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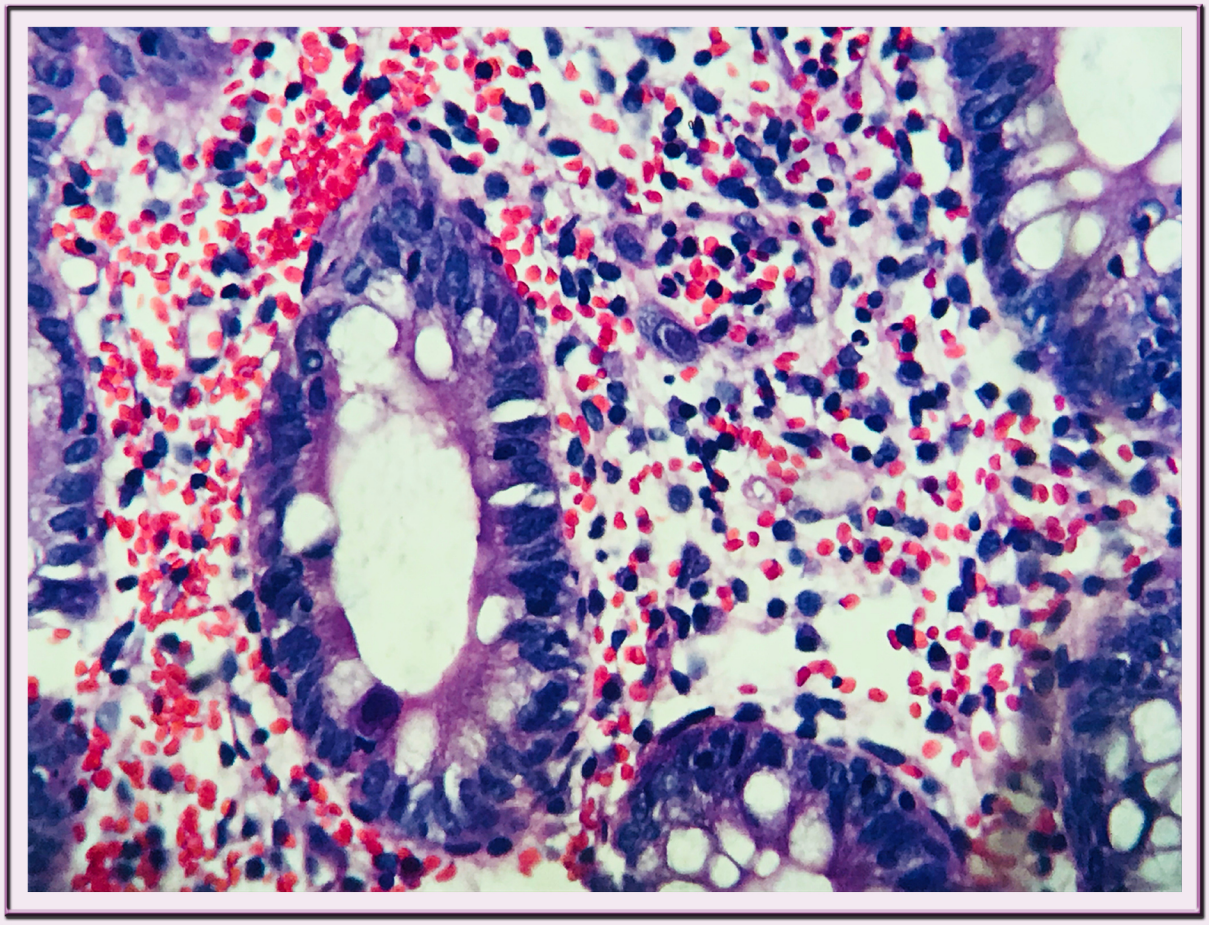

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Contents / Contenido

Original research

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Pulmonary function and ventilatory capacity in hemodialysis patients according to exposure to intra-dialysis physical training

Función pulmonar y capacidad ventilatoria en pacientes hemodializados según exposición a entrenamiento físico intradiálisis

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Abstract

Introduction: The chronic kidney disease (CKD) is an irreversible progressive process which leads to a terminal state, where patients need permanent dialysis or even a transplant. It has been shown that the lung function and ventilatory capacity are compromised in these patients, increasing the alteration with exposure to hemodialysis and sedentarism.

Objective: To compare the lung function and ventilatory capacity of hemodialysis patients, according to exposure to intradialysis physical training.

Material and Methods: Study of quantitative type, not experimental, descriptive and transverse. The study population included 12 ambulatory patients between 40 and 80 years old, undergoing hemodialysis with arteriovenous fistula in the dialysis unit of Valdivia's Central Hospital, and who obtained more than 24 points in the Minimental Test. The statistical analysis was performed with the SPSS program (version 11.5 for Windows) and the level of statistical significance through the Wilcoxon and Mann-Whitney test ($p<0.05$).

Results: The comparison of the initial and final pimometry in patients with and without physical training did not show a statistically significant difference ($p>0.05$), however it was observed that the subjects exposed to physical training have higher values in the initial and final maximum inspiratory pressure compared to those who have not been trained.

Conclusion: Intradialysis physical training causes a positive effect on the respiratory system. The subjects submitted to hemodialysis tend to present under predicted values in both lung function and ventilatory capacity, being mostly affected with aging and time of exposure to hemodialysis.

Keywords: Renal dialysis, renal insufficiency, chronic, exercise therapy, diagnostic techniques, respiratory system.
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Resumen

Introducción: la enfermedad renal crónica es un proceso progresivo e irreversible; con frecuencia lleva a un estado terminal, donde los pacientes necesitan de diálisis o trasplante. Se ha demostrado que la función pulmonar y la capacidad ventilatoria se ven comprometidas en estos pacientes, y se incrementan con la exposición a hemodiálisis y el sedentarismo.

Objetivo: comparar la función pulmonar y la capacidad ventilatoria de pacientes hemodializados, según exposición a entrenamiento físico intradiálisis.

Materiales y métodos: estudio de tipo cuantitativo, no experimental, descriptivo y transversal; la población de estudio comprendió 12 pacientes hemodializados mediante fístula arteriovenosa, entre 40 y 80 años de edad, en la unidad de diálisis del Hospital Base de Valdivia y que obtuvieron más de 24 puntos en el test Minimental. El análisis estadístico se realizó con el programa SPSS (versión 11.5 para Windows) y el nivel de significancia estadística a través de la prueba de Wilcoxon y Mann-Whitney ($p<0,05$).

Resultados: la comparación de la pimometría inicial y final en los pacientes con y sin entrenamiento kinésico no mostró una diferencia estadísticamente significativa ($p>0,05$); sin embargo, se observó que los sujetos sometidos a entrenamiento kinésico presentan mayores valores en la presión inspiratoria máxima inicial y final en comparación con aquellos que no han sido entrenados.

Conclusión: el entrenamiento físico intradiálisis provoca un efecto positivo en el sistema respiratorio. Los sujetos sometidos a hemodiálisis tienden a presentar valores bajo el predicho tanto en función pulmonar como en capacidad ventilatoria, siendo mayormente afectados con el envejecimiento y el tiempo de exposición a hemodiálisis.

Palabras clave: diálisis renal, insuficiencia renal crónica, terapia por ejercicio, técnicas de diagnóstico del sistema respiratorio.

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Introduction

Chronic kidney disease (CKD) is the presence of alterations in kidney structure or function for at least three months and with implications for health.[1] The diagnostic criteria for CKD are the so-called markers of kidney damage or a reduction in glomerular filtration rate (GFR) below 60 ml/min/1.73 m^2. CKD is a harmful and expensive disease, associated with extremely high morbidity and mortality even in the earliest stages.[2] Diabetes is one of the leading causes of CKD worldwide. It has been estimated that it affects around 425 million people in the world, and it has been projected that it will increase to more than 629 million people by the year 2045. More than 40% of people with diabetes develop CKD, including a significant number who develop end-stage CKD, requiring dialysis and transplantation.[3]

In Chile, the number of patients undergoing HD has experienced a growth greater than 30-fold in the last 30 years, reaching until the year 2018 a prevalence of 1264 patients per million inhabitants, which is higher than the Latin American average.[4]

The lungs can be seriously damaged due to CKD; as GFR decreases, pulmonary edema and respiratory muscle dysfunction become more common due to the fluid retention and cardiovascular, metabolic, and endocrine alterations. However, the evaluation of lung function is not a routine clinical practice.[5] Treatment with HD causes a series of consequences in all systems, causing fatigue and muscle weakness as common symptoms in these patients, which ultimately alter their quality of life.[6] From the ventilatory point of view, it has been observed that the values of the maximum inspiratory pressure (MIP) and the maximum expiratory pressure (MEP) in dialyzed patients are lower than those predicted according to age and gender.[7] Some studies have suggested that there is a decrease in the values of forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC), reflecting a deterioration in lung capacity.[7,8] From the point of view of physical therapy, the main interventions performed in these patients are aerobic work and strength/resistance work of the muscles of the lower limbs, which have been shown to improve hemodialysis adequacy, exercise capacity, depression and quality of life mainly.[9]

Given the foregoing, the following research question arises: How is the lung function and ventilatory capacity of hemodialysis patients according to exposure to intradialysis physical training? The general objective of the research is to compare the lung function and the ventilatory capacity of hemodialysis patients according to exposure to intradialysis physical training. On the other hand, the specific objectives are to describe the pulmonary function parameters prior to the hemodialysis session, to analyze the parameters of the inspiratory muscle strength pre- and post-hemodialysis session, and to compare the maximum inspiratory strength pre- and post-hemodialysis session in patients with and without kinesic training.

Therefore, the hypothesis of this research is that hemodialysis patients undergoing intradialysis kinesic training have better lung function and ventilatory capacity than those who have not undergone kinetic training.

Materials and methods

A quantitative, non-experimental, descriptive and cross-sectional study, which compared the lung function and ventilatory capacity of two groups, one made up of hemodialysis patients undergoing intradialysis physical exercise and the other group consisting of hemodialysis patients who have not been subjected to physical exercise. The variables considered were: exposure to physical exercise, lung function and maximum inspiratory pressure.

The collection of the information was carried out through a census, since the size of the study population consisted of a small number of individuals.

The study population included all outpatients between 40 and 80 years of age who underwent HD with arteriovenous fistula (AVF) in the dialysis unit of the *Hospital Base de Valdivia* (HBV); therefore, the census was carried out with 49 patients, 12 of whom

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(7 men and 5 women) were outpatients undergoing a process of HD with AVF for more than 12 months, treated in the dialysis unit of the *Hospital Base de Valdivia* (HBV) and who obtained a score higher than or equal to 24 points in the mental status test «Mini mental state examination». Of the 12 patients, 5 were practicing intradialysis physical exercise.

In addition, patients with a lack of understanding and/or collaboration during the evaluation, with some primary respiratory disorder, and all those who had smoking habits during the last two months were excluded. Through the informed consent, which was signed by the 12 patients, the evaluations to be performed (pimometry and spirometry) were revealed, together with the final objective of the study and its importance for future research. In addition, emphasis was made in that the patient could withdraw when deemed necessary.

Through the review of the clinical record of each patient, the date of admission to the dialysis service and the start of HD treatment with AVF were obtained and, in turn, through an interview, it was established the number of patients subjected to intradialysis physical exercise program, which is conducted by students of the School of Kinesiology of the *Universidad Austral de Chile* (UACh) who develop their clinical practice in the dialysis unit of the HVB, and consists in aerobic exercise performed with a cycle ergometer attached to the dialysis stretcher and exercises of strength/resistance of the lower limbs using free weights or elastic bands.

The different parameters of lung function, either FEV1/FVC, FVC, FEV1 or FEF 25-75%, were obtained through the spirometry assessment based on the protocol of Gutiérrez *et al.*,[10] which was performed by one of the properly trained evaluators. This was carried out during the week, depending on the shift and the schedule of each patient, either on Monday-Wednesday-Friday or on Tuesday-Thursday-Saturday, prior to the HD session. The equipment used for these evaluations was a Datospir Micro C Sibelmed® spirometer.

The ventilatory capacity was determined by the evaluation of the pimometry, based on the technique described by Black and Hyatt.[11] The MIP was assessed before and after hemodialysis by two evaluators; one of them performed the initial pimometry (predialysis) and the other the final pimometry (post-dialysis). For this technique, an aneroid manometer calibrated in cmH_2O (Airlift/Carefore Medical Inc.), an anti-reflux «T» piece, (Nif-Tee®), a nose clip (DHD, USA.), protective filters and reusable mouthpieces with an external diameter of 22 cm (Airlift/Carefore Medical Inc.) were used.

It should be noted that before starting the evaluations considered for this study, the approval of the Research Ethics Committee of the Valdivia Health Service was obtained and the patients received informed consent approved by this entity.

The data analysis was performed through the SPSS (Statistical Package for the Social Sciences) software in its version 11.5 for Windows, summary measures such as mean and standard deviation were determined, and box-and-whisker plots were constructed. The Wilcoxon sign-rank and the Mann-Whitney non-parametric statistical tests were used to establish significant differences. A p-value <0.05 was considered statistically significant.

On the other hand, the spirometric values were compared with the Chilean P5 proposed by Gutiérrez *et al.*,[10] and the pimometry values were compared with the values proposed by Costa *et al.*[12]

Results

The final sample of the study included 12 patients (men 58.3% and women 41.7%) with end-stage CKD belonging to the Dialysis Unit of the *Hospital Base de Valdivia*. Their mean age was 54.2 ± 9.8 and the time of exposure to hemodialysis was 5.0 ± 3.1. 42% of patients were part of an intradialysis exercise program and 58% did not perform any type of exercise.

The pulmonary function parameters (FEV1/FVC, FEV1, FVC, FEF 25-75%) of the patients prior to the HD session are shown in Table 1. There is no

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Table 1. Parameters of pulmonary function prior the HD session.

	FEV1/FVC		FEV1		FVC		FEF 25-75%	
	Obtention	Reference	Obtention	Reference	Obtention	Reference	Obtention	Reference
Men								
40-49	74.18	80.08	2.73	3.82	3.68	4.77	40-49	74.18
50-59	79.50	77.11	2.52	3.10	3.17	4.02	50-59	79.50
60-69	67.61	74.24	1.44	3.17	2.13	4.27	60-69	67.61
70-79	-	-	-	-	-	-	70-79	-
Women								
40-49	73.28	82.82	1.92	2.70	2.62	3.26	40-49	73.28
50-59	87.83	77.52	1.66	2.38	1.89	3.07	50-59	87.83
60-69	-	-	-	-	-	-	60-69	-
70-79	82.35	72.92	1.68	1.75	2.04	2.4	70-79	82.35

FEV1/FVC: Tiffeneau index; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; FEF 25-75%: forced expiratory flow between 25 and 75% of vital capacity. The values correspond to the means.

significant difference (p> 0.05) when comparing both gender and age. However, it is observed that as age increases, the values decrease, this being more noticeable in women. In addition, a trend of obtained values lower than the predicted is evidenced, especially in FEV1 and FVC, except for the value of FEV1/FVC. There was no significant difference (p> 0.05) between the mean of the initial and the final pimometry.

Table 2 shows the mean of the initial and final pimometry of the total of patients evaluated (n = 12). However, the data show a downward trend in the final pimometry.

When comparing the initial and final pimometry values according to age and gender, there was no statistically significant difference (p> 0.05) between the age ranges and gender, as shown in Table 3, but it was observed that women present lower baseline values both in the initial and final pimometry compared to men. In addition, it should be noted that as age increases, these values decrease, this being more noticeable in women.

The comparison of the initial and final pimometry in patients with and without intradialysis physical exercise did not show a statistically significant difference (p> 0.05); However, it was observed that the subjects exposed to exercise had higher values in the initial and final pimometry compared to those who have not done any exercise. Furthermore, there is a greater variation between initial and final MIP in trained versus untrained patients. All of this can be seen in Figure 1.

There are no significant differences (p> 0.05) when comparing the average of the values obtained

Table 2. Analysis of initial and final pimometry.

	n	Mean	SD	Maximum	Minimum
Initial MIP	12	71.75	39.162	24	160
Final MIP	12	68.67	33.277	16	130

MIP: maximum inspiratory pressure. SD: standard deviation. There is no statistically significant difference (p> 0.05) between the means of the initial and final pimometry.

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Table 3. Analysis of initial and final pimometry according to age and gender.

Age	MIP	MIP
	Initial value	Final value
	Men	Men
40-49	>120	>120
50-59	89.25 ± 22.91	89.25 ± 4.79
60-69	70.50 ± 21.92	73.50 ± 10.61
70-79	-	-
	Women	Women
40-49	56.50 ± 0.71	60 ± 7.07
50-59	31 ± 9.90	19 ± 4.24
60-69	-	-
70-79	28	32

MIP: maximum inspiratory pressure. The values correspond to the means ± SD. There is no statistically significant difference (p>0.05) between age ranges and gender.

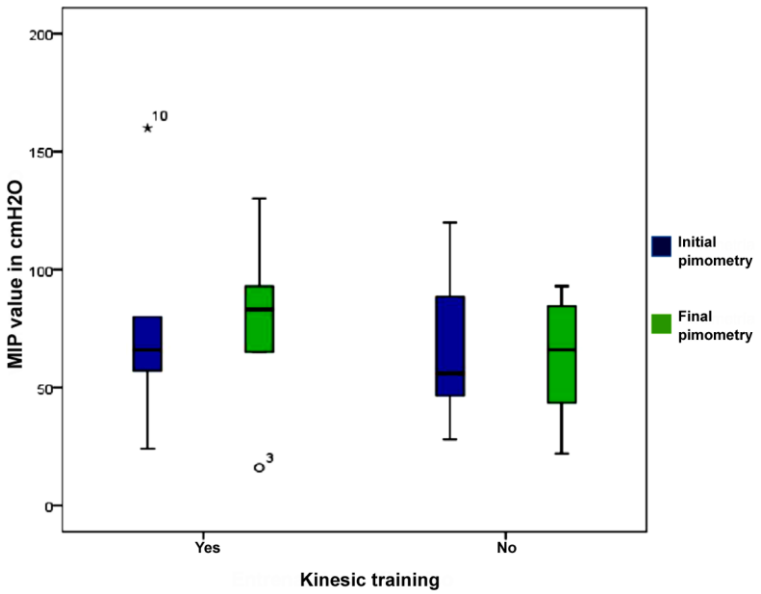

Figure 1. Comparison of initial and final pimometry in patients with and without kinesic training.

for FEV1, FVC, FEV1/FVC and FEF 25-75% between the trained and untrained subjects (Table 4). However, it was observed that the trained subjects showed better values than those untrained (with the exception of FEV1/FVC).

The subjects who performed physical exercise had values of FEV1 higher than those who had not been trained (Figure 2), as well as the values of FEF 25-75% that are shown in Figure 3.

Discussion

According to the results obtained in the study, patients undergoing hemodialysis show lower values

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Table 4. Comparison of the lung function prior to HD session in trained and untrained patients.

Variable	Kinesic training	Mean	Standard deviation	Minimum	Maximum	*p* Value
FEV1	Yes	2.306	0.518	1.57	2.73	0.222
	No	1.865	0.472	1.35	2.81	
FVC	Yes	2.996	0.714	1.81	3.68	0.222
	No	2.382	0.552	1.97	3.53	
FEV1/FVC	Yes	77.7	7.814	66.45	87.05	0.755
	No	78.322	8.261	67.11	88.45	
FEF 25-75%	Yes	2.13	0.585	1.18	2.75	0.372
75%	No	1.788	0.687	0.83	2.54	

FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; FEV1/FVC: Tiffeneau index; FEF 25-75%: forced expiratory flow between 25 and 75% of vital capacity. A *p*-value <0.05 is considered statistically significant.

