdiagnosed entity[2].

Early diagnosis and treatment improve kidney outcomes, however, patients with significant poor prognostic indicators may benefit most from palliative care[3].

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Date of reception: 10-07-2023
Date of acceptance: 15-02-2024
DOI: 10.24875/NEFRO.23000036

Available online: 17-05-2024
Nefro Latinoam. 2024;21:41-42
www.nefrologialatinoamericana.com

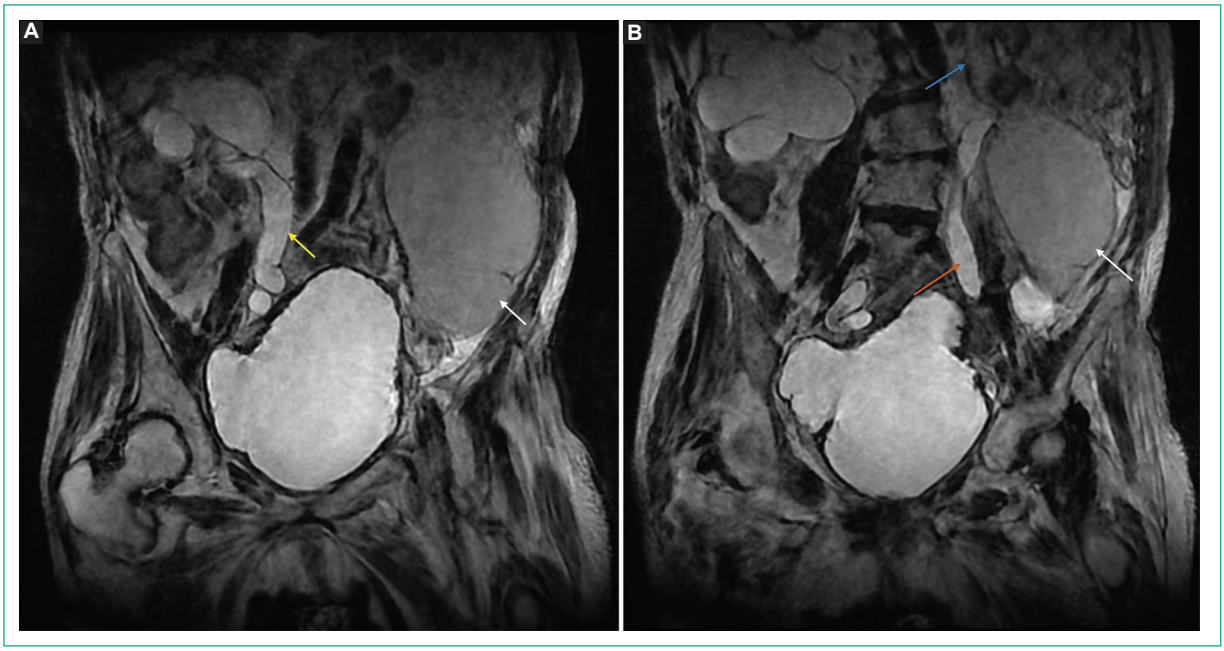

Figure 1. Magnetic resonance imaging, in the coronal plane, demonstrates urinary bladder presenting with diffuse irregular wall thickening, **A:** right hydronephrosis (yellow arrow) and **B:** left hydronephrosis (orange arrow). Bilateral loss of corticomedullary differentiation is markedly enlarged on the left kidney (blue arrow) due to a cystic ovarian lesion (white arrow).

Funding

The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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