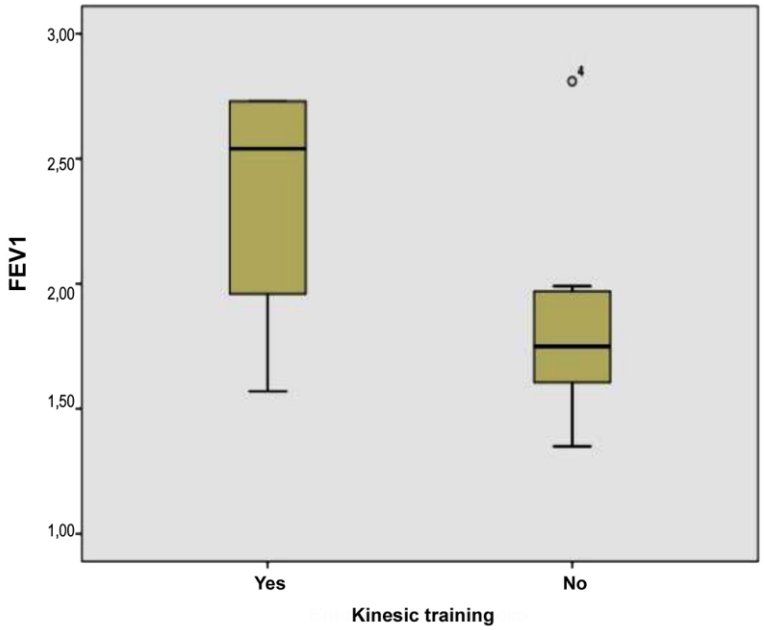

Figure 2. Comparison of mean FEV1 values between trained and untrained subjects.

in the spirometry parameters (FEV1, FVC, FEF 25-75%), except in FEV1/FVC, compared with the reference values of the Chilean population, according to Gutiérrez *et al.*[10] (Table 1). Similar results have been reported in a study carried out in 20 patients with CKD, where it is clearly reflected that the main spirometric parameters, except FEV1/FVC, are under the predictive value[13]; likewise, this is corroborated by a research carried out by Mukai *et al.*, where it was evidenced that the 404 patients with chronic kidney disease who were evaluated showed lung function outcomes under the reference values: the lower the GFR, the greater the respiratory dysfunction.[5]

In the present study, when a comparison of the spirometry parameters between both genders was made, it was observed that women had lower values

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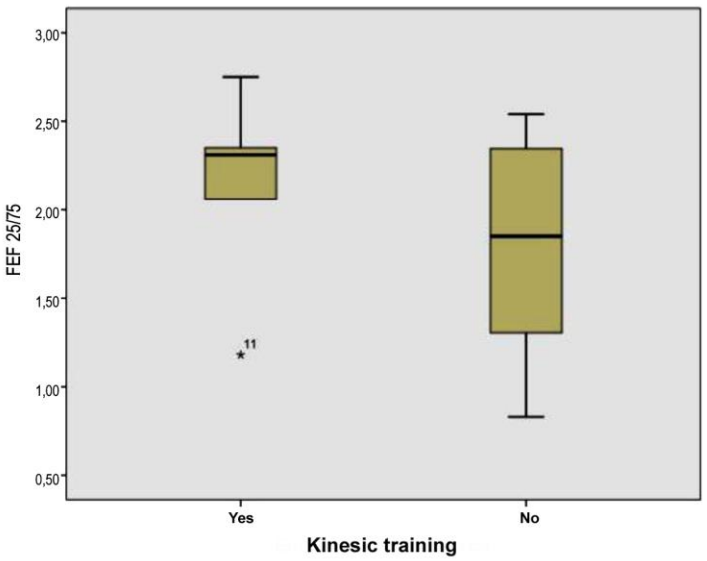

Figure 3. Comparison of mean FEF 25-75% values between trained and untrained subjects.

compared to men, which is consistent with the study conducted by Rojas and Denis, who described the baseline spirometry parameters according to sex and found that women had lower values[14]; this is explained by the study conducted by LoMauro and Aliverti, who argue that the height, more than the gender, is the main differential factor of the functional implications described.[15] On the other hand, it could be observed that at an older age, the values of the spirometry parameters decrease, which is consistent with the study conducted by Yilmaz *et al*.; this may be mainly due to the changes that occur in the respiratory system as a result of the aging process.[16] A study concluded that the level of alteration of FVC, FEV1 and FEF 25/75 in dialysis patients is due to a set of factors, including aging, inflammation, nutritional status, edema and the presence of associated comorbidities.[17] In addition, it should be noted that the decrease in the values of spirometric parameters may be mainly due to exposure to HD; this is explained by what is proposed by Palamidas *et al*., who indicate that this exposure reflects an alteration in the smaller airways and poor distribution of ventilation.[18]

On the other hand, given the FEV1/FVC values and when a comparison with the reference spirometric values at the lower limit of normality (P5) was made, the evaluated patients showed a tendency to restrictive disorders, which is corroborated by the study conducted by Sharma *et al*.[17] Some authors propose that these disorders are directly associated with circulating uremic toxins, or indirectly with fluid overload, anemia, immunosuppression, extraosseous calcification, malnutrition, electrolyte disorders and acid-base imbalances.[16]

On the other hand, when the difference between the mean of the initial and final MIPs was analyzed, a decrease in these values was observed after the HD; however, there is no significant difference between the means. These results are not consistent with those obtained by Palamidas *et al*. and Tavana *et al*., who obtained values under the predicted pre-HD and tending to increase post-HD.[18,19]

These results are similar to those published by Karacan *et al*., where lower MIP values were found after a HD session; the authors explain that this is due to the catabolic effects of HD, which also leads to carnitine depletion due to loss through the dialysis membranes, causing muscle symptoms and altered exercise capacity.[20]

In turn, when the variation of the MIP values according to the age range was analyzed, it was observed that in some groups there was an increase

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in the MIP at the end of the HD, which can be attributed to the fact that there were subjects who obtained values very far from the mean, which alters the average by age range. The increase in the MIP after HD coincides with the results published by Rocha and Araujo, where an increase in MIP was observed after a HD session, mainly in those patients who initially showed lower MIP values (less than 60 cm H_2O), as in the study conducted by Palamidas *et al*., where the MIP values tend clearly upwards after the HD; the authors associate this with the unloading of the respiratory muscles and consequent improvement in the mechanics of the thorax.[18,21] On the other hand, the increase in MIP values post HD could have been influenced by the learning process of the test, since both evaluations were carried out on the same day, and it can be attributed to a better understanding of the evaluation by the patient on the second time. Another factor that could have affected the result is the interevaluator variability, since the initial and final pimometries were performed by different evaluators, which can be considered as a bias of the test.

Furthermore, it was observed in the study that the subjects who had been exposed to physical exercise had higher values in the initial and final pimometry compared to those who had not received any exercise; although it was not a significant result ($p>0.05$), there was a trend, and this is consistent with a study in which the effects of inspiratory muscle training on inspiratory muscle strength, lung function and functional capacity in CKD patients undergoing HD were evaluated and where there was also an increase in the distance covered in the 6-minute walk test; therefore, aerobic exercise can be correlated with inspiratory muscle strength.[22] It should be noted that the muscles involved in inspiration, such as the diaphragm and the intercostal muscles, are classified as skeletal muscles and there m'ay be a decrease in muscle mass, strength and endurance due to the so-called uremic sarcopenia,[23] so it can be inferred that a lack of both muscular and aerobic training leads to a lower result in the MIP, compared to those subjects who undergo constant exercise.

At the lung function level, the parameters evaluated (FEV1, FVC, FEV1/FVC and FEF 25/75) show a clear trend, where better values are observed in those subjects who are exposed to kinesic training, with the exception of FEV1/FVC, where the untrained subjects showed on average slightly higher values, which can be attributed to a value being above the mean of the group. Even though there is no statistically significant difference, a clinically significant difference can be established.

The group of patients exposed to intradialysis physical exercise showed higher FEV1 values, which is consistent with what was proposed by Fatima *et al*., where a group of healthy patients subjected to aerobic training showed better values compared with the group without training; and the FVC and FEV1/FVC values also improved.[24]

On the other hand, in the study published by Silva *et al*., an increase in FEV1 values was also observed after a training program for subjects with CKD; however, this training focused specifically on the inspiratory muscles, which suggests to carry out a work focused on improving the performance of the ventilatory muscles.[22] Aerobic training has a positive effect on inspiratory muscles, but aerobic training combined with inspiratory training is suggested in order to achieve better results.[25]

Among the limitations of the study is the low number of patients, which was mainly due to the inclusion and exclusion criteria; on the other hand, many patients refused to participate and others dropped out during the evaluations. One of the biases that cannot be ruled out is the existence of a learning process for the evaluations, which might have influenced the results.

It should be highlighted that although there was no statistically significant difference, a clinically significant difference could be confirmed.

Conclusions

Patients undergoing the hemodialysis process have a lung function and ventilatory capacity under predictive values. Those patients who have exercised or who are in an intradialysis exercise

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program, either aerobic, strengthening or combined, present better spirometric and pimometric values than those who have not carried out any type of exercise.

It is necessary to carry out intradialysis training programs that not only include aerobic work and limb muscle strengthening exercises, but that also include ventilatory work, to know if the inclusion of the latter improves even more the respiratory and cardio-respiratory parameters of these patients.

Acknowledgments

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Conflict of interest and funding

The authors declare that there is no conflict of interest. The present study was partially funded by the School of Kinesiology of the *Universidad Austral de Chile* (Austral University of Chile).

Ethical responsibilities

Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

Data confidentiality

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

Right of privacy and informed consent

The authors declare that patient data do not appear in this article

Contribution of the authors

This research is original and unpublished. All authors have contributed significantly to the present study from the conception to the submission of the manuscript.

Paula Moscoso was the manager of the research idea, constant guide of the study, literature reviewer and organizer of the manuscript to be submitted to this scientific journal; Yessica Aliante, Nayareth Becerra and Keren Quezada were the evaluators of the hemodialysis patients, literature reviewers, and writers of the initial article. Luis Ojeda was the constant statistical advisor of the study.

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Original research

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Effectiveness of a cardiorespiratory, muscular and ventilatory training program in the aerobic performance of hemodialysis patients

Efectividad de un entrenamiento cardiorrespiratorio, muscular y ventilatorio en el rendimiento aeróbico de pacientes hemodializados

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Abstract

Introduction: End stage kidney disease causes fatigue and progressive muscle weakness, which affects not only the muscles of the extremities, but also the respiratory. There are several studies of combined training in dialysis patients, but not including respiratory work. Therefore, the present study aims to determine the effectiveness of an aerobic, lower limb resistance and inspiratory muscle resistance combined training in the generation of changes in aerobic performance of patients undergoing hemodialysis.

Material and methods: Randomized controlled trial which included 11 hemodialysis patients from Valdivia's Central Hospital. The sample was divided into two groups, the first one included: an aerobic, lower limbs and inspiratory muscle training (ARM+V) (n=6) and the second one included an aerobic and lower limbs muscle training (ARM) (n=5). The training was performed during 8 weeks and three variables were measured in both groups pre and post intervention, inspiratory muscle strength (Carefore Airlift NIF-gauge ®), aerobic endurance (6MWT) and pulmonary function (Sibelmed Datospir Micro Spirometer 120D ®).

Results: ARM+V group obtained significant improvements ($p<0.05$) in 6MWT performance ($p=0.027$) and MIP ($p=0,001$). Likewise, performance improved in 6MWT ($p=0.022$) and MIP ($p=0.002$) at ARM group, but decreased in spirometry values: FEV1 ($p=0.004$), FVC ($p=0.005$) and FEV1/FVC ($p=0,038$).

Conclusion: Both training protocols were effective in the aerobic endurance improvement, however the patients in the ARM+V group presented better changes than the ARM group. Neither of the two training programs improved pulmonary function.

Key words: Renal dialysis, exercise therapy, respiratory muscles.

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Resumen

Introducción: la enfermedad renal crónica terminal provoca fatiga y debilidad muscular progresiva, que afecta no solo la musculatura de extremidades, sino también la respiratoria. Existen diversos estudios de entrenamiento combinado en pacientes dializados, pero sin incluir trabajo respiratorio. Por esto, el presente estudio pretende determinar la efectividad de un entrenamiento combinado aeróbico, de resistencia de miembro inferior y de resistencia muscular inspiratoria, en el rendimiento aeróbico de pacientes hemodializados.

Materiales y métodos: ensayo clínico aleatorizado que incluyó 11 pacientes hemodializados del Hospital Base Valdivia. Fueron divididos en dos grupos, uno sometido a un programa de entrenamiento con ejercicio aeróbico, de resistencia muscular de miembros inferiores y de musculatura inspiratoria (ARM+V) (n=6), y el otro, a un programa de entrenamiento con ejercicio aeróbico y de resistencia muscular de miembros inferiores (ARM) (n=5). La intervención fue realizada durante 8 semanas evaluando el rendimiento pre y post intervención de capacidad aeróbica (TM6M), fuerza inspiratoria máxima (Carefore Airlift NIF-gauge®) y función pulmonar (Sibelmed Datospir Micro Spirometer 120D®) en ambos grupos.

Resultados: el grupo ARM+V obtuvo mejoras significativas ($p<0,05$) en el rendimiento del TM6M ($p=0,027$) y PIM ($p=0,001$); así mismo el grupo ARM mejoró en el TM6M ($p=0,022$) y PIM ($p=0,002$) y en la espirometría se mostró una disminución significativa en VEF1 ($p=0,004$), CVF ($p=0,005$) y VEF1/CVF ($p=0,038$).

Conclusión: ambos entrenamientos fueron efectivos en la mejora del rendimiento aeróbico, pero el grupo ARM+V obtuvo mejoras significativamente superiores en este ítem. Ninguno de los dos entrenamientos obtuvo mejoras en los valores espirométricos.

Palabras clave: diálisis renal, terapia por ejercicio, músculos respiratorios.

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Introduction

Chronic kidney disease (CKD) is a general term for heterogeneous disorders that affect the kidney structure and function.[1] The CKD has different stages, of which stage 5 corresponds to the progressive and permanent loss of kidney function, where the only treatment available is exposure to hemodialysis (HD) or finally, kidney transplantation.[2] It is currently a serious public health problem, since only in Chile in the year 2017, HD reached a prevalence of 1208 people per million.[3]

HD treatment causes a series of consequences in all systems, of which the most affected are the cardiovascular and musculoskeletal, causing fatigue and muscle weakness[4]; this subsequently leads to a progressive loss of muscle mass.[5]

These are reasons that give importance to physical exercise in this type of patients, for whom intradialysis physical training programs which use aerobic and resistance exercises of the lower limbs (LL)[4,6,7]; in this way, positive results are obtained, which are reflected not only in the increase in the aerobic capacity and muscle strength in these patients, but also in the improvement of the effectiveness of HD and a significant decrease in the level of disability.[6]

On the other hand, the respiratory system is highly affected in these patients, since degenerative muscle changes occur by the decrease of contractile tissue due to uremic toxins, leading to a decreased strength of the ventilatory muscles.[8,9] This also brings consequences in the decrease of the forced expiratory volume in the first second (FEV1) and the forced vital capacity (FVC) values, reflecting a deterioration in the lung capacity of patients undergoing HD.[10]

In 2010, Silva *et al*.[11] carried out a protocol of ventilatory muscle strength exercises in patients under HD treatment, using an inspiratory threshold valve. After 8 weeks of training, a statistically significant improvement ($p<0.05$) in the aerobic capacity and in the maximum inspiratory pressure (MIP) was observed in the experimental group. This study proves the relationship between ventilatory training and aerobic capacity; however, there are no protocols that demonstrate whether the ventilatory work combined with an aerobic and/or LL resistance training has better results in the increase of the aerobic capacity in hemodialysis patients.

This is why the main objective of the present study is to determine the effectiveness of an aerobic, lower limb resistance and inspiratory muscle resistance training in generating changes in the aerobic performance of patients undergoing hemodialysis; and the hypothesis generated is that a training that combines aerobic, lower limb resistance exercise, and that also includes inspiratory muscular resistance training, is more effective in generating changes in aerobic performance in hemodialysis patients.

Materials and methods

Study design and population

The design of the present study is experimental, corresponding to a randomized clinical trial. We worked for 8 weeks with patients undergoing HD in the dialysis unit of the Hospital Base de Valdivia from October 2015 to February 2016, belonging to the three shifts of Mondays, Wednesdays and Fridays, and to the second and third shifts of Tuesdays, Thursdays and Saturdays.

Outpatients undergoing HD via arteriovenous fistula (AVF) with a treatment longer than three months and with a result equal to or higher than 24 points in the Mini-Mental Test were included. The exclusion criteria included the use of antihypertensive drugs in the hour preceding the HD, suffering from diabetes and uncontrolled hypertension, mental confusion, lower limb amputation, acute cardiac syndrome, isolated patients, patients with an acute lung disease, and presenting class III or IV angina. Of the total population of 118 patients, 21 met the selection criteria; 15 of them agreed to be part of the study. Of the latter, 4 were excluded for the following causes: problems with the arteriovenous fistula, patients under cardiac study and presence

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of pulmonary edema. Given the above, the final sample included 11 patients (6 women and 5 men).

The 11 patients studied were randomly divided into two groups. Using a tombola, one person outside the study chose numbers from 1 to 11 corresponding to each patient and divided them interspersed in each group; one group (n=6) was assigned to an aerobic exercise training, of LL muscles resistance and inspiratory muscle training (ARM+V); and only aerobic exercises and of LL muscle resistance (ARM) were assigned to the other group (n=5). All the participants, both those in the ARM + V group and those in the ARM group, were blinded to the group assignment, since they were in different rooms and did not know what the intervention of the group was about. The evaluators and the treating team were not blinded, since they were the same researchers of the study who knew in advance the nature of each group.

Measurement of variables

Measurements were made in the two groups both at the beginning and at the end of the eight weeks of intervention. The measured parameters included aerobic capacity, pulmonary function and inspiratory muscle strength.

The aerobic capacity was determined by the distant covered in the six minute walking test (6MWT) which was obtained by counting the number of laps fully covered plus the final meters where the patient stopped at the end of the 6 minutes.[12] The test was carried out using the protocol and recommendations of the ATS.[13]

The lung function was measured with the spirometry test, using a Datospir Micro® Sibelmed spirometer. The forced expiratory volume in one second (FEV1), Tyffenau index (FEV1/FVC) and forced vital capacity (FVC) values were measured. This evaluation was conducted according to the protocol of the Chilean Society of Respiratory Diseases.[14]

Ventilatory muscle strength was determined by evaluating the maximum inspiratory pressure (MIP), based on the pimometry technique described by Black and Hyatt.[15] A Carefore Airlift® aneroid manometer, calibrated in cmH2O, was used for this technique.

Exercise protocol

The patients were trained with a frequency of three times per week divided into Monday, Wednesday and Friday, and Tuesday, Thursday and Saturday. The trainings were conducted during the first two hours of HD to avoid any adverse effect. It was applied an 8-week training program in which the ARM+V group performed aerobic, LL muscle resistance and inspiratory muscle resistance exercises, while the ARM group only performed aerobic and LL muscle resistance exercises. Each session lasted 45 to 60 minutes. The eleven patients worked uninterruptedly for the eight weeks; only the assigned protocol was applied to each group.

Aerobic training protocol

The training consisted in performing exercises, during 25 to 30 minutes for both groups, in a static pedal, involving only the lower limbs; the work intensity (pedal load) was measured and controlled through the heart rate reserve (HRR). They worked at moderate intensities between 40 and 60% of the HHR (calculated with the formula proposed by Karvonen). In addition, the parameters were controlled to monitor the condition of the patients and their perception of effort associated with exercise during the beginning, the middle and the end of training. These parameters were HHR, oxygen saturation, blood pressure and the subjective sensation of effort; the latter was measured using the modified Borg scale.[16,17]

Lower limb strength training protocol

Isotonic exercises were performed using free weights, with a duration of 10 to 15 minutes per session for both groups. These exercises consisted in knee extensions from 90 to 0°, where the weight was located at the distal end of the leg segment, allowing full movement of the involved joint.[7] The amount of weight used and the subsequent

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progression were established according to the motor performance of each patient and the perception of effort in relation to the LL strength, measured by the OMNI-RES scale.

Inspiratory muscle training protocol

The ventilatory training protocol was applied only to the ARM+V group and consisted in inspiratory muscle resistance work. This training was performed using a Phillips Respironics® Threshold IMT loading valve; the patient was sitting and with the valve regulated at 40% of the MIP[11]; he exercise consisted in inspiratory maneuvers applied in series of five repetitions with one minute of rest between them, with a total duration of 15 minutes. Progression was made one month after starting training, when the MIP was evaluated again in order to continue maintaining the ventilatory work at 40% of the MIP.

Data analysis

For the statistical analysis, specialized tests were used in small samples to disprove the null hypothesis (Ho). The normality of the variables was determined using the ShapiroWilk test, so that the variables with normal distribution were expressed as mean ± standard deviation. The t test for related samples was used to establish significant differences between initial and final data. The SPSS software (Statistical Package for Social Sciences) version 20.0 for Windows was used for data analysis. A p-value <0.05 was considered statistically significant.

Ethical responsibilities

The present study was approved by the ethics committee of the Valdivia Health Service and was carried out under the ethical standards of the World Medical Association and the Declaration of Helsinki.

The confidentiality of the data of the people intervened was maintained and under no circumstances names, initials or numbers of clinical records have been used to identify the patients of this trial.

Furthermore, prior to any evaluation and/or intervention, written informed consent was obtained from all participating patients and/or subjects referred to in the article.

Results

The final sample of the study included 11 patients with CKD belonging to the Dialysis Unit of the Hospital Base de Valdivia (women 54.5% and men 45.5%, with an average age of 50.8 ± 18.3 years) who were under HD treatment three times per week for 35.7 ± 32.7 months. The patients were divided into two groups, where six made up the group with aerobic, LL resistance and ventilatory training (ARMV), while five belonged to the group with aerobic and LL resistance training (ARM). Table 1 shows the characteristics of each group. The evolution in the performance of the 6MWT pre- and post-intervention of both groups is reflected in Table 2.

There are significant changes ($p<0.05$) between the averages of the final and initial results both in the patients belonging to the ARM ($p=0.022$) and in those of the ARM+V group ($p=0.027$); however, the patients belonging to the ARM+V group achieved significantly higher deltas ($p=0.024$) regarding the meters covered pre- and post-intervention than those of the ARM group (Figure 1).

The changes in the initial and final pimometry for both groups are shown in Table 3, where we can see that in both groups the pre and post-intervention evolution deltas were statistically significant ($p <0.05$).

Although the differences in the cmH2O obtained pre- and post-intervention of the ARM+V group were significantly greater ($p=0.01$) than those of the ARM group (Figure 2).

As for the results of the spirometric values reflected in Table 4, statistically significant values were found in the ARM ($p<0.05$) for the FEV1, FVC and FEV1/FVC functions, where there was a decrease in their post-intervention values. On the other hand, in the ARM+V group no significant differences were found ($p> 0.05$) for any of the pulmonary function parameters, despite the fact that

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Table 1. Characteristics of the population.

	Characteristics of the sample	
	ARM (n=5)	
Age (years)*	51.6 ± 22.39	**Age (years)***
Number of women (%)	4 (80%)	**Number of women (%)**
Number of men (%)	1 (20%)	**Number of men (%)**
HD time (months)*	31.8 ± 33.8	**HD time (months)***
Diabetes *mellitus*	4 (80%)	**Diabetes *mellitus***
Weight (kg)*	82.4±8.5	**Weight (kg)***
Height (cm)*	157.2±5.4	**Height (cm)***
Arterial hypertension	2(40%)	**Arterial hypertension**

HD: Hemodialysis, *data shown as mean ± standard deviation. ARM: aerobic and LL resistance training. ARM+V: aerobic, LL resistance and inspiratory muscle training.

Table 2. Pre- and post-intervention 6MWT results.

	Pre-intervention	Post-intervention	p*	Control delta-experimental delta**
ARM (n=5)	412.6 ± 143.94	434 ± 182.29	0.022	0.024

The variables are shown in meters as mean ± standard deviation; *paired T test for normal distribution of samples.
**T test for independent samples. Statistically significant test when p<0.05. ARM: aerobic and LL resistance training. ARM+V: aerobic, LL resistance and inspiratory muscle training.

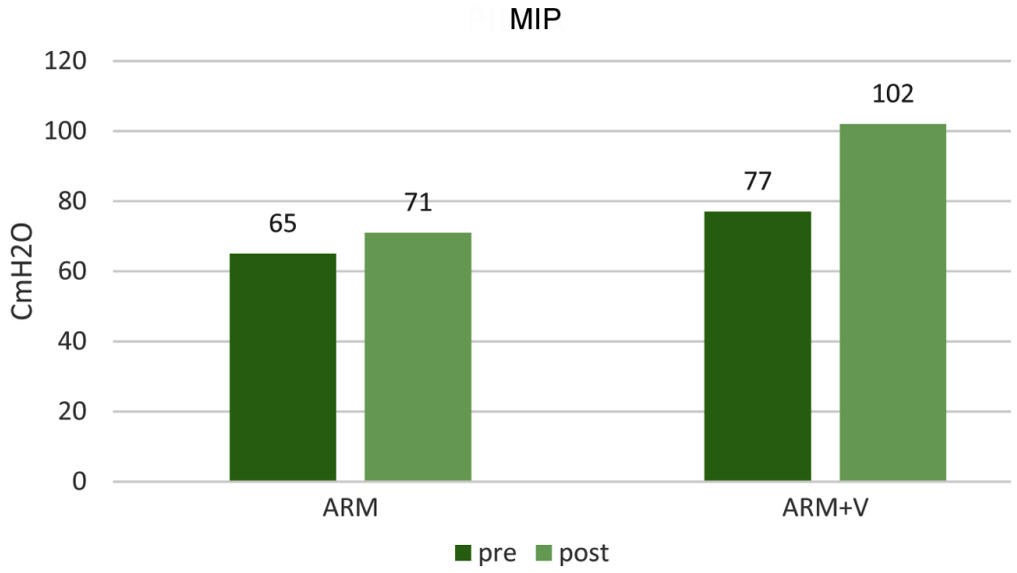

Figure 1. Comparison of the mean number of meters covered in 6MWT post- and pre-intervention between the ARM group and the ARM+V group. * Delta ARM group: 22 m. ** Delta ARM+V group; 130 m. ARM: aerobic and LL resistance training. ARM+V: aerobic, LL resistance and inspiratory muscle training.

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Table 3. Results of MIP pre- and post-intervention.

	Pre-intervention	Post-intervention	p*	Control delta-experimental delta**
ARM (n=5)	65 ± 22.36	71 ± 20.54	0.002	0.001
ARM +V(n=6)	77.5 ± 12.9	102.5 ± 11.02	0.001	

The variables are shown in cm H2O as mean ± standard deviation; * Paired t test for normal distribution of samples. ** T test for independent samples. Statistically significant test when p<0.05. ARM: aerobic and LL resistance training. ARM+V: aerobic, LL resistance and inspiratory muscle training.

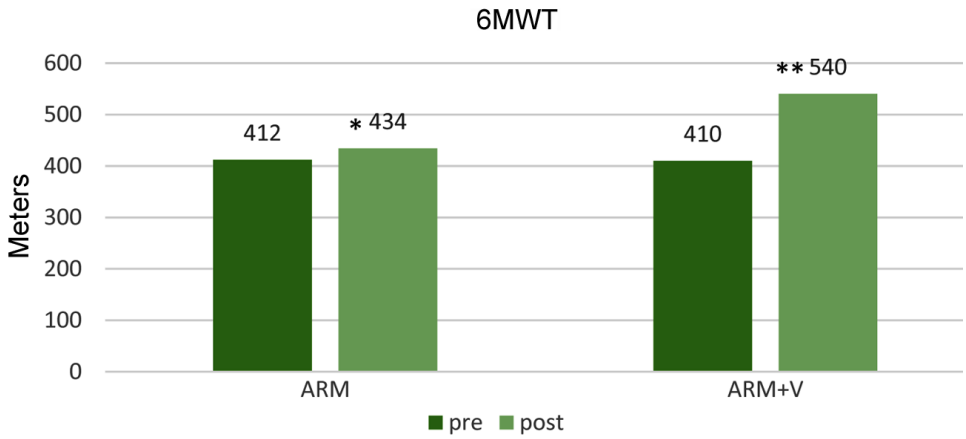

Figure 2. Comparison of the average of cmH O obtained in the post- and pre-intervention MIP between the ARM and ARM+V groups. * Delta ARM group: 8 cmH O. ** Delta ARM+V group: 25 cm. ARM: aerobic and LL resistance training. ARM+V: aerobic, LL resistance and inspiratory muscle training.

Table 4. Results of spirometry values pre- and post-intervention.

	Group	Pre-intervention	Post-intervention	p-value*
FEV1 (L)	ARM	1,97 ± 0.38	1.86 ± 0.46	0.004
	ARM+V	2.42 ± 0.54	2.40 ± 0.97	0.116
FVC (L)	ARM	2.19 ± 0.43	2.22 ± 0.49	0.005
	ARM+V	3.04 ± 0.72	3.12 ± 0.80	0.062
FEV1/FVC (%)	ARM	87.84 ± 3.57	83.53 ± 7.06	0.038
	ARM+V	79.82 ± 5.35	79.03 ± 3.66	0.396

The variables are shown as mean ± standard deviation. *Paired T test for normal distribution of samples. Statistically significant test when p<0.05. FEV1: forced expiratory volume in one second; FVC: forced vital capacity; FEV1/CVF (%): Tiffeneau index. ARM: aerobic and LL resistance training. ARM+V: aerobic, LL resistance and inspiratory muscle training.

the values of all these variables were maintained or increased.

The variables are shown as mean ± standard deviation. *Paired T test for normal distribution of samples. Statistically significant test when p <0.05. FEV1: forced expiratory volume in one second; FVC: forced vital capacity; FEV1/FVC (%): Tiffeneau index. ARM: aerobic and LL resistance training. ARM+V: aerobic, LL resistance and inspiratory muscle training.

Discussion

The eight-week training in hemodialysis patients was effective in generating changes in aerobic capacity (6MWT), both in the group that maintained an aerobic and LL resistance training (ARM), and in the group that had an aerobic, LL muscle resistance and ventilatory resistance (ARM+V) training. Nevertheless, this improvement is significantly greater in the group with ventilatory training that obtained an increase of 31.7% in meters covered in the 6MWT compared with 5.2% in the group without ventilatory training.

This increase of 32% in the performance obtained in the 6MWT in the ARM+V group, compared with the 5% of the ARM group, is not related to the learning effect, because the test was applied to each subject only once during the beginning and the end, since the learning effect has been demonstrated mainly in repeated measurements at more than three consecutive times.[13]

The results obtained in our study in the 6MWT performance were higher than those of Oliveros *et al*.,[7] who implemented an aerobic and lower-limb resistance training in 15 patients on HD treatment for 16 weeks, resulting in an improvement of 5.7% in the performance of the 6MWT; despite our intervention lasted 8 weeks and the group with ARM training had similar results, the group with ARM+V training obtained a notably greater increase in the meters covered in the 6MWT. On the other hand, the results of the ARM+V training are higher than those presented by Silva et al.,[11] in which 15 hemodialysis patients performed an intradialysis inspiratory muscle training for 8 weeks, increasing by 22% the distance covered in the 6MWT; this difference alludes to the fact that ventilatory training combined with aerobic and muscular resistance training is more effective than ventilatory training alone.

Most of the interventions of the studies were carried out during 12 weeks,[18-20] but it has been demonstrated that during 8 weeks of intervention a significant difference is achieved in terms of the meters covered in the 6MWT,[7] as shown in our study, where a training program of only eight weeks was sufficient to induce a clinically significant improvement, since according to Puhan *et al*.[21] a difference of 25 to 35 meters in the performance of the 6MWT already generates functional improvements in the patients. It should be noted that studies that positively associate the performance of exercise with the quality of life in patients undergoing HD have been conducted,[22,23] in such a way that physical inactivity in hemodialysis patients has been associated with an increase in their mortality[24]; hence the importance of physical training in these patients, even more so when its simplicity and adherence make it feasible in any environment in which patients undergo dialysis sessions.[25]

In the present study, lung function did not show statistically significant differences when comparing the values of spirometries performed before training with those performed after 8 weeks of training for the ARM+V group, which is probably due to the fact that the threshold loading valve is aimed at improving inspiratory force and not lung volumes or capacities[11]; however, this training indeed contributed to the fact that at the end of the training they maintained the values obtained in the initial spirometries and did not have a significant loss of the parameters, as happened in the case of the ARM group which obtained a loss of 5.5% in the FEV1, of 1.3% in the FVC and of 4.31% in the FEV1/FVC.

As for pimometry, there were significant changes in both groups; however, the greatest increase was in the ARM+V group with 32.2%. This increase has not been previously found in studies carried out in

hemodialysis patients, as in the case of Silva *et al*.,[12] where no significant changes were found in the final values of pimometries after eight weeks of training at 40% of the MIP three times per week. On the other hand, the ARM group achieved an increase of 9.2%. Although this percentage is much lower than that of the ARM+V group, it is a statistically significant increase and responds to the fact that although this group did not train said musculature, the muscles involved in inspiration are skeletal muscles and, therefore, can generate a decrease in the muscle strength and endurance due to the uremic myopathy[26]; that is why aerobic and muscle resistance exercises during dialysis have been shown to increase blood flow in the muscle, which dynamizes the flow of urea and toxins from the tissues to the vascular compartment, also favoring the ventilatory muscles,[6] so it can be inferred that both muscle resistance and aerobic training led to a better result in the MIP values; however, it was proven in this study that these values in pimometry are higher in those patients who perform training with the threshold load valve.

Conclusions

The combined modality of intradialysis training with aerobic, LL and inspiratory muscle resistance exercises, proved to be more effective than training without ventilatory muscles resistance exercises, since there was a greater increase in the meters covered in the 6MWT, an increase in the maximum inspiratory strength, and the spirometric values of the hemodialysis patients were also maintained. This suggests that inspiratory muscle strength contributes to exercise tolerance and functional capacity.

The study has some limitations such as the small study sample, which was mainly due to the inclusion and exclusion criteria, the health status of these patients and the refusal to participate. One of the biases found in the study is the interruption of training due to patient safety criteria, since a drop in blood pressure is very common and therefore the training could not be fully completed during the sessions.

It is necessary to conduct studies with a larger population, also including a variable of quality of life or level of disability, in order to better determine the effectiveness of each of the programs established for the different groups.

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The authors declare that no experiments were performed on human beings or animals for this research.

Data confidentiality

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

Right of privacy and informed consent

The authors declare that patient data do not appear in this article.

Contribution of the authors

This research is original and unpublished. All authors have contributed significantly to the present study from conception to submission of the manuscript.

Paula Moscoso was the manager of the research idea, constant guide of the study, literature reviewer and organizer of the manuscript to be submitted to this scientific journal; Cathalina Arismendi, Rocío Bahamondes and Rosa Soto were the trainers of the hemodialysis patients, literature reviewers, and writers of the initial article. Luis Ojeda was the constant statistical study advisor.

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Original research

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Personality profile of kidney transplant patients: the alternative five factor model

Perfil de personalidad en pacientes con trasplante renal: el modelo alternativo de los cinco factores

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Abstract

Background: There is limited research on personality traits that characterizes kidney transplant patients. The aim of this study was to describe the personality profile of kidney transplant patients using the Alternative Five Factor Model (AFFM), and compare it with the Spanish standard population.

Method: Personality was assessed using the Zuckerman-Kuhlman Personality Questionnaire (ZKPQ). A sample of 207 kidney transplant patients was matched by age and gender with 207 standard range controls. A logistic regression analysis was utilized to study the contribution of each ZKPQ dimension to describe the distinctive transplant patient's profile.

Results: Significant differences were showed in Neuroticism-Anxiety (p=.001), Aggression-Hostility (p=.009), and Activity (p=.001) dimensions, with lower scores in transplant patients compared with the standard population. But Sociability (p=.024) was significantly higher in kidney transplant patients. In logistic regression analysis low scores on Neuroticism-Anxiety (p=.005) and Activity (p=.001) were the significant predictors to characterize personality traits of kidney transplant patients.

Conclusions: Kidney transplant patients had a differential profile under the AFFM compared to standard range sample, with lower scores on Neuroticism-Anxiety and Activity dimensions.

Key words: Personality, kidney transplantation, biobehavioral sciences, population surveillance.

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Resumen

Introducción: la investigación sobre rasgos de personalidad en pacientes con trasplante renal es limitada. El objetivo de este estudio fue describir el perfil de personalidad de pacientes con trasplante renal, utilizando el modelo alternativo de cinco factores (AFFM), y compararlo con población estándar española.

Material y métodos: la personalidad fue evaluada mediante el Zuckerman-Kuhlman Personality Questionnaire (ZKPQ). Una muestra de 207 pacientes con trasplante renal se emparejó por edad y género con 207controles de la población estándar. El análisis de regresión logística permitió estudiar la aportación de cada dimensión del ZKPQ al perfil distintivo de los pacientes trasplantados.

Resultados: aparecieron diferencias significativas en las dimensiones de Neuroticismo-Ansiedad (p=.001), Agresión-Hostilidad (p=.009) y Actividad (p=.001), con puntuaciones bajas en pacientes trasplantados en comparación con la población estándar. La sociabilidad (p=.024) fue significativamente mayor en pacientes trasplantados. En el análisis de regresión, las bajas puntuaciones en Neuroticismo-Ansiedad (p=.005) y Actividad (p=.001) fueron predictores significativos para caracterizar los rasgos de personalidad de pacientes trasplantados.

Conclusiones: desde el AFFM, los pacientes con trasplante renal muestran un perfil diferente de personalidad comparado con la población estándar, con bajas puntuaciones en las dimensiones de Neuroticismo-Ansiedad y Actividad.

Palabras clave: personalidad, trasplante de riñón, ciencias bioconductuales, vigilancia de la población.

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Introduction

Kidney transplantation is one of the best treatment options for end-stage kidney disease. This intervention provides health-related quality of life indexes with values similar to those of the general population.[1] In 2017, Spain reached an annual rate of 70.5 transplants per million population (including all combinations), surpassing 3100 kidney transplants.[2]

Studies that relate personality traits with the adherence to health behaviors have emerged in the scientific literature. It should be noted that in no case we refer to personality disorders as a diagnostic entity, in this sense, previous studies indicate that the prevalence of personality disorders in transplant patients is similar to that of the general population.[3] In the studies on personality, the Big Five Factor Model (BFFM) stands out, using the NEO-PI-R as assessment instrument.[4] The basic assumption of this model is that the most outstanding and socially relevant individual differences of people are encoded in the linguistic terms of their respective languages. These differences are grouped into five large areas or dimensions that describe personality; they would be Openness to Experience, Responsibility, Extraversion, Kindness and Neuroticism or Emotional Instability.[4] Within this model, studies carried out in kidney transplant patients indicate that high scores on Neuroticism, medium scores on Kindness and Extraversion, and low scores on Openness to experience are related to good glomerular filtration rate in the post-transplant.[5] In addition, a higher score in Responsibility is associated with higher vital satisfaction[6] and adherence to treatment after transplantation.[7] However, in other studies, high scores on Neuroticism are associated with difficulties in disease acceptance and poorer health-related quality of life.[8] Low scores on Openness to experience are related to behaviors that are not adherent to immunosuppressive treatment.[9] While in patients on the waiting list for kidney transplantation, a low score in Neuroticism and a high score in Extraversion account for a variance of 20% on the performance of self-care behaviors.[10]

In the face of the BFFM based on a lexical or cultural approach, the Alternative Five Factor Model (AFFM) is considered, using as measurement instrument the Zuckerman Kuhlman Personality Questionnaire (ZKPQ)[11]; this questionnaire was developed from a series of factorial analyses in basic personality dimensions arising from neurobiological research in humans to assess normal personality. This model contains five basic personality traits: Neuroticism_Anxiety (N_Anx), Activity (Act), Sociability (Sy), Sensation Seeking_Impulsivity (ImpSS) and Aggression_ Hostility (Agg_Host). In the AFFM, unlike the cultural approach, Activity and Sociability constitute two separate factors of Extraversion, and the dimension of Neuroticism differed in the factors of Impulsivity and Hostility.[11]

This is one of the first studies where the personality traits in kidney transplant patients are assessed from the AFFM personality model. The objective of the study was, first, to describe the characteristic personality profile of kidney transplant patients using the Zuckerman-Kuhlman questionnaire (ZKPQ), and to compare it with an age- and gender-matched control group of the Spanish standard population; second, to determine the discriminant capacity of the dimensions of the ZKPQ when evaluating kidney transplant patients.

Materials and methods

Participants

The study was conducted from the Nephrology and Renal Transplant Service of a General University Hospital, during the period between March 2012 and December 2016. As inclusion criteria, it was taken into account that the patients were kidney transplant recipients, over 18 years of age and that were under outpatient follow-up by the Nephrology Service. Patients with concomitant disease or acute infection, or significant cognitive impairment that would prevent them from completing the questionnaire due to reading or comprehension difficulties were excluded.

A total of 299 patients were proposed to participate in the study, of them, 207 (69.23%) agreed to complete the questionnaire. The reasons for not

participating in the study were lack of interest (*n*=19), more than 50% of incomplete items in the questionnaire (*n*=31), physical discomfort (*n*=17), language comprehension difficulties (*n*=15), loss of kidney graft (*n*=8) or death (*n*=2). No significant differences were observed between participants and non-participants regarding age, gender and educational level. The control sample consisted of 207 individuals drawn from a standard population sample, stratified by gender and age, of 741 men and 937 women with an age range between 18 and 93 years. This sample of the standard population was part of a larger study carried out to obtain the ZKPQ scales in the Spanish population, complying with the census projections in the distribution by gender and age of the Statistical Institute of Catalonia (IDESCAT).[12] To meet the objective of this study, both samples were stratified by gender and age, being the educational level included as a covariate variable.

Measurements

Socio-demographic and clinical variables from each patient, such as age, gender, marital status, educational level, cause of kidney disease, and previous renal replacement therapy were collected.

The personality dimensions were assessed using the Spanish version of the Zuckerman Kuhlman Personality Questionnaire (ZKPQ).[12,13] This is a self-administered questionnaire with 99 items of dichotomous response, true or false. Five personality factors are assessed: Neuroticism_Anxiety (N_Anx, 19 items), consisting of items referring to be worried, fearful or undecided and sensitive to the criticism from others or lacking self-confidence; Activity (Act, 17 items), includes the need for having a continuous activity, incapacity to rest or the preference for challenging jobs with a high degree of energy to work or perform multiple task simultaneously; Sociability (Sy, 17 items), referring to the number of friends and the time spent with them, or preference for the company of others in contrast to being alone and doing solitary activities; Impulsivity and Sensation Seeking (ImpSS, 19 items), referred to the lack of planning and the general need for adventure and excitement or preference for situations; and Aggression_Hostility (Agg_Host, 17 items), referring to the predisposition to express verbal aggression, having a rude and careless behavior towards others and impatience. In addition, an Infrequency scale (Infreq, 10 items), is included as a measure of quality of the response to the questionnaire. The psychometric properties of the Spanish version show adequate values of reliability in the total score (α=.77) and in the subscales, with an α value in the range of .70 to .85.[14]

Procedure

One month after performing the kidney transplant surgical intervention, the patients were interviewed by a clinical psychologist, and responded to a structured interview to collect data on socio-demographic and clinical characteristics, and fill in the ZKPQ questionnaire. The data were collected in a single evaluation. The evaluation protocol lasted about 20 to 30 minutes. The data collection and the patient interview were carried out in an outpatient clinic adjacent to the hospital.

The candidates for the study received oral and written information about the project, and those who agreed to participate signed the informed consent. This study followed the ethical standards of the Declaration of Helsinki[15] and the Declaration of Istanbul,[16] and was approved by the Research Ethics Committee of the hospital.

Statistical analysis

The data analysis was carried out in two parts. First, the socio-demographic and clinical characteristics analyzed with descriptive statistics and measures of central tendency were recorded, and the normality in the distribution was verified. Means, standard deviation and Cronbach's alpha were calculated for both groups, and differences between groups were analyzed using the Student's t test for independent samples. In addition, Cohen's *d* was calculated. To evaluate the discriminant capacity of the ZKPQ scales in transplant patients with regard to the control group of the standard

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population, a logistic regression analysis was performed. The five personality dimensions of the ZKPQ were introduced as predictor variables, and the dichotomous response of the participants as the dependent variable. The step-by-step method was used to enter the variables, and the contribution of each dimension of the ZKPQ was calculated to describe the distinctive personality profile in kidney transplant patients. The educational level, because it did not follow a normal distribution, and the Infrequency scale, because it was not considered a dimension of the theoretical model, both were introduced as adjustment variables.

All statistical analyzes were bilateral and the assumed alpha risk was 5%. The data were collected and analyzed with the SPSS version 21.0 statistical package.

Results

Patients

Table 1 describes the sociodemographic and clinical characteristics of the patients who participated in the study. The majority were men with an age range between 18 and 76 years, married or with a partner, and middle grade educational level. The most prevalent renal insufficiency is due to glomerulonephritis, with a previous renal replacement therapy by hemodialysis.

Table 1. Sociodemographic and clinical characteristics of kidney transplant patients (n= 207).

Age		
Mean (SD)	**51.92 (13.12)**	
	Number of patients (n)	**Percentage (%)**
Gender		
Men	139	67.1
Women	68	32.9
Marital status		
Married/with a partner	140	67.6
Single	39	18.8
Divorced/widowed	28	13.6
Educational level		
Elementary	84	40.6
High school	111	53.6
University	12	5.8
Nephropathy		
Glomerulonephritis	52	25.1
Unknown causes	36	17.4
Polycystosis	34	16.4
Tubulointerstitial	27	13
Vascular	25	12.1
Diabetic	24	11.6
Other	9	4.4
Previous renal replacement therapy		
Hemodialysis	123	59.4
Peritoneal dialysis	56	27.1
None	28	13.5

Comparison between kidney transplant patients and the standard population in the dimensions of the ZKPQ

In Table 2 are shown the means, standard deviations, Cronbach's alpha, t-test and Cohen's d test of the dimensions of the ZKPQ for both samples. In the kidney transplant group, the internal consistency of the five personality dimensions ranges from an alpha of.68 to.84, with a mean of.75.

These reliability indices are similar to those of the control sample, to the standard population, and to those obtained in other population samples that use the ZKPQ.[17] Both groups are significantly different in all dimensions of the ZKPQ, except for ImpSS, with a medium to small effect size. When comparing the values of the standard population with those of kidney transplant patients, there are differences in the dimensions of Neuroticism_Anxiety (t=3.48, p=.00), Activity (t=3.22, p=.00), and Aggressiveness_Hostility (t=2.63, p=.00) being the lowest scores in kidney transplant patients, while they are high in the

Table 2. Mean difference of the dimensions of the ZKPQ between kidney renal patients and control group, Cronbach's alpha and Cohen's *d*.

	Transplant (*n* = 207)			Control (*n* = 207)					
	M	*SD*	*α*	*M*	*SD*	*α*	*t*	*p*	*Cohen's d*
ZKPQ									
N_Anx	5.79	4.24	.84	7.29	4.55	.83	3.49	.001	0.34
Act	7.30	3.18	.69	8.38	3.64	.75	3.22	.001	0.32
Sy	7.20	3.06	.68	6.46	3.52	.77	-2.26	.024	-0.22
ImpSS	6.08	3.52	.75	6.63	4.01	.80	1.49	.138	0.15
Agg_Host	6.11	3.44	.78	6.95	3.04	.67	2.64	.009	0.26
Infreq	3.04	1.42	_	2.19	1.65	_	-5.62	.001	0.55

Note. ZKPQ: Zuckerman Kuhlman Personality Questionnaire; N-Anx: Neuroticism-Anxiety; Act: Activity; Sy: Sociability; ImpSS: Impulsivity-Sensation Seeking; Agg-Host: Agression-Hostility; Infreq: Infrequency.

Sociability scales (t= -2.26, p=.02) for kidney transplant patients.

Discrimination capacity of the ZKPQ scales in kidney transplant

To evaluate the discriminant capacity of the personality dimensions of the ZKPQ, and differentiate kidney transplant patients from the control group, which was the standard population, a logistic regression was performed using the method of steps for the introduction of variables (Table 3). The five dimensions of the ZKPQ were entered in the regression analysis as predictor variables, and the group of origin (coded as 1 to the kidney transplant group, and 0 to the control group) as the dependent variable. Since both groups were significantly different in the educational level (X^2= 67.78, p>.001) and the Infrequency scale is not considered a dimension of the theoretical model, these two variables were entered in the model as adjustment variables.

The model resulted statistically significant (X^2= 123.84, p=.001). Of the five dimensions of the ZKPQ entered in the regression analysis, only two dimensions, Neuroticism_Anxiety (p=.005) and Activity (p=.001), were significant. According to this result, low scores on the dimension of Neuroticism_Anxiety and low in the dimension of Activity of the ZKPQ increase the probability of being fit for the kidney transplant group (Table 3).

Discussion

This is one of the first studies where the personality traits in kidney transplant are assessed from the AFFM model. The kidney transplant

Table 3. Logistic regression analysis of the ZKPQ scales.

Scale	*B*	*Wald*	*p*	*Exp(B)*	95% CI
Neuroticism_Anxiety	- 0.08	8.04	.005	0.93	0.88-0.98
Activity	-0.13	14.14	.001	0.88	0.82-0.94
Constant	0.89	4.62	.032	2.45	

Note*:* Control group: 0; kidney transplant patients: 1; CI: confidence interval

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patients obtain low scores on Neuroticism_Anxiety, Activity and Agressiveness_Hostility and high in the Sociability scale. Low scores in Neuroticism facilitate acceptance of the disease and the perception of Low scores in Neuroticism facilitate acceptance of the disease and the perception of a good health-related good quality of life.[8,18] In our study, low scores in Neuroticism are linked with high values in sociability, which from the BFFM model is assessed with the Extraversion dimension, and appears to be a significant predictor in the performance of self-care behaviors for patients on the waiting list for kidney transplant.[10]

Low scores on the Neuroticism_Anxiety dimension and in the Activity dimension of the ZKPQ characterize the group of kidney transplant patients. In this sense, the low scores on these two dimensions, Neuroticism and Activity, are the ones that best correlate with the absence of risk behaviors (consumption of tobacco, drugs, alcohol…).[19] Thus, the lack of adherence to treatment in kidney transplant patients has been associated with an active style of coping with the disease.[20] On the other hand, from the BFFM model, it is agreed that low scores in Openness to Experience characterize the good evolution of the kidney transplant patient, with little interest in new or out-of-routine activities, and a tendency to maintain the usual lifestyle.[5] This style of behavior, conventional and resistant to new experience is also manifested in patients who received heart or lung transplants.[21]

We highlight from these results that in the face of a chronic disease that requires an adaptation of the lifestyle, the behavior does not appear to be a response determined by fixed personality traits, but rather, in the face of health maintenance, the personality traits are conditioned by a range of physical, social and economic factors, which determine the final behavior of the individual. Given the characterization of the personality profile of kidney transplant patients carried out in this study, it would be of interest for future lines of research to evaluate the results associated with these personality traits, that is, in relation to health-related quality of life indices or adherence to treatment or include, also, biochemical values, such as glomerular filtration rate and creatinine level.

Some limitations of the present study should be noted, such as having carried out the evaluations in a single center, which makes it difficult to generalize the results. In addition, the study was conducted with a cross-sectional design that makes it difficult to assess the changes associated with the progress of the disease, which would require replication of the study with a longitudinal design.

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Conflict of interest

The authors declare that there is no conflict of interest in this work.

Ethical responsibilities

Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

Data confidentiality

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

Right of privacy and informed consent

The authors declare that patient data do not appear in this article.

Contribution of the authors

GCR has participated in the conception, writing and design of the manuscript.

SVV participated in the analysis and interpretation of the data.

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FM and GPP gave their approval to the final version of the manuscript before it was sent for publication.

DSM cooperated in the conception and design of the study, and in the approval of the final version of the manuscript before its submission for publication.

MGF actively contributed to the critical review of the manuscript with meticulous contributions to its content.

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Original article

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Effect of pharmacological therapies for glycemic control in patients with type 2 diabetes mellitus on vascular outcomes

Efecto de terapias farmacológicas para el control glicémico en pacientes con diabetes mellitus tipo 2 en los desenlaces vasculares

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Abstract

Introduction: In the last 5 years the publication of knowledge related to vascular disease and type 2 diabetes mellitus (T2D) has been increasing. However, due to the absence of a review that collects all the vascular outcomes of T2D, the current review of the literature aims to group all vascular outcomes related to T2D and describe how hypoglycemic drug therapy can be effective for the control of these outcomes. Cardiovascular events as the main outcome show that innovative antidiabetic drugs such as empagliflozin and liraglutide can add significant benefits for patients with T2D.

Materials and methods: Systematic search of the literature, from which 141 references were obtained, after eliminating duplicates, for paired screening. Subsequently, 21 references were identified that met the inclusion criteria to be considered in the analysis.

Results: The effect of good glycemic control on clinical outcomes, specifically in the progression of diabetic kidney disease, has been the objective of multiple large-scale studies, both in type 1 diabetic patients and type 2 diabetics. Micro and macrovascular outcomes are the primary results of T2DM, which increase the incidence of comorbidities and in turn represent greater morbidity.

Conclusions: Among the main causes of morbidity and mortality of patients with T2D, are those with vascular damage, especially cardiovascular disease and renal involvement. In this context, the pharmacological treatment of diabetes mellitus has focused on finding drugs that reduce the importance of cardiovascular events and that at the same time delay the onset of nephropathy or its progression. Thiazolidinediones, DPP4 inhibitors (alogliptin, saxagliptin and sitagliptin), insulin glargine and degludec have demonstrated cardiovascular safety, but not incremental cardiovascular benefits, in patients with T2D who are at high risk of atherosclerotic cardiovascular disease.

Key words: Liraglutide, empagliflozin, vascular diseases, diabetes mellitus, type 2, hypoglycemic agents.

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Resumen

Introducción: en los últimos 5 años la publicación de conocimiento relacionado con la enfermedad vascular y la diabetes mellitus tipo 2 (DT2) ha ido en aumento. Sin embargo, debido a la ausencia de una revisión que recopilara todos los desenlaces vasculares de la DT2, la presente revisión de literatura tiene como objetivo agrupar todos los desenlaces vasculares relacionados con la DT2 y describir cómo la terapia farmacológica hipoglicemiante puede ser eficaz para lograr el control de estos desenlaces. Los eventos cardiovasculares como desenlace principal demuestran que los medicamentos antidiabéticos innovadores como la empagliflozina y la liraglutida pueden agregar un beneficio significativo para pacientes con DT2.

Materiales y métodos: búsqueda sistemática de la literatura, de la cual se obtuvieron 141 referencias, después de eliminar duplicados, para la tamización pareada. Posterior a esto, se identificaron 21 referencias que cumplían con los criterios de inclusión para ser considerados en el análisis.

Resultados: el efecto de un buen control glucémico, sobre los resultados clínicos, específicamente en la progresión de la enfermedad renal diabética, ha sido objetivo de múltiples estudios a gran escala, tanto en pacientes diabéticos tipo 1 como en diabéticos tipo 2.

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Los desenlaces micro y macrovasculares son los principales desenlaces de la DMT2, que incrementan la incidencia de comorbilidades y representan, a su vez, una mayor morbilidad.

Conclusiones: dentro de las principales causas de morbilidad y mortalidad de los pacientes con DT2, se encuentran las relacionadas con daño vascular, en especial enfermedad cardiovascular y compromiso renal. En este contexto, el tratamiento farmacológico de la diabetes mellitus se ha enfocado en encontrar medicamentos que reduzcan de manera significativa los eventos cardiovasculares y que al mismo tiempo retrasen la aparición de nefropatía o su progresión. Las tiazolidinedionas, los inhibidores de DPP4 (alogliptina, saxagliptina y sitagliptina), la insulina glargina y degludec han demostrado seguridad cardiovascular, pero no beneficio cardiovascular incremental en pacientes con DT2 que tienen alto riesgo de enfermedad cardiovascular aterosclerótica.

Palabras clave: liraglutida, enfermedades vasculares, diabetes mellitus tipo 2, hipoglucemiantes.

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Introduction

The prevalence of type 2 diabetes *mellitus* (T2D) is increasing worldwide, with the consequent increase in morbidity and mortality associated with its vascular complications. These vascular disorders increase with the severity of hyperglycemia and the time of evolution, which is related to metabolic alterations.[1] The goal of the treatment of diabetes *mellitus* is to decrease the hyperglycemia, thus avoiding acute and chronic (microvascular and macrovascular) complications.

The complications of diabetes have traditionally been divided into macrovascular (coronary artery disease added to cardiomyopathy and diabetic dysautonomia; cerebrovascular disease and peripheral vascular disease) and microvascular (albuminuric or non-albuminuric nephropathy, proliferative or non-proliferative retinopathy, and neuropathy). According to the literature, half of patients with T2D present microvascular complications and 27% macrovascular complications, that are usually already advanced or established at the time of diagnosis.[2] The relative risk of microvascular and macrovascular involvement in patients with diabetes is at least 10 to 20-fold higher and 2 to 4-fold higher, respectively, compared with non-diabetic individuals.[3]

T2D and its complications contribute significantly to the burden of mortality and disability, the latter with a substantial increase in recent years, adding a decrease in general productivity. 10.7% of all deaths in the population between 20 and 79 years of age worldwide are attributed to this condition and it is one of the top 10 causes of decreased life expectancy across the world, which represents a high impact on the global public health.[4]

Recent clinical studies dedicated to evaluate cardiovascular events as the main outcome show that innovative antidiabetic drugs such as empagliflozin[5] and liraglutide[1] can add a significant benefit for patients with T2D, even for those with already established atherosclerotic cardiovascular disease, especially in reducing mortality due to cardiovascular causes.

This article provides an updated view of the cardiovascular and renal ((two of the most affected target systems) impact of T2D, and in turn, of the therapeutic role of the current pharmacological agents for the treatment on these specific outcomes.

Materials and methods

A generic search strategy was designed based on the key terms for the development of the literature review of the effect of pharmacological therapies for glycemic control in T2D on cardiovascular and renal outcomes. Therefore, the terms «Diabetes Mellitus, Type 2», «Cardiovascular Diseases», «Diabetic Nephropathies», «Hypoglycemic Agents» and «Diabetes Complications» were included. Subsequently, a systematic and exhaustive literature search was carried out, from which 141 references were obtained after eliminating duplicates, for the execution of the paired screening. Then, 22 references were identified for review in full text, of which 21 met the inclusion criteria to be considered in the analysis. The selection of systematic reviews of clinical trials or observational studies in the last five years, all available as a full publication, was prioritized.

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Main target organs affected

Cardiovascular disease

Cardiovascular disease (coronary heart disease, peripheral arterial disease and cerebrovascular disease) is one of the leading causes of morbidity and mortality worldwide.[6] (Patients with T2D have twice the risk of developing cardiovascular disease,[7] which has an early onset (14.6 years earlier than in the general population), a greater clinical severity[8-10] and higher mortality.[10] Thereby, men of 60 years of age with T2D and a history of cardiovascular disease (myocardial infarction or cerebrovascular event) will have a life expectancy 12 years shorter, mainly due to a 58% increase in the risk of death of cerebro-cardio-reno-vascular origin.[11]

The incidence of cerebrovascular attack in patients with T2D is two to four times higher than that of the population without this pathology; in addition, diabetic patients have a worse prognosis and a higher risk of recurrence. Subcortical cerebrovascular disease is significantly associated with the presence of T2D and the panorama becomes complicated, as both hyperglycemia and hypoglycemia cause cognitive impairment.[12]

Diabetic cardiomyopathy, coronary atherosclerosis, valvular heart disease or congenital heart disease are the main cardiac diseases related to T2D and represent a major impact on the health of these patients. Diabetic cardiomyopathy is associated with an incidence of heart failure 2 to 4 times higher than in the general population, which manifests in its early stages with systolic dysfunction and microvascular angina or coronary small vessel disease.[13,14]

Kidney disease

The incidence of diabetic kidney disease has doubled in the last decade, mainly due to the increase in the prevalence of patients with T2D, in whom kidney involvement is frequent; it is estimated that about 25% have diabetic kidney disease at some point in their life, defined as persistent albuminuria, a decreased estimated glomerular filtration rate (eGFR), or both.[15] Diabetes mellitus causes approximately 44% of incident cases of end-stage chronic kidney disease[6] and is the most frequent cause of dialysis. Nearly 10% of the mortality in diabetic patients is attributed to kidney failure.[16] The advent of new classes of drugs for the treatment of T2D, including renal sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, which besides lowering the glycemia, they have other beneficial effects for the cardiovascular and renal systems, such as weight loss and the reduction of the blood pressure. The outcome trials showed that SGLT-2 inhibitors and GLP-1 receptor agonists can reduce cardiovascular events and all-cause mortality, as well as the progression of kidney disease, in patients with T2D. The available evidence on the cardioprotective and nephroprotective effects of SGLT-2 inhibitors and GLP-1 analogs is overwhelming; today, in light of these clinical studies, the guidelines of the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD) and the American Association of Clinical Endocrinology (AACE) include them in their different algorithms and recommendations as first-line drugs in the treatment of patients with chronic kidney disease (CKD) and T2D with diabetic kidney disease (DKD) and CKD.[5,17]

Vascular disease

The vascular complications of diabetes, initiated by endothelial dysfunction, are serious manifestations of the disease. Systemic atherosclerosis and diabetic kidney disease are the main reasons for the shorter life expectancy in patients suffering from this condition. Although the decrease in hyperglycemia delays the onset of nephropathy and retinopathy, its impact on cardiovascular disease is less clear, since a lesser benefit of glycemic control on these macrovascular changes has been observed. Thus, insulin resistance and its biological effects on various tissues might be a more important factor than hyperglycemia in mediating atherothrombotic complications. Despite the advances in prevention, diagnosis and treatment of diabetes, complications are still a serious public health problem.[18]

Meanwhile, peripheral arterial disease has a prevalence of 20 to 30% in diabetic patients. Both

http://dx.doi.org/10.22265/acnef.7.1.372

the duration of the diabetes and the degree of glycemic control are related to the incidence and severity of peripheral arterial disease.[19] In a meta-analysis conducted in 2016 that evaluated the impact of diabetes on peripheral arterial disease outcomes, it was found that diabetes is associated with a statistically significant increase in the risk of critical limb ischemia (Odds Ratio: 2.38, 95% CI: 1.22- 4.63, P<0.001) as the most serious form of peripheral vascular disease,[20] and is the most common cause of amputations.

At the end of August 2019, the guidelines for diabetes, prediabetes and cardiovascular diseases of the European Society of Cardiology, developed in conjunction with the European Association for the Study of Diabetes, were published.[21] A strong point of these guidelines is the categorization of cardiovascular risk, which allows favoring the comprehensive treatment of cardiovascular risk factors in individuals with T2D. Another strong point of the guidelines is the discussion addressed to the management of the different cardiovascular risk factors such as hypertension, dyslipidemia, CKD, coronary heart disease, and so on. One of the most notable aspects related to a change in the treatment paradigm is the establishment of a specific classification of cardiovascular risk for people with diabetes (Table 1).

The purpose of the classification is that the management will be oriented towards cardiovascular risk and the control of risk factors, even moving away from the concept of primary and secondary prevention.

Atherosclerosis

The nature of the atherosclerotic lesions in patients with diabetes is similar to that of patients with other characteristics, although the lesions are earlier, and more accelerated and aggressive. Apolipoprotein B and oxidized LDL cholesterol, accumulated in the arterial intima are recruited by adhesion molecules expressed in the endothelium. The cytokines and chemokines released from foam cells and other immune cells recruit others with similar characteristics. Additionally, insulin resistance causes endothelial dysfunction, which is manifested by increased expression of adhesion molecules.[22] In summary, the alterations in vascular homeostasis due to dysfunction of the endothelium and the vascular smooth muscle cells are the main characteristics of diabetic vasculopathy that favors a prothrombotic and pro-inflammatory state that ultimately leads to atherothrombosis.[9]

The main microvascular and macrovascular effects of hyperglycemia are described in Figure 1.

Effects of glycemic control on vascular outcomes

HbA1c and estimation of the mean blood glucose

Based on two international studies that sought to evaluate the correlation between the glycated hemoglobin (HbA1c) levels and blood glucose, the

Table 1. Classification of cardiovascular risk in diabetic individuals. Modified from ESC Guidelines 2019.[21]

Category	Data
Very high cardiovascular risk	With any of the following items: • Established cardiovascular disease. • Target organ damage. • Three or more risk factors (age, hypertension, tobacco, dyslipidemia, obesity). • Early onset of long-standing type I diabetes (>20 years).
High cardiovascular risk	Patients with disease duration of more than 10 years, without target organ damage plus a risk factor.
Moderate cardiovascular risk	Young people (type 1 diabetes <35 years; type 2 diabetes <50 years) with less than 10 years of disease duration and without risk factors.

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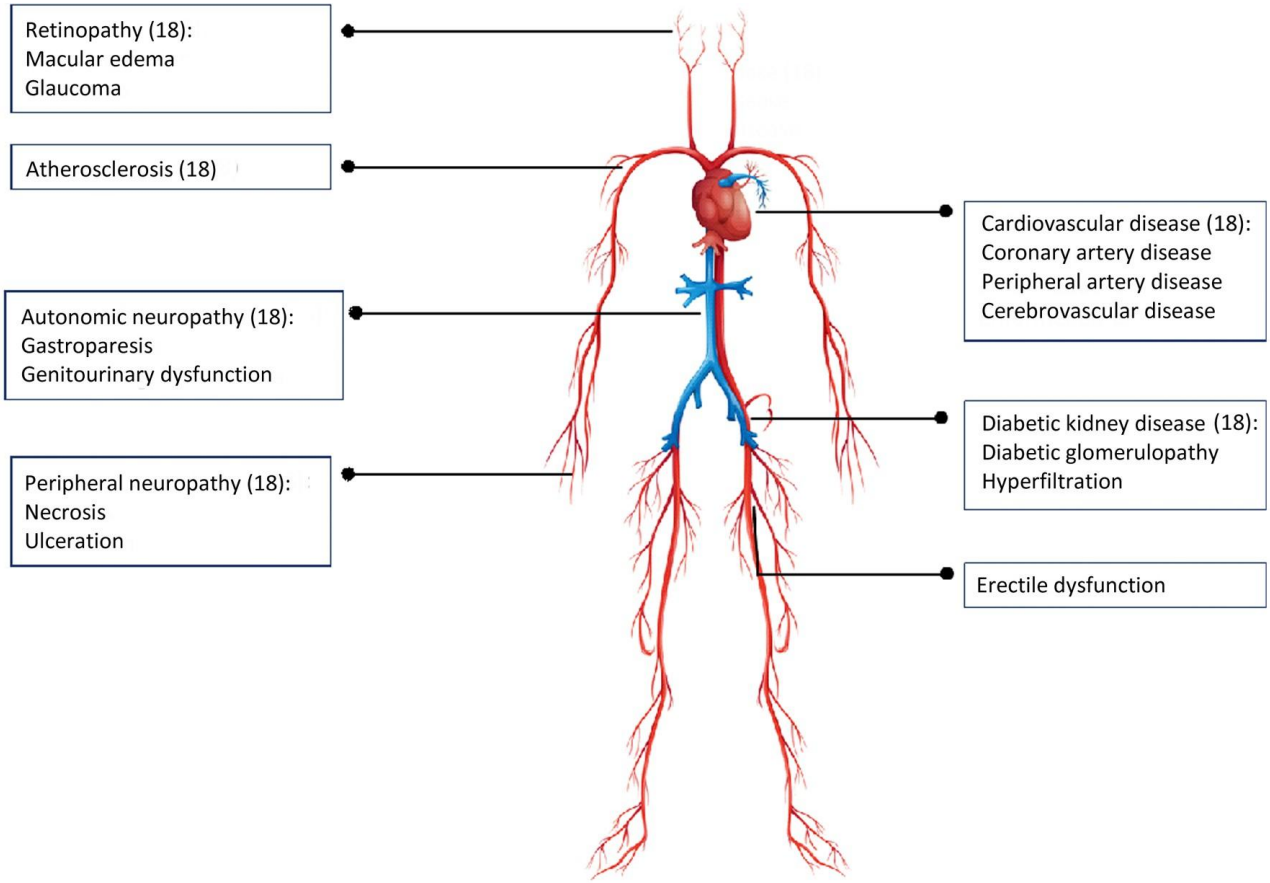

Figure 1. Micro and macrovascular manifestations of type 2 diabetes mellitus. Source: own elaboration. Image taken from vectorstock.com/1855392

American Diabetes Association (ADA) and the American Association for Clinical Chemistry determined that the correlation found in the studies (r 0.92) was strong enough to report the HbA1c result with a figure of the estimated average blood glucose.[23] However, recent studies have demonstrated that HbA1c can underestimate or overestimate the mean blood glucose level, due to factors that can alter the results (e.g. intra- and interlaboratory measurement variability, duration of exposure of the erythrocyte to glucose, and the effect of frequent pathologies in diabetics such as chronic kidney disease and anemia).

HbA1c goals

Despite its limitations (for example, it does not detect or discriminate patients with postprandial peaks, which generate greater endothelial damage), it is accepted that HbA1c reflects the average glycemia of the last three months and has a strong predictive value for the complications of diabetes.[18,24]

The assessment of the levels of HbA1c should be individualized according to the characteristics of the patient and the non-glycemic factors that can affect the HbA1c. In addition to this measurement, the clinician must rely on clinical data and ideally on blood glucose monitoring to optimize medical management.[25,26] According to the Standards of Medical Care in Diabetes, published in 2018 by the American Diabetes Association (ADA), the recommendations for measurement and goals of HbA1c are the following:

- Twice a year in patients with T2D with stable glycemia and within the treatment goals.[25]

- Approximately every 3 months in patients with treatment modifications on in those who have not reached the treatment goals.[25]

- Unstable patients or those who are under intensive management may require tests more frequently than every 3 months, remembering that HbA1c does not detect glycemic variations, which are the most vasculotoxic. [25]

- A reasonable goal for HbA1c is 7.5-8%; except in pregnant women, which is 7%. Stricter HbA1c goals (6.5%) in some cases.[25]

Even though the ADA proposes optimal HbA1c ranges, it is necessary to individualize the goals for each patient, taking into account their preferences, and always in order to avoid hypoglycemia and any other adverse effect related to the treatment.[1] Intensive glycemic control plays an important role in primary prevention in patients with type 1 and newly diagnosed type 2 diabetes.[22] However, in advanced disease it is not beneficial and it could be potentially deleterious. Thus, patients with long-standing diabetes, a known history of hypoglycemia or advanced atherosclerosis, as well as elderly or frail patients, may benefit from less aggressive goals.[27]

There is evidence of endothelial damage caused by hypoglycemia, which increases the production of reactive oxygen species (oxidative stress) and inflammatory biomarkers such as C-reactive protein and interleukins 6 and 8; favors platelet aggregation, the production of factor VIII, Von Willebrand factor and the processes involved in atherothrombosis; potentiates vasoconstriction and endothelin production, and acutely enhances the sympathetic-adrenergic response with an increased incidence of arrhythmias and sudden cardiac death.[28,29]

Pharmacological strategies for glycemic control and their effects on vascular outcomes

As described in previous sections, patients with diabetes have an increased risk of vascular morbidity and mortality, and consequently, risk stratification is currently recommended in clinical practice for the prevention of such events.[30] It is considered that glycemic control should be multifactorial and individualized with intervention in the lifestyle, therapeutic management of blood pressure, lipids, antithrombotic agents and glycemic control.[27,31,32] The main pharmacological strategies are summarized in Table 2.

In recent years, regulatory bodies such as the U.S. FDA and the European Medicines Agency (EMA) have required studies to demonstrate the cardiovascular safety of the new drugs for glycemic control.[27] The available evidence on the vascular impact of the drugs for glycemic control, by pharmacological class, highlighting the studies that support their vascular safety and their location in current treatment guidelines is described below.

Biguanides

They are oral hypoglycemic molecules, and metformin is part of this pharmacological group. This drug is the most commonly prescribed oral medication in the world for the management of T2D, because it has a good safety profile, even among patients with kidney failure.[33] Early combination with other drugs should be considered on individual basis to achieve good glycemic control, reduction of cardiovascular risk and renal protection.[1,30] If metformin is tolerated and not contraindicated, it should be continued when used in combination with other agents, including insulin.[25]

Sulphonylureas

Sulfonylureas are another very important and very effective oral hypoglycemic agent in glycemic control. These molecules stimulate insulin secretion from pancreatic beta cells and reduce fasting plasma glucose by 36 to 72 mg/dL and HbA1c levels by 1 to 2%.[9] The available sulfonylureas are variably associated with events of moderate and severe hypoglycemia (20-40% and 07.01%, respectively). They also alter ischemic preconditioning, and therefore they are contraindicated in patients with coronary artery disease (except for gliclazide).

Thiazolidinediones

These molecules are oral hypoglycemic agents that were originally developed as lipid-lowering agents.[34]

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Table 2. Comparison between the different therapeutic alternatives for the treatment of type 2 diabetes *mellitus*.

Pharmacological class	Drug for glycemic control	Study	intervention	Comparator	Primary outcome	n	Cardiovascular status	Follow-up mean (years)
Biguanides	Metformin	UKPDS (UKPDS34 subgroup analysis)	Intensive control of blood glucose with metformin (fasting glucose below 6 mmol/L)	Conventional therapy	All-cause mortality	17704	Time until the first diabetes-related outcome (sudden death, death from hyperglycemia or hypoglycemia, fatal or non-fatal myocardial infarction, angina, heart failure, stroke, kidney failure, amputation [for at least one digit], vitreous hemorrhage , retinopathy requiring photocoagulation, blindness in one eye or removal of cataracts),	10.7
Thiazolidinediones	Pioglitazone		Pioglitazone		Death, MI, stroke, ACS, vascular intervention, amputation	5238	Macrovascular disease	2.9
	Rosiglitazone	RECORD	Addition of Rosiglitazone to metformin or sulfonylurea	Combination of metformin and sulfonylurea	CV death, MI, cardiovascular hospitalization	4447	Exclusion in the presence or history of heart failure. ischemic heart disease 5-20%	5,5
Insulins	Insulin glargine	ORIGIN	Insulin glargine	Conventional therapy	CV death, MI or cerebrovascular event	12537	CV risk factors (recent angina, stroke, MI, or revascularization)	6.2
	Insulin degludec	DEVOTE	Insulin degludec	Insulin glargine	CV death, MI or cerebrovascular event	7637	CVD or kidney disease or CV risk in ≥ 60 years	1.9
Sulfonylureas	Sulfonylureas	Meta-analysis	First and second generation sulfonylureas as a group	Placebo/no intervention or other hypoglycemic therapies	All-cause mortality, CV death, MI or cerebrovascular event			
SGLT2 inhibitors	Empaglifozin	EMPAREG OUTCOME	Addition of empaglifozin (10 mg and 25 mg)	Placebo	CV death, MI or cerebrovascular event	7000	CVD or high cardiovascular risk	3.1
	Canaglifozin	CANVAS program	Canaglifozin (100 mg and 300 mg)	Placebo	CV death, MI or cerebrovascular event	10142	Pre-existing CVD or high cardiovascular risk	1.5
DPP-4 inhibitors	Sitagliptin	TECOS	Addition of sitagliptin	Placebo	CV death, MI, unstable angina or stroke	14724	Pre-existing CVD	3
	Saxagliptin	SAVOR-TIMI 53	Addition of saxagliptin	Placebo	CV death, MI or cerebrovascular event	18206	CVD or high cardiovascular risk	2.1
	Alogliptin	EXAMINE	Addition of alogliptin	Placebo	CV death, MI or cerebrovascular event	5380	Acute coronary syndrome (15-90) days before	1.5
GLP-1 receptor agonists	Liraglutide	LEADER	Liraglutide	Placebo	CV death, MI or cerebrovascular event	9340	CVD or vascular disease, heart or kidney failure in ≥ 50 years or high CV risk in ≥ 60 years	3.8
	Semaglutide	SUSTAIN-6	Semaglutide (0.5 mg and 1.0 mg)	Placebo	CV death, MI or cerebrovascular event	3299	Pre-existing CVD in ≥ 50 years or pre-CVD in ≥ 60 years	1.9
	Exenatide	EXSCEL	Exenatide once a week	Placebo	CV death, MI or cerebrovascular event	14752	73.1% with previous CVD	3.2
	Lixisenatide	ELIXA	Addition of lixisenatide	Placebo	CV death, MI,unstable angina or cerebrovascular event	6076	ACS (<=180) days before	2.1

CV cardiovascular. CVD Cardiovascular disease. CKD Chronic kidney disease. ACS Acute coronary syndrome. MI Myocardial infarction. Conventional therapy: lifestyle modification and/or metformin and/or sulfonylurea

PPAR gamma receptors (PPARg) are expressed mainly in adipocytes, muscle, and liver, and are involved in glucose and lipid metabolism; and it is through these receptors that thiazolidinediones exert their pleiotropic effect.[34] The action of thiazolidinediones is focused on stimulating insulin sensitivity in skeletal muscle, liver, and adipose tissue due to their ability to activate the peroxisome proliferator-activated receptor.

DPP-4 inhibitors

Dipeptidyl peptidase-4 (DPP4) inhibitors are analogs of these peptides and act by inhibiting the enzyme DPP-4. Their mechanism of action is of the incretin type, that inhibits the degradation of protease by DPP4, which prolongs the half-life and biological activity of GLP-1, increases the physiological secretion of insulin and suppresses the release of glucagon, with moderate effects on blood glucose reduction.[27] These molecules are indicated in monotherapy or in combination therapy in special situations, such as metformin intolerance, chronic kidney disease (GFR lower than 30 ml/minute), mild to moderate liver failure, among others.[35]

SGLT-2 inhibitors

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are involved in the first step in the reabsorption of glucose from urine, with the transport of glucose from the tubules to the peritubular capillaries through the tubular epithelial cells. Glucosuria induced by the sodium glucose cotransporter 2 inhibitor promotes mild diuresis and calorie loss, leading to modest reductions in body weight; significant reduction in the blood pressure, especially in the systolic, as well as favorable effects on arterial stiffness, possible determinants of positive outcomes for the patients with T2D.[36]

Insulin

Insulin is a drug used by more than 30% of patients with diabetes worldwide,[22] and in clinical practice it has been considered an essential component of the treatment strategy for patients who do not achieve glycemic goals with other therapies.[33]

Glargine is the most commonly used insulin worldwide due to its cardiovascular safety in people with T2D with or without previous cardiovascular events. Evidence suggests that in patients with altered fasting glucose, glucose intolerance or T2D, followed up for 7 years, the comparison of insulin glargine versus conventional therapy (lifestyle modification and/or metformin and/or sulfonylurea) did not show statistically significant differences in the composite outcomes of myocardial infarction, stroke, and cardiovascular death, or in the extended composite that included revascularization and hospitalizations for heart failure.[22,37] Meanwhile, insulin degludec is a long-acting basal insulin analog that is administered once a day. The DEVOTE clinical trial shows the cardiovascular safety of insulin degludec versus an active comparator (insulin glargine), each one added to conventional therapy.[38] The primary outcome (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) occurred in 8.5% of patients treated with degludec and in 9.3% of patients treated with glargine (RR 0.91; non-significant p-value), which does not demonstrate inferiority. However, regarding the secondary outcome, the patients treated with degludec experienced significantly lower rates of severe hypoglycemia compared with the glargine U100 group ($p<0.001$).[39]

GLP-1 agonists

Glucagon-like peptide 1 (GLP-1), secreted by enteroendocrine L cells after food intake, increases insulin secretion. The glucagon-like peptide 1 receptor agonists, also known as GLP-1 receptor agonists or incretin mimetics, increase insulin secretion depending on glucose concentration and generate an inhibition of glucagon secretion, with long-lasting effects on pancreatic beta cells. The expression of the GLP-1 receptor in the vascular endothelium and in the smooth muscle cells has a demonstrated favorable impact on the cardiovascular system, body weight, blood pressure, endothelial function and low-density lipoproteins.

Evidence suggests that GLP-1 agonists improve glycemic control and reduce body weight compared to placebo, with a similar gastrointestinal tolerance profile between them.

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When long-acting agents (semaglutide, dulaglutide, liraglutide, and exenatide once a week) were compared to short-acting agents (exenatide twice a day and lixisenatide), they were superior in reducing HbA1c and fasting blood glucose levels.[40] The use of liraglutide is recommended in patients with intolerance to metformin, or added to it to reduce major adverse cardiovascular events such as non-fatal infarction, non-fatal stroke and cardiovascular mortality in a population with established atherosclerotic disease and glomerular filtration rate higher than 15 cc/min.[25,30]

Discussion

The effect of a good glycemic control on clinical outcomes, specifically on the progression of diabetic kidney disease, has been the objective of multiple large-scale studies, both in type 1 and type 2 diabetic patients.

The main evidence of good glycemic control in type 1 diabetic patients is The Diabetes Control and Complications Trial (DCCT), a randomized controlled clinical trial with 1441 patients, which compared the intensive glycemic control (target HbA1c lower than 6.0%) versus the conventional glycemic control with insulin, with an average follow-up of 6.5 years. The average HbA1c was 7.3% for the group with intensive control versus 9.1% for the group with conventional control (difference of almost 2%), and demonstrated an association of intensive glycemic control with a decrease of 54% in the progression of nephropathy.[41] Later, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, which continued the follow-up of the DCCT cohort (1375 patients with 4-year follow-up), also demonstrated the benefit of strict glycemic control on the microvasculature.[42]

The available data from patients with type 2 diabetes include the Kumamoto Study[43] and the UK Prospective Diabetes Study (UKPDS),[44] which confirmed the findings described and their long-term persistence. The United Kingdom Prospective Diabetes Study (UKPDS), where HbA1C in the intensive treatment group was 0.9% lower than in that with conventional therapy, concluded after 10 years of follow-up that there was a 25% reduction in microvascular complications in the intensive treatment group, and that for every 1% reduction in HbA1C, there was a 21% reduction in the risk of any primary outcome of diabetes or death, a 37% reduction in microvascular complications, and a 14% reduction in the risk of myocardial infarction.[45,46] It is important to mention that in this study the average time of diagnosis of diabetes was not longer than one year; that is, vascular damage and/or metabolic memory were not yet established, according to studies that suggest the need for very early active treatment to minimize long-term diabetic complications.[47]

Three large clinical studies with the participation of approximately 25,000 patients assessed the potential beneficial effect of intensive glycemic control in type 2 diabetic patients. The Action to Control Cardiovascular Risk in Diabetes (ACCORD),[48] Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE)[49] and Veterans Affairs Diabetes Trial (VADT)[50] studies showed that low HbA1c levels were associated with a late onset or slowing of the progression of some microvascular complications. It should be taken into account that the patients in these studies had been diagnosed with diabetes for several years, with vascular damage and metabolic memory already established. In addition, the risk of hypoglycemia and the need for polypharmacy to achieve these glycemic goals must be considered, therefore these studies support the recommendation to adjust HbA1c goals individually.

The available evidence raises doubts about the impact of metformin on vascular disease. The cardiovascular benefits of metformin come primarily from the UK Prospective Diabetes Study (UKPDS), in which 3,867 patients with newly diagnosed T2D were randomly assigned to receive sulfonylureas or insulin versus conventional therapy. The intensive therapy with metformin was assigned to 342 individuals with overweight (with more than 120% of the ideal body weight), while 411 received conventional diet measures. The analysis of this subgroup of patients showed a reduction of deaths related with diabetes, overall mortality and non-fatal myocardial infarction of 42% (p=0.017), 36% (p=0.011) and 39% (P=0.01), respectively, in the group treated with metformin. These protective effects of metformin were observed even in the 10

years of follow-up of the patients, despite achieving HbA1c goals in all treatment arms.[9]

Although the results of the UKPDS favor metformin, the statistical power of this trial is limited. In recent meta-analyzes that included the UKPDS, all outcomes, with the exception of stroke, favored metformin, but none of them reached statistical significance.[51] The clinical trials developed to date did not demonstrate the ability of metformin to modify clinically relevant vascular outcomes, and also confirmed an increase in cardiovascular risk and mortality with the addition of metformin to sulfonylureas versus sulfonylurea alone (HR 1.60; 95% CI, 1.02-2.52).[9]

Regarding the evaluation of the safety of DPP4 inhibitors and they effectiveness in patients with T2D, three clinical trials that assessed the cardiovascular outcomes were conducted: with saxagliptin (SAVOR-TIMI 53),[52,53] with alogliptin (EXAMINE)[54] and with sitagliptin (TECOS).[55] All of these determined statistical non-inferiority compared to placebo for the combined outcome of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke).[27] On the other hand, recent meta-analyses and the SAVOR-TIMI 53 clinical trial report that the use of saxagliptin increased hospitalizations for heart failure by 27% and reduced progressive albuminuria regardless of the initial kidney function.[52] Although the EXAMINE did not report significant differences in heart failure with the use of alogliptin versus placebo, *post hoc* analyses showed that the incidence of this pathology increased in patients with signs of heart failure at the time of randomization (RR 1.76, 95% CI, 1.07-2.90). The findings described have led to regulatory warnings for saxagliptin and alogliptin.[56] Among the patients with T2D and established cardiovascular disease, sitagliptin added to conventional therapy did not increase the risk of major adverse cardiovascular events, hospitalization for heart failure (even after adjusting for pre-existing heart failure), or other adverse events.[9,55]

The data described suggest that the increased risk of heart failure is not a class effect of DPP-4 inhibitors,[9,57] with further evidence of superiority of these drugs compared with sulfonylureas regarding hospital admission for heart failure. In the same way, clinical trials with DPP4 inhibitors reported no significant differences in microvascular outcomes[27]; i.e., they improve glycemic figures but have not been shown to have an impact on the outcomes. The most recent recommendations on DPP4 inhibitors consider them reasonable and safe options to achieve glycemic control,[30] preferably for patients who are not eligible for an SGLT2 inhibitor or a GLP-1 receptor agonist, as well as in all stages of chronic kidney disease including patients on dialysis (hemodialysis or peritoneal dialysis).[1]

In the EMPAREG OUTCOME5 study it was evidenced that empagliflozin (SGLT-2 inhibitors), compared with placebo, showed a significant reduction in the primary composite outcome (HR 0.86; 95% CI 0.74-0.99), as well as in cardiovascular death (HR 0.62; 95% CI 0.49-0.77), hospitalizations for heart failure (HR 0.65; 95% CI 0.50-0.85) and all-cause mortality (HR 0.68; 95% CI 0.57-0.82). This study was the first with adequate statistical power that showed a reduction in cardiovascular risk with the use of a new antidiabetic drug. In the CANVAS program, which integrated data from two clinical trials with a total of 10,142 participants with T2D and high cardiovascular risk, it was evidenced that the composite outcome of mortality from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke was less frequent in patients treated with canagliflozin than in those with placebo (HR 0.86, 95% CI 0.75 – 0.97; p<0.001 for non-inferiority; p = 0.02 for superiority).[58]

Regarding the renal impact of SGLT2 inhibitors, it was observed that the onset or progression of nephropathy was significantly reduced by 39% with empagliflozin, doubling of serum creatinine was reduced by 44%, and the combination of incidental nephropathy or progression and cardiovascular death was reduced by 39%.[59] It was also observed a possible benefit of canagliflozin with respect to the progression of albuminuria (HR 0.73, 95% CI 0.67-0.79) and in the composite outcome by a sustained reduction of 40% in the estimated glomerular filtration rate, the need for renal replacement therapy or death from renal causes (HR 0.60, 95% CI 0.47-0.77).[58] Similar results have also been observed with dapagliflozin, that is, it can

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also have nephroprotective effects (decrease in kidney outcomes). In Colombia, this drug is currently recommended for patients with an estimated GFR higher than 60 ml/min/1.73 m.[60]

The recommendations of the ADA (2018) include the use of empagliflozin in combination with metformin, in patients with T2D and established atherosclerotic cardiovascular disease, in order to reduce major adverse cardiovascular events and cardiovascular mortality, according to the characteristics of the patient.[25] Empaglifozin is currently approved for use in patients with a GFR higher than 45 cc/min. It is not recommended in type 2 diabetic patients with lower GFR.

To date, there are four studies of cardiovascular safety with GLP receptor agonists: ELIXA (with lixisenatide), LEADER (with liraglutide), SUSTAIN-6 (with semaglutide) and EXSCEL (with Exenatide). Regarding the vascular outcomes, the meta-analysis findings describe a significant reduction in the risk of death from all causes versus the control group (RR 0.888; CI 0.804-0.979; p=0.018) and in the risk of cardiovascular death (RR 0.858; CI 0.757-0.973; p=0.017). It was also reported that GLP1 agonists did not affect the risk of myocardial infarction, cerebrovascular accident, retinopathy and nephropathy (RR 0.866; CI: 0.625-1.199; p=0.385).[61]

In the EXSCEL study, which assessed the cardiovascular effects of the treatment with exenatide in patients with T2D and which included 14,752 patients, it was found a HR of 0.91 (95% CI 0.83-1.00) for the composite outcome of the occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. Thus, the rates of death from cardiovascular causes, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, hospitalization for heart failure and hospitalization for acute coronary syndrome, and the incidence of acute pancreatitis, pancreatic cancer, medullary carcinoma of the thyroid and serious adverse events was not different between exenatide and placebo.[62]

From the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Results (LEADER) study, the secondary renal outcomes of liraglutide compared with placebo were determined, finding a HR of 0.78 (95% CI 0.67-0.92; p = 0.003) for the composite outcome consisting of persistent macroalbuminuria of recent onset, persistent doubling of serum creatinine level, end-stage renal disease, or death from renal disease. This outcome is mainly related to the reduction in persistent macroalbuminuria, which occurred in a smaller number of participants in the group treated with liraglutide (HR 0.74, 95% CI 0.60-0.91; p = 0.004).

In the LEADER trial, which included patients with high cardiovascular risk, liraglutide significantly reduced the occurrence of major adverse cardiovascular events by 13%, cardiovascular death by 22%, and all-cause mortality by 15%, without significant effects on non-fatal myocardial infarction, non-fatal stroke and hospitalization for heart failure. The cardiovascular benefits of liraglutide were observed much earlier than in the classical trials of glycemic control in diabetes (Diabetes Control and Complications Trial [DCCT], UKPDS).

Conclusions

Among the main causes of morbidity and mortality in patients with T2D are those related to vascular damage, especially cardiovascular disease and kidney commitment. In this context, pharmacological treatment of diabetes mellitus has been focused on finding drugs that significantly reduce cardiovascular events and at the same time delay the onset of nephropathy or its progression. Thiazolidinediones, DPP4 inhibitors (alogliptin, saxagliptin, and sitagliptin), insulin glargine, and degludec have demonstrated cardiovascular safety, but no incremental cardiovascular benefit in T2D patients who are at high risk for atherosclerotic cardiovascular disease.

Large randomized controlled clinical trials have been conducted in recent years, which have reported statistically significant decrease in cardiovascular events, in general for SGLT2 inhibitors (empaglifozin, canaglifozin and dapaglifozin) and for some GLP-1 agonists (liraglutide, semaglutide and dulaglutide) in diabetic patients with atherosclerotic cardiovascular disease. The risk of hypoglycemia from these drugs is low and they have an adequate safety profile.

Finally, it is important to mention the reduction in the onset or progression of diabetic kidney disease with these drugs, even in patients with stage 3 chronic kidney disease with HbA1c higher than 7% but lower than 8%. Since the worsening of diabetic kidney disease is an important risk factor for a wide range of complications of atherosclerotic cardiovascular disease, including heart failure, the adequate use of these drugs could contribute to further closing of the prognosis gap in patients with atherosclerotic cardiovascular disease and diabetes

Thus, for patients with T2D who have atherosclerotic cardiovascular disease, it is recommended to incorporate an agent with strong evidence of cardiovascular risk reduction to the treatment with metformin, especially those with proven benefit in both major adverse cardiovascular events and cardiovascular death, after considering the characteristics and preferences of the patient on an individual basis. However, it is important to keep in mind that the fundamental axis in the management of the diabetic patient is the achievement of persistent lifestyle changes.

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Conflict of interest

Dr. Castillo reports that he has received fees from AstraZeneca, Boehringer-Ingelheim, NovoNordisk, Bayer, Pfizer, Sanofi, Abbott, Novartis, Amgen and Merck. These fees were not related to the performance of this work. Dr. Ibatá Bernal reports that she has received fees from Novartis, Astellas, AbbVie and Abbott which were not related to the performance of this work. Dr. Martínez Rojas reports that she has received grants from Novonordisk during the study; fees from Novartis, Astellas, Abbvie y Abbott, out of the work presented. Dr. Gómez has been a speaker for Novonordisk, Medtronic, Abbott, Boeringher, Astrazeneca and mSD. Dr. Rico Fontalvo, Dr. Ramírez Rincón, Dr. Melgarejo Rojas, Dr. Lopera and Dr. Rico Fontalvo declare that they have no conflict of interest.

Ethical responsibilities

Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

Right of privacy and informed consent

The authors declare that patient data do not appear in this article.

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Review article

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Cardiorenal continuum: A proposal for the prevention of cardiovascular and renal disease

El continuo cardiorrenal: una propuesta para la prevención de las enfermedades cardiovasculares y renales

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Abstract

Cardiovascular risk factors such as arterial hypertension, type 2 diabetes mellitus (DM2) and dyslipidemia are commonly involved with chronic kidney disease (CKD) and its contribution to long-term cardiovascular morbidity. Diffuse endothelial dysfunction and atherosclerosis are believed to be part of the common pathophysiology in diabetic and non-diabetic CKD, particularly in the elderly. Age is the main determinant of glomerular filtration rate (GFR) and effective renal plasma flow and it has been reported that the presence of hypertension at baseline enhances the yearly decline in creatinine clearance. Dyslipidemia may directly affect the kidney by causing deleterious renal lipid disturbances (renal lipotoxicity), as well as indirectly through systemic inflammation and oxidative stress, vascular injury, hormones change and other signaling molecules with renal action. Several cross-sectional studies found that impaired glucose tolerance, as well as the presence of left ventricular hypertrophy, is associated with an increase in the slope of the inverse relationship between age and GFR in subjects with never-treated essential hypertension. Most of the drugs used to reduce the burden of risk factor on cardiovascular disease also benefit the renal function. So, we propose the cardiorenal continuum as a preventive strategy to protect both organs and reduce the deleterious impact of the cardiovascular risk factors on the renal function considering both organs as a functional and physiopathological binomial.

Keywords: Cardiorenal continuum, cardiovascular disease, chronic kidney disease, albuminuria, risk factors, hypertension, dyslipidemia, diabetes.

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Resumen

Los factores de riesgo cardiovascular (FRCV) como hipertensión arterial (HTA), diabetes mellitus tipo 2 (DM2) y dislipidemia suelen estar involucrados con la enfermedad renal crónica (ERC) y su contribución a la morbilidad cardiovascular.

La disfunción endotelial difusa y la aterosclerosis están conceptualizadas como La disfunción endotelial difusa y la aterosclerosis están conceptualizadas como parte de la fisiopatología de la ERC en diabéticos y no diabéticos, particularmente en ancianos.

La edad es el principal determinante de la tasa de filtración glomerular (TFG) y flujo plasmático renal efectivo y se ha reportado que la presencia de HTA favorece la declinación en la depuración de creatinina. La dislipidemia puede afectar directamente el riñón causando trastorno renal lipídico (lipotoxicidad renal) e indirectamente a través de la inflamación sistémica y estrés oxidativo, agresión vascular y cambios humorales y de otras moléculas de señalización con acción renal. Varios estudios transversales han encontrado que el deterioro a la tolerancia glucosada y la presencia de hipertrofia ventricular izquierda están asociados con un aumento en la pendiente de la relación inversa entre edad y TFG en sujetos con HTA no tratada.

La mayoría de las drogas empleadas para reducir la carga de los FRCV también son beneficiosas para la función renal. De tal forma que se propone al continuo cardiorrenal como una estrategia preventiva para proteger ambos órganos y reducir el impacto deletéreo de los FRCV sobre la función renal partiendo del punto de vista de un binomio funcional y fisiopatológico.

Palabras clave: continuo cardiorrenal, enfermedad cardiovascular, enfermedad renal crónica, albuminuria, factores de riesgo, hipertensión arterial, dislipidemia, diabetes.

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Introduction

It is well known that the worldwide incidence of cardiovascular and kidney diseases tends to increase, mainly due to the greater longevity of the population and the increase in cases of type 2 diabetes mellitus (DM2) and arterial hypertension (AHT). The latter represents the greatest burden as it causes a high proportion of morbid events related to the cardiovascular, cerebrovascular and renal spheres, with a greater weight within the countries with middle and low income.[1]

Epidemiological and observational studies have allowed us to know that there is a close relationship between renal and cardiac function, where the major cardiovascular risk factors affect both organs equally. However, little importance has been given to this link.

In the series of 4102 patients hospitalized for heart failure published by Amsalem *et al.*,[2] 57% were bearers of kidney failure, but in almost 50% of them it was unknown since the serum creatinine levels were within normal values and they only presented alteration in the urinary albumin to creatinine ratio, which indicates renal damage.

Cardiorenal syndrome (CRS) is a clinical situation conditioned by the involvement of the heart and the kidney, where the damage to each of these organs potentiates the other in an accelerate way, feeding back each other with a high percentage of mortality after a few years[3]; this is a situation where there is rarely going back.

On the contrary, the cardiorenal continuum is a concept for the early preventive approach that aims to avoid damage to both organs, with which it distances itself from the CRS, given that this long-term vision implies a more proactive and more dynamic activity in the short-term to ensure the preservation or prolongation of the optimal functioning of both organs.[4]

As indicated by its name, the cardiorenal continuum is nothing more than a succession of events where it is clearly possible to intervene in order to prevent damage to both organs. It is not a clinical entity like CRS, but rather a more effective form of intervention by the physician.[4]

The elementary conception of the kidney as a simple filtering organ undergoing the onslaughts of an insufficient pump has been displaced by the understanding of a complex and robust interaction between the heart and the kidney. The above is put in evidence by Guyton,[5] who established that both one and the other are regulators of vital functions such as, for example, blood pressure (BP), vascular tone, diuresis, natriuresis, circulating volume homeostasis, peripheral perfusion and tissue oxygenation. They also have endocrine functions (related to calcium/phosphorus balance and glucose absorption/excretion) and are capable of cellular and humoral signaling.[6]

Cardiorenal continuum and interaction between cardiovascular risk factors and kidney damage

Current literature establishes that the hemodynamic regulation of the heart and the kidney is a complex and dynamic system in which changes in the function of an organ can lead to a spiral of dysfunction of both through the alteration in the balance of nitric oxide and reactive oxygen species, systemic inflammation, activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS), major cardiovascular risk factors (AHT, dysglycemia, dyslipidemia, smoking and obesity) and the influence and interaction of several substance such as cytokines, growth factors, chemotactic factors, endothelin, prostaglandins, vasopressin, and natriuretic peptides.[4,7] (Figure 1).

In fact, the contribution of non-invasive imaging techniques has been essential to know that almost two thirds of patients with chronic kidney disease (CKD) are bearers of subclinical atherosclerosis, which progresses, in just 24 months, in more than half from them.[8,9] Moreover, a significant correlation has been described between the estimated glomerular filtration rate (eGFR) and an increase in the carotid intima-media thickness in subjects with normal or near normal renal function.[10,11]

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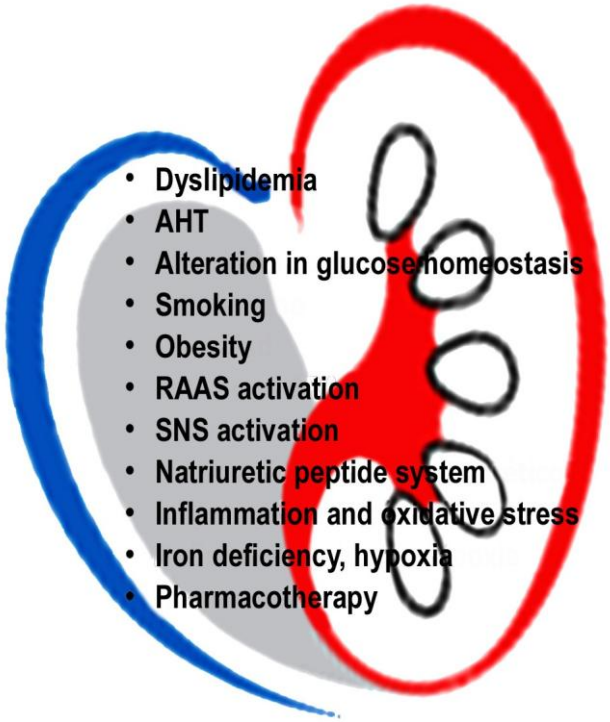

Figure 1. Dynamic and complex interactions between the heart and the kidney. AHT: Arterial hypertension; RAAS: Renin-angiotensin-aldosterone system; SNS: sympathetic nervous system. *Source: Own elaboration.*

Traditionally, it has been recognized the leading role of hypertensive disease and DM2 regarding the impact on endothelial function (vascular and renal), whose deleterious effect is expressed early in both pathologies,[12,13] especially when other cardiovascular risk factors (CVRF) such as dyslipidemia, smoking or obesity, which favor the progression of atherosclerosis and deterioration in the function of both organs are present.[14,15] The high prevalence of AHT and atherogenic dyslipidemia in patients bearers of DM2 and CKD is well known, which further darkens the prognosis of these patients[16] and obliges to an earlier, intensive and thorough management in these cases.

The updated versions of the guidelines for treatment of AHT by the American College of Cardiology/American Heart Association (ACC/AHA)[17] and the European Society of Cardiology (ESC)[18] have established blood pressure values for patients with CKD lower than in previous editions:

• ACC/AHA: <130/80 mmHg

• ESC: 130 to 139/70 to 79 mmHg

Both guidelines are highly influenced by the results of the Systolic Blood Pressure Intervention Trial (SPRINT),[19] in which it was documented that intensive treatment aiming at the goal of systolic blood pressure <120 mmHg reduces the risk of cardiovascular disease and mortality in non-diabetic adults with high cardiovascular risk, many of whom were bearers of CKD. However, its results are questioned by the methodology used in the measurement of blood pressure, so it is worth mentioning that although intensive treatment can reduce clinical events, it does not slow the progression of the CKD.

As for the alterations in glucose homeostasis (prediabetes and established diabetes), the importance of the impact of the duration of exposure to hyperglycemia in the prevention of DM2 or, at least, in the delay in its appearance is recognized today; in fact, subjects who become diabetic before 50 years of age have a higher cardiovascular and renal risk than those who remain normoglycemic,[20,21] being that the increase in 18 mg/dL above 106 mg/dL in blood glucose is associated with an increase in the risk of cardiovascular death of 11%, of major coronary events of 10%, of ischemic stroke of 8%, of vascular occlusive disease of 8% and an increase in the risk of intracerebral hemorrhage of 5%.[22] as a consequence, it is not risky to state that elevated values in plasma fasting glucose are associated with an increase in the GCVR in non-diabetic subjects.

Dyslipidemia is an important factor for progression of CKD that increases the risk of developing atherosclerosis and its complications. The participation of oxidized low-density lipoproteins that promote greater endothelial damage in the glomerular capillary, the decrease in the concentration of high-density lipoproteins and their functional capacity for the reverse cholesterol transport, the increase in the concentration of triglyceride-rich lipoproteins, the atherosclerosis of extra and intra-renal arteries, the accumulation of lipoproteins in the mesangium, and the tubular reabsorption of filtered proteins that induce fibrosis in

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the renal interstitium[14,23-25] had been proposed among the mechanisms responsible for the kidney damage.

It is worth highlighting that more than a third of hypertensive patients are also bearers of atherogenic dyslipidemia, which is why it is reasonable to think that the association of both entities produces greater kidney damage.

For several years and due to the excessive increase in overweight/obesity rates in the world population, the impact of these diseases on the cardiorenal continuum has been evidenced, especially because they are important conditioning factors in the development of AHT and DM2, a trilogy of fatal consequences that feeds back and leads to severe heart, renal and arterial lesions. In fact, McMahon *et al*.[26] state that the risk of CKD is 1.71 times higher in obese individuals than in general population (95% CI: 1.14-2.59) and Chang *et al*.[27] demonstrate that the rate of decline in eGFR is more accelerated as higher the body mass index.

As it would be expected in a very complex condition where numerous actors of first, second and third order intervene, the explanation of the pathophysiological mechanism(s) becomes more difficult to clarify. However, briefly, it can be said that the state of sodium retention; the hyperinsulinemia/insulin resistance/ lipotoxicity; intraglomerular hypertension, glomerular hypertrophy with or without secondary focal segmental glomerulosclerosis; the increase in glomerular functional demand with hyperfiltration and albuminuria, and the activation of the humoral machinery of the adipocyte with greater production of angiotensin II and stimulation of pro-inflammatory cytokines intervene in the cardiovascular continuum.[28-30]

In relation to the metabolically normal obese, there is a very particular phenotype that apparently protects these subjects from the metabolic complications of obesity but not from the risk of kidney damage,[31,32] thus, obesity, independently of the metabolic status, is an important risk factor for the deterioration of kidney function.

As for smoking, there is no doubt about the systemic harmful effect of cigarette smoke, in addition, the information related to the impact on the kidney is similar to that observed in the cardiovascular system, thus becoming the most important modifiable risk factor for both systems.

It is clear that the risk of increased urinary albumin excretion is higher in smokers. The data from the study conducted by Kuller *et al*.[33] indicate that, at least in men, smoking increases the risk of end-stage kidney disease; in fact, it is accepted that smoking is «nephrotoxic» in older adults, in hypertensive and/or diabetic subjects and in those with pre-existing kidney disease. The magnitude of the impact of the adverse renal effect of smoking is independent of the underlying kidney disease[34] and can be exerted by the following mechanisms:

- Nicotine induces apoptosis of the podocytes through the generation of reactive oxygen species and the consequent promotion of oxidative stress associated with downstream signaling of mitogen-activated protein kinases (MAPKs).[35,36]
- Nicotine favors the proliferation and hypertrophy of mesangial cells via neuronal and non-neuronal nicotinic acetylcholine receptors.[35-37]
- Blood pressure rises, especially in hypertensive patients, during and after each cigarette.

Clinical relevance of the cardiorenal continuum

It has been briefly exposed the solid connection between the CVRFs and kidney damage, which as such is the basis of this proposal to conceptualize the cardiorenal continuum (Figure 2) as a form of approach of early intervention in cardiovascular and renal protection to reduce the morbidity and mortality derived from the involvement of both organs, since pathophysiological alterations in one lead to deterioration in the function of the other.[4] In other words, "*when the heart suffers, the kidney cries and vice versa*.»

The fundamental goal of prevention is to avoid the appearance of the CVRFs in the general population. Once they are present, they influence the development and progression of endothelial

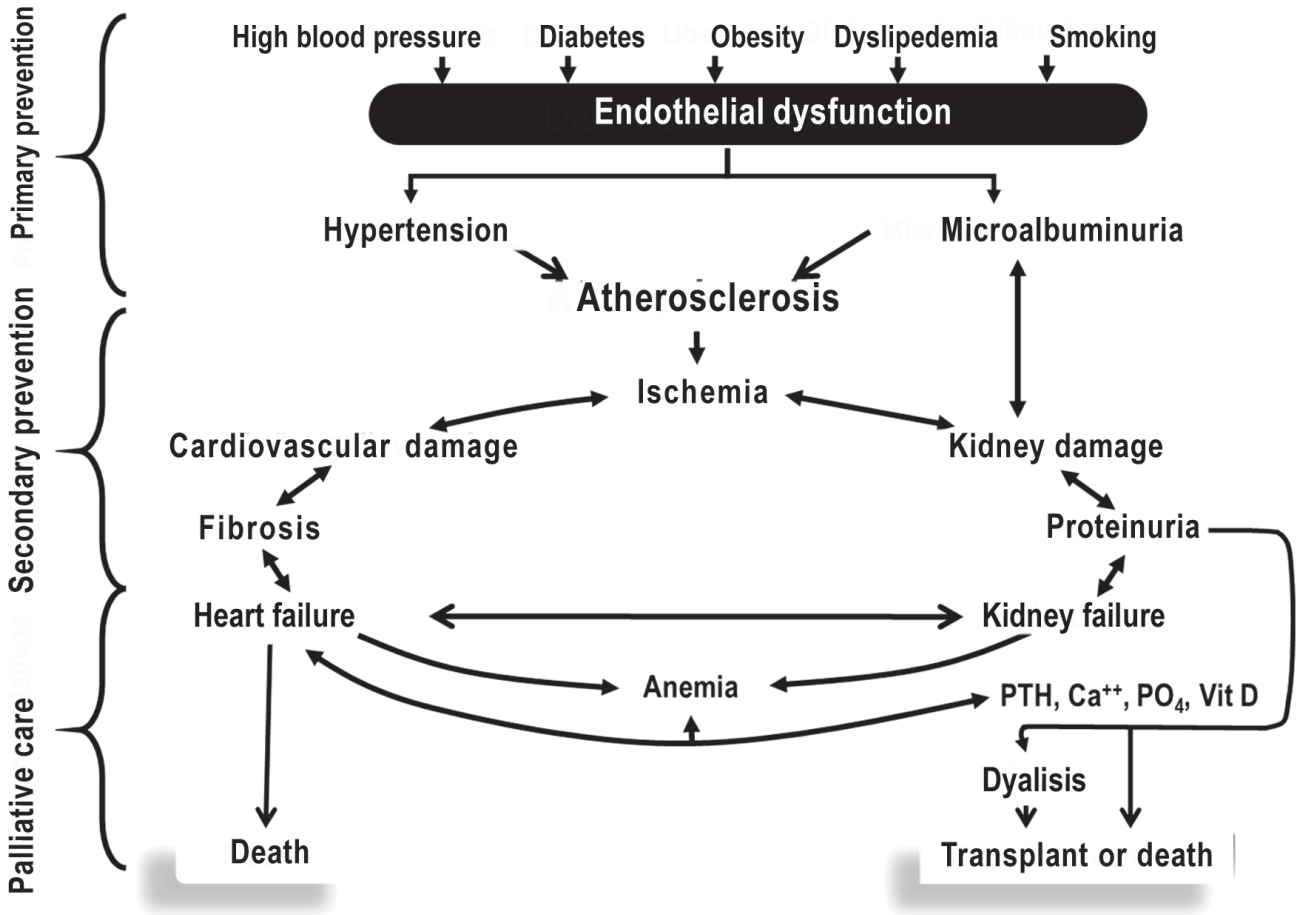

Figure 2. Vision of the cardiorenal continuum. PTH: parathyroid hormone; Ca++: calcium; PO4: phosphate; Vit D: vitamin D. *Source: Elaboration based on Arocha & Amair.*[4]

dysfunction, which could be expressed by accentuation of the elevated BP or by albuminuria, with which atherosclerosis is favored and begins the cycle of cardiac and renal damage until developing heart failure or kidney failure, two conditions that interact with a high mortality.

The actuation windows had been placed in the left margin: primary prevention on the CVRFs and secondary prevention to delay cardiac and renal damage and palliative care in the last evolutionary phase.

The major risk factors for the development of cardiovascular diseases are: obesity, AHT, DM2, dyslipidemia and smoking, which are also the main producers of kidney damage and acceleration of the progression of the kidney disease; therefore, they are fundamentals of the cardiorenal continuum for renal protection.

The presence of kidney disease is included as an independent risk factor for cardiovascular disease in various guidelines for the management of AHT.[17,18,38] In fact, the percentage of patients with kidney disease who die during follow-up due to cardiovascular complications is very high compared to those who progress to renal replacement therapy.[39]

In the studies conducted by Ruilope *et al.*[40] and Mann *et al.*,[41] patients with plasma creatinine between 1.3 and 1.4 mg/dL showed a significantly

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higher incidence of primary cardiovascular events and cardiovascular and global mortality compared to those who had normal renal function; therefore, a small elevation of creatinine (even taking into account its imprecision, since to increase the plasma creatinine concentration, renal function must decrease by 50%) indicates evident kidney damage and an increased risk of cardiovascular disease.

Relationship between renal function and cardiovascular morbidity and mortality

The interconnection between kidney damage and cardiovascular morbidity and mortality is notable and increasing as the deterioration of renal function progresses, to the point that cardiovascular mortality in dialysis patients is 500 times higher than that of the general population.[42]

Go *et al*.,[43] in a large database with more than 1.1 million adults, studied the relationship between the glomerular filtration rate estimated by the Modification of Diet in Renal Disease formula and the risk of mortality, cardiovascular events and hospitalization. After adjusting for age, gender, race, comorbidity, and socioeconomic status, the authors evidenced an increased risk of any of these three outcomes as glomerular filtration rate decreased.

Meanwhile, Keith *et al*.[44] conducted a longitudinal follow-up study of 27,998 patients with a glomerular filtration rate <90 mL/min/1.73 m^2 in two determinations and pointed to the AHT, the coronary heart disease and congestive heart failure as the entities most associated with CKD.

The follow-up study conducted by Cerasola *et al*.[45] demonstrated the close relationship between the abdominal circumference and the systolic blood pressure with early deterioration of kidney function in hypertensive patients without repercussion on target organs. For their part, Hemmelgarn *et al*.,[46] in another community-based observational study aimed at analyzing the relationship between deterioration of eGFR, proteinuria, and clinical outcomes in nearly 1 million patients, concluded, after a 35-month follow-up, that the risks of death, myocardial infarction, and progression to renal failure were associated with a given level of eGFR (<60 mL/min/1.73 m^2) and increased independently in patients with a higher level of proteinuria.

Therapeutic strategies in cardiorenal protection

Because it is a very extensive and well-known topic, this review supports that the therapeutic measures widely recognized and used in cardiovascular medicine – such as antihypertensive agents, RAAS inhibitors, beta-blockers, statins, platelet antiaggregants and proprotein convertase subtilizing/kexin type 9 inhibitors have also demonstrated to be nephroprotective.[47-51]

Consequently, it is essential to insist that they should be used at the correct dose, early and for a prolonged or indefinite period to guarantee adequate protection of both organs and to remember that clinical and therapeutic inertia is responsible for the failure of early intervention and/or dose adjustment with the consequent vascular and kidney damage.[4]

Conclusions

The heart-kidney interrelationship constitutes a pathophysiological and clinical reality with multiple common etiological factors and complications that interact with each other, hence its integration in the cardiorenal continuum allows, in the one hand, to understand the need for early and energetic control and treatment of the common risk factors and, on the other, to intervene since the earliest stages (primordial prevention and primary prevention) to avoid the development and progression of cardiovascular and renal damage, especially in high risk groups such as the population over 60 years of age, prediabetics (including those with metabolic syndrome) and diabetics, hypertensive patients and subjects with obesity.[4,7,14,17,18]

Early evaluation of renal function in all patients belonging to the aforementioned higher risk categories allows early detection and intervention

to reduce the risk of cardiovascular events, kidney failure and death. Furthermore, it is clear that all those interventions aimed at slowing the progression of renal function deterioration pay off by reducing cardiovascular risk and vice versa.

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Conflict of interest

None declared by the authors.

Ethical responsibilities

Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

Right of privacy and informed consent

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Contribution of the authors

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Review artiche

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Urinary tract infection in chronic kidney disease patients

Infección del tracto urinario en la enfermedad renal crónica

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Abstract

Infections in chronic kidney disease patients are a major cause of morbidity and mortality. Renal patients have specific risk factors for acquiring infections, which also tend to be more severe and have a more rapid progression and slower resolution than in the healthy individuals. Urinary tract infection in renal patients is often complicated due to the presence of diabetes, multiresistant microorganisms, anatomic or functional abnormalities of the urinary tract, metabolic disturbances and the frequent use of urinary catheters. It causes one of the highest rates of hospitalization among dialysis patients and is highly prevalent in kidney transplantation. The aim of this work is to review the etiology, microbiological diagnosis and treatment of urinary tract infections in chronic kidney disease patients.

Key words: Urinary tract infections, chronic kidney disease, renal replacement therapy, dialysis, kidney transplantation, hospitalization.

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Resumen

Las infecciones en personas con enfermedad renal crónica son una causa importante de morbimortalidad. Los pacientes renales presentan factores de riesgo específicos para la adquisición de infecciones, que además suelen ser más graves, de progresión más rápida y de resolución más lenta que en sujetos sanos. La infección del tracto urinario en esta población es a menudo complicada debido a la presencia de diabetes, microorganismos multirresistentes, anomalías anatómicas o funcionales del tracto urinario, alteraciones metabólicas y el uso frecuente de sonda vesical. Las infecciones urinarias ocasionan una de las tasas más altas de hospitalización en diálisis y son muy prevalentes en el trasplante renal. Este trabajo tiene como objetivo revisar la literatura publicada sobre la etiología, el diagnóstico microbiológico y el tratamiento de las infecciones del tracto urinario en pacientes con enfermedad renal crónica.

Palabras clave: infecciones urinarias, insuficiencia renal crónica, terapia de reemplazo renal, diálisis, trasplante de riñón, hospitalización.

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Introduction

Urinary tract infection (UTI) includes a heterogeneous group of processes with a variable clinical symptomatology. Its incidence in the population has changed in the last decade, with an increase in the prevalence of community-based UTI, among other reasons due to the increase in life expectancy, while the prevalence of nosocomial UTI has decreased significantly, due to the reduced use of urinary catheters and the replacement of open circuits with closed ones.[1]

Chronic kidney disease (CKD) is defined as the presence for at least three months of an estimated glomerular filtration rate (eGFR) lower than 60 ml/min/1.73 m^2 or the existence of kidney injury, defined by the presence of structural (detected by ultrasound) or functional (presence of albuminuria or alterations of the urinary sediment or electrolyte secondary to glomerular, vascular or tubulointerstitial damage) renal abnormalities.[2]

Infectious complications in CKD constitute an important source of morbidity and mortality, especially in patients undergoing renal replacement therapy (RRT), either hemodialysis, peritoneal dialysis or kidney transplantation, presenting an infectious process with a three-fold higher frequency.[3-7] The occurrence of infections in CKD is independently associated with progression to end-stage CKD, cardiovascular ischemia, congestive heart failure, and mortality.[8]

The patient with CKD has more often risk factors for acquiring different infections. On the one hand, uremia causes alterations in the humoral response, the lymphocyte function, the macrophages and the polymorphonuclear cells. On the other hand, the underlying cause of CKD is sometimes a condition that compromises the normal voiding of urine and the integrity of the urinary tract, or implies its manipulation (vesicoureteral reflux, neurogenic bladder, urethral valves, prostatism, bladder catheterization, renal catheterization, complicated lithiasis, polycystosis). In other cases, diabetes is the underlying cause of both CKD and the greater susceptibility to the appearance of UTI and its worse evolution, especially in elderly and female patients.

The incidence of UTI in CKD increases as the disease progresses and the defense mechanisms against the infection become deteriorated.[9] In patients on dialysis they are responsible for high hospitalization rates, followed only by lung infection and sepsis.[4] In the case of kidney transplant recipients, bacteriuria is even more frequent (35-80%) as well as its progression to UTI due to previous infections in the transplanted kidney, manipulation of the urinary tract and immunosuppressive medication.[10] The occurrence of UTI is the first cause of bacteremia in these patients and implies an increased risk for emergence of renal failure and graft failure.[11]

Despite the undoubted increase in the number of patients with CKD in recent years, there are few publications on UTI in this population, in which the antibiotic treatment is also an especially problematic issue, since it entails the risk of nephrotoxicity and the need for pharmacological adjustment to renal function or dialysis; the low pH in the urinary medium and the endothelial alterations in turn tend to reduce the effectiveness of the treatments.

The objective of this review is to offer a complete, practical and updated view on the particularities of the management of complicated and uncomplicated UTI in patients with CKD.

Classification of UTI

According to their anatomical location, urinary infections are classified as: 1) lower tract infections: urethritis, cystitis, prostatitis, and epididymo-orchitis; and 2) of the upper urinary tract: acute pyelonephritis, intrarenal abscess, perinephric abscess and infectious papillary necrosis. The first group is more frequent and is triggered via ascending route, while the second group can originate both by ascending route and hematogenous route (bacteremia). Although the symptomatic location of the UTI is defined at a certain level, all the tissues of the urinary tract can be partially affected. The symptomatology, the prognosis, and the therapeutic guidelines are different in each clinical situation.

Asymptomatic bacteriuria is defined by the presence of more than 100,000 CFU/ml in two urine

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samples in the absence of clinical symptoms, although it is accompanied by overt leukocyturia in the majority of diabetic and elderly patients. In general, asymptomatic bacteriuria does not require treatment, except in the following cases, in which its systematic detection is recommended: pregnant women (if not treated, it can lead to pyelonephritis in 20-40% of cases),[12] children under 5 years of age (especially if they present vesicoureteral reflux), patients undergoing manipulation of the urinary tract (risk of bacteremia), neutropenic patients (risk of sepsis) and kidney transplant recipients (per protocol in the first 3-6 months after transplantation due to the risk of sepsis and graft failure).[13]

It is considered an **uncomplicated UTI** the one which affects individuals with a structurally normal urinary tract and whose defense mechanisms are intact. The majority of these infections respond well to antibiotic treatment. Cystitis is characterized by dysuria, frequency of urination and imperious mictional urge (voiding syndrome), often accompanied by suprapubic pain, bad-smelling urine and hematuria; in women –and especially in elderly women- urinary incontinence is relatively frequent. In women with voiding syndrome, the differential diagnosis of cystitis with infectious or traumatic urethritis and with vaginitis can be considered; in young or middle-aged men with voiding syndrome and absence of urological pathology or manipulation of the urinary tract, urethritis should be ruled out, especially if there is urethral suppuration, or prostatitis, if the infection is recurrent.

We talk about **complicated UTI** when it affects patients with anatomical or functional abnormalities of the urinary tract, urinary tract instrumentation, indwelling urinary catheter, CKD, diabetes, metabolic abnormalities, immunosuppression, or the presence of multi-resistant microorganisms (Table 1). Diabetic patients are more susceptible to the progression of the infection to the renal parenchyma, especially in UTI due to enterobacteria[14] and when there are associated risk factors such as advanced age, proteinuria, low body mass index, CKD, autonomic neuropathy and a history of recurrent UTI.[15] Early diagnosis and adequate treatment are essential to avoid complications that cause the deterioration of kidney function.[16,17]

Acute pyelonephritis should be suspected in the presence of fever, chills, impaired general condition, low back pain or positive fist percussion; and with less frequency, nausea or vomiting. Around 30% of patients with cystitis suffer from silent infection of the renal parenchyma, especially men and pregnant women, children under 5 years of age, diabetics, immunosuppressed individuals, patients with CKD, anatomical or functional abnormality of the urinary tract or UTI due to *Proteus*. Acute pyelonephritis usually presents with leukocytosis with a left shift and bacteremia in 20-30% of cases, of which one third results in septic shock. Kidney function can be impaired by sepsis, endotoxemia, hypotension, and renal hypoperfusion.[18]

Chronic pyelonephritis arises in patients with significant anatomic alterations, such as obstructive

Table 1. Factors that define a complicated UTI.

Structural abnormalities
Urinary tract obstruction, prostatitis, renoureteral lithiasis, urinary diversion procedures, renal cyst infection, urinary catheters, bladder catheter, vesicoureteral reflux, neurogenic bladder, renal abscess, urinary tract fistulas
Metabolic abnormalities
Diabetes, pregnancy, kidney failure
Immunity alterations
Solid organ transplantation, neutropenia, congenital or acquired immunodeficiencies
Unusual or multidrug-resistant pathogens
Fungi, *Mycoplasma*, *Pseudomonas aeruginosa* and other resistant bacteria, producers of ESBL and carbapenemases, stone-forming bacteria (*Proteus*, *Corynebacterium urealyticum*).

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uropathy, struvite stones or, more frequently, vesicoureteral reflux, which occurs in 30-45% of children with symptomatic infections.[19] This chronic, patchy and often bilateral infection of the kidneys produces calyceal atrophy and deformation, with scarring of the overlying parenchyma, and constitutes, together with chronic interstitial nephritis and proportionally to increasing age, the etiology of end-stage CKD in 11-28.6% of patients under RRT with dialysis or kidney transplantation, according to the most recent data available from the Spanish Registry of Renal Patients.[20]

Microbial etiology of UTI in CKD

The pathogenic microorganisms that can cause UTI are very varied and come from all levels of the biological kingdom: bacteria, fungi, viruses and parasites.

The infection is bacterial and monomicrobial in more than 95% of cases; the rest are found in hospitalized, instrumentalized or surgically intervended patients for urological pathology, with neurogenic bladder and/or permanent urinary catheter bearers.[21]

The etiology of UTI varies depending on the type of infection, the existence of predisposing factors, previous antimicrobial treatments, and the acquisition context (community or nosocomial). Most episodes are produced by microorganisms that come from the colon and, therefore, the fecal microbiota of the patient conditions to a great extent the etiology of the UTI; the rest have an exogenous etiology, due to microorganisms introduced into the urinary tract during its manipulation. Acute pyelonephritis of hematogenous origin is rare and is usually produced by *Staphylococcus aureus* and yeasts.

UTI in CKD patients has a microbial etiology similar to that of the rest of the population, with a predominance of gram-negative bacilli over gram-positive cocci.[22] However, the frequency of gram-positive cocci and yeasts in the UTI of patients with CKD is much higher than in the general population. As a reference, in a review of 21,083 positive urine cultures of patients from the Puerta del Mar de Cádiz University Hospital (Spain), we found 24.9% of UTIs due to gram-positive cocci and 6% due to yeasts in patients with CKD in relation to 7.9% and 1.7% in the general population, respectively (Table 2). Another important fact is that the frequency of mixed infections and by microorganisms resistant to conventional antimicrobials increases in patients with CKD.[22] In the case of our series, we found 6.4% of strains of extended spectrum beta lactamases (ESBL) producing *Escherichia coli* and 7.3 and 9.1% of ESBL and carbepenemases producing *Klebsiella pneumoniae* respectively.

Escherichia coli is the microorganism most frequently implied in any type of patient, both in the hospital and out-of hospital settings, and in complicated and uncomplicated UTI.[23,24] Its frequency is lower in treated patients and in chronic infections, at the expense of other opportunistic microorganisms in the presence of comorbidity, antibiotic therapy, immunosuppression, urological instrumentation and surgical maneuvers. The existence of colonization factors, such as pili or fimbriae in *E. coli*, with high affinity for P1 glycosphingolipids of the cells of the urethral epithelium, gives it greater adherence and rapid invasion of the urinary tract, although not all strains have the same ability to infect the urinary system. Four phylogenetic groups have been identified in *E. coli*, which are referred to as A, B1, B2 and D. Extraintestinal pathogenic *E. coli* strains, including the uropathogenic ones, derive mainly from the B2 group and to a lesser extent from the D group and harbor genes encoding extraintestinal virulence factors. The isolates of *E. coli* of the B2 group cause 69% of cystitis, 67% of pyelonephritis and 72% of urinary sepsis.[24]

In patients with CKD, there is an increased frequency of UTI produced by other gram-negative bacilli of the group of enterobacteriacea different from *E. coli*, such as *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Morganella morganii* and *Citrobacter freundii*, together with *Pseudomonas aeruginosa*, generally present in patients bearers of Foley catheters and in complicated infections. In the abovementioned series we have observed a higher proportion of UTIs caused by *Proteus mirabilis* in

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Table 2. Microbial etiology of UTI in CKD vs. without CKD.

Microorganisms	699 patients with CKD		20,384 patients without CKD	
	Number	Percentage (%)	Number	Percentage (%)
Escherichia coli	296	42,35	13.123	64,38
Klebsiella pneumoniae	55	7,87	1.554	7,62
Pseudomonas aeruginosa	46	6,58	1.017	4,99
Proteus mirabilis	28	4,01	1.628	7,99
Enterobacter cloacae	25	3,58	278	1,36
Morganella morganii	14	2	292	1,43
Enterobacter aerogenes	6	0,86	227	1,11
Acinetobacter baumannii	6	0,86	211	1,03
Citrobacter freundii	5	0,72	3	0,01
Serratia marcescens	2	0,29	94	0,46
Total Gram-Negative bacilli	483	69,1	18.427	90,4
Enterococcus faecalis	89	12,73	1.042	5,11
Enterococcus faecium	26	3,72	26	0,13
Staphylococcus epidermidis	24	3,43	166	0,81
Streptococcus agalactiae	14	2	159	0,78
Staphylococcus aureus	9	1,29	123	0,6
Staphylococcus saprophyticus	7	1	85	0,42
Staphylococcus coagulase (-)	5	0,72	16	0,08
Total Gram-Positive cocci	174	24,89	1.617	7,93
Candida albicans	36	5,15	300	1,47
Candida glabrata	4	0,57	28	0,14
Candida parapsilosis	2	0,29	12	0,06
Total yeasts	42	6,01	340	1,67

*Data from the Puerta del Mar University Hospital, Cádiz.

the general population and a slight predominance of *Enterobacter aerogenes*, *Acinetobacter baumannii* and *Serratia marcescens*. Regarding the gram-positive cocci, *Enterococcus faecalis*, *Enterococcus faecium*, *Streptococcus agalactiae* and the various species of *Staphylococcus* constitute, in CKD patients, the etiology of the UTI not caused by gram-negative bacilli, with a frequency clearly higher than in the general population.[25] The same happens with yeasts, especially with the *Candida albicans* species, responsible for ITUs in immunosuppressed patients, even more in diabetics and in those who have indwelling catheters.[26]

E. coli and *Klebsiella pneumoniae* strains that produce extended spectrum beta-lactamases (ESBL) and carbapenemases deserve a special mention. Resistance to carbapenems may be due to the production of carbapenemases or of enzymes that alter the action of carbapenems in association with other mechanisms such as alterations in the permeability of the wall of the strain, due to modifications in its porins.[27,28] CKD patients more frequently have one or more risk factors for developing infections with ESBL (+) strains, such as diabetes, the use of urinary or vascular catheters, hemodialysis treatment and the previous use of

broad-spectrum cephalosporins and quinolones.[29] In addition, ESBL-producing strains are often resistant to other groups of antimicrobials, including aminoglycosides and fluoroquinolones, further limiting treatment options.[30]

Diagnosis of UTI

The diagnosis of UTI is usually established by the symptoms and the presence of leukocytes, nitrites, leukocyte esterase and bacteria in the urinary sediment. Even though the guidelines do not recommend this method in the general population except in doubtful cases, symptomatic recurrence, or limited therapeutic options due to intolerance or allergies to antibiotics,[31] in the population with CKD, this suspicion should be confirmed, if possible, by the demonstration of the etiologic agent by urine culture,[32] given the higher risk of multidrug resistance in this population.

Urine culture. The urine culture is a method of study of the UTI that has not been superseded by automated techniques. It is essential to distinguish an accidental contamination from significant bacteriuria. It is performed taking into account the urinary sediment and/or the Gram stain of a drop of non-centrifuged urine.

Urine culture is aimed at the isolation of the highest number of microorganisms with the lower number of culture media; the use of at least two plates is recommended: one of blood agar or chocolate agar, for the quantitative estimation of the bacteriuria by means of the colony count, and another of a lactose selective agar (MacConkey agar), for the differentiation of enterobacteria and other gram-negative bacilli.

Most UTIs have bacterial counts equal to or greater than 100,000 CFU/ml, but 20% have counts between 1,000 and 100,000 CFU/ml.[33] The quantitative appreciation of the bacteriuria is subject to numerous circumstantial factors: collection of the urine, physicochemical conditions thereof, speed of the exam, presence of labile microorganisms, and the circumstances of the patient and the infection. The following situations can be considered:

- In urine obtained by suprapubic puncture or nephrostomy, any count is indicative of infection.
- Bacteriuria between 1,000 and 10,000 CFU/ml suggests contamination, especially if it is of mixed flora. Some microorganisms, such as *Staphylococcus* and *Candida*, should be assessed with low counts.
- If there are between 10,000 and 100,000 CFU/ml of a single microorganism, a UTI should be suspected. The repetition of the culture, the presence of leukocyturia and the symptoms help to the correct interpretation. A repeated culture with more than 50,000 CFU/ml of the same organism confirms the UTI.
- Counts equal to or higher than 100,000 CFU/ml are indicative of UTI. Mixed infections are rare and are generally the result of inadequate sample collection, except in patients with indwelling catheters or anatomical abnormalities.

The urine culture may be negative or of doubtful assessment in the following cases: UTI due to microorganisms with culture exigencies, presence of L-forms, prostatitis, urethritis, chronic and recurrent pyelonephritis, urinary obstruction due to lithiasis, increased diuresis, recent previous urination and presence of antimicrobials in the urine.

Diagnosis of UTI in patients with CKD. As mentioned, patients with CKD at any stage, as well as those with kidney transplants, present different degrees of immunosuppression that make it necessary to be alert about the possible appearance of a complicated UTI. In the case of a UTI with fever, it is necessary to rule out the elevation of acute phase reactants, such as C-reactive protein and erythrocyte sedimentation rate, as additional data of severity and markers of evolution. However, the absence of a febrile response in patients on RRT and kidney transplant recipients is not uncommon, therefore, given the affectation of the general condition; such determinations should be made in this group of patients.

Unlike the general population, in which the hyperechogenicity of the parenchyma studied by

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renal ultrasound may be a finding suggestive of its involvement with the development of pyelonephritis, patients with CKD present this abnormality at baseline, so its appearance will not mean the development of this complication in the absence of other data thereof. Even so, the technique may be useful in suspected UTI complicated by renal abscess, xanthogranulomatous pyelonephritis, emphysematous pyelonephritis, coraliform lithiasis, and urinary tract obstruction.

Additionally, the following particularities of the diagnosis of UTI in patients with CKD must be taken into account:

- The prevalence of diabetes is high in the population with CKD and the symptoms may be scarce when it is present.
- Patients on hemodialysis are often anuric, so the symptoms can be reduced to suprapubic pain. Likewise, the presence of UTI should be suspected in an anuric patient on hemodialysis who suddenly recovers spontaneous voiding.
- In peritoneal dialysis, the diagnosis of UTI must be accompanied by a vigilant attitude regarding the eventual appearance of peritonitis as a complication thereof.

Treatment of UTI in CKD

The treatment of UTI is based on two fundamental pillars: adequate patient instruction and bacteriological surveillance. Besides prescribing antimicrobials, measures to prevent UTI should be established: adequate water intake, frequent urination, complete emptying of the bladder (abdominal press), hygienic measures after defecation and antibiotic prophylaxis prior to manipulation (cystography, flowmetry, urethral dilation, double J replacement, etc.).

In antimicrobial treatment, it is necessary to consider the etiological variability and the circumstances that predispose to infection, as well as the different clinical forms thereof, which will entail special treatment guidelines in each case. The main purpose of treatment is to eradicate the microorganism from the entire urinary tract, taking into account whether it is a simple or complicated UTI in which the urinary emptying mechanism is affected or there are foreign bodies.

Antimicrobial treatment is administered under the following recommendations:

- Oral route is recommended.
- Bactericidal antibiotics are preferred over bacteriostatic agents.
- They should not be associated with each other, since a microorganism in bacteriostasis is less sensitive to a bactericidal agent.
- The antimicrobials with the highest urinary elimination in active state are chosen, considering the pH.
- Those with a limited spectrum of action are preferably used to modify the patient's flora as least as possible. In case of reinfection, it will be changed for another until the orientation of the antibiogram is known.[34]
- Caution will be taken with nephrotoxic antibiotics, adjusting the dose according to creatinine clearance or, if not available, to the estimated glomerular filtration rate.
- Those antimicrobial agents for which local resistance is greater than 20% in the case of cystitis and greater than 10% in the case of pyelonephritis should be avoided in empirical treatment.[34]
- Peritoneal dialysis and hemodialysis are capable of filtering out different antimicrobials, which should be avoided, adjusted or administered after dialysis[35] (Table 3).

There is no evidence in the medical literature that antimicrobial treatment can prevent the complications of a serious UTI. The poor correlation between the severity of the symptoms and the risk of permanent kidney damage, which is very small in terms of the

Table 3. Antimicrobials dialyzed in peritoneal dialysis and hemodialysis

Antimicrobial		
Dialyzed	**Dialyzed**	**Dialyzed**
Aminoglycosides	Cotrimoxazole	Amphotericin B
Amoxicillin	Erythromycin Fluoroquinolones	Ethambutol
Ampicillin	Vancomycin	Isoniazid
Aztreonam		Methycillin
Carbenicillin		Rifampicin
Cephalosporins		Teicoplanin
Fluconazole		
Metronidazole		

progression of the CKD, leads to not exceeding the prescription of antibiotics beyond the necessary to suppress the acute inflammatory reaction.[36]

Urine pH and osmolality can influence the antibacterial efficacy, especially in the case of aminoglycosides.[37] All penicillins reach high concentrations in urine, but ciprofloxacin has levels higher than amoxicillin with clavulanic acid.[38] The same occurs with levofloxacin, but not with other quinolones such as gemifloxacin and moxifloxacin, which have low urinary concentrations. Nitrofurantoin is not indicated in patients with creatinine clearance lower than 40 ml/min due to little or no excretion in urine.[39]

Antimicrobial treatment of **complicated UTI** (it is by definition in patients with CKD) will be carried out with a single dose of 3 g of fosfomycin, or treatment with nitrofurantoin for seven days (provided that the GFR is higher than 40 ml/min).[31] Other alternatives are seven days with amoxicillin-clavulanate or a fluoroquinolone (only if local resistance is low for these agents) in case of allergy to beta-lactam antibiotics.[40] In pyelonephritis, the choice of the antibiotic is conditioned by the special need for penetration into the renal parenchyma and the duration is 10-14 days, parenterally at the beginning if the patient meets the admission criteria. Quinolones are more effective in penetrating the parenchyma, but they do not show activity against enterococci, so they are not recommended in our environment.

In patients with CKD and **community-acquired pyelonephritis** without specific risk factors for colonization by multidrug-resistant enterobacteria, empirical treatment with cefuroxime or a third-generation cephalosporin is recommended, which will be replaced in case of allergy by fosfomycin, or as a last resort by aztreonam or an aminoglycoside (taking special care due to its nephrotoxicity). In the case of risk factors for the presence of multiresistant microorganisms (diabetes *mellitus*, indwelling urinary catheter, hemodialysis), ertapenem is recommended, although other carbapenems or piperacillin-tazobactam are accepted alternatives. In case of allergy to penicillin, the alternative is the use of intravenous fosfomycin sodium, resorting to amikacin as the last option under close monitoring of renal function due to its nephrotoxicity. (In the case of a patient already on dialysis, nephrotoxicity will not constitute a limitation for its use at the doses that correspond to this condition).[31]

In the case of **healthcare-associated pyelonephritis**, the first choice is a carbapenem with anti-pseudomonal activity, or piperacillin-tazobactam. In allergic patients, aztreonam, intravenous fosfomycin sodium, amikacin should be considered as a last

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resort, or the combination of the latter two agents (Table 4). It is recommended to associate coverage for enterococcus in patients with nosocomial pyelonephritis and severe sepsis or risk of endocarditis (e.g., for being a heart valve bearer). As soon as the antibiogram is available, antibiotic therapy should be adjusted reducing coverage. If in the next 48-72 hours the patient with pyelonephritis is afebrile and stable, is switched to oral treatment according to the antibiogram and is maintained for 10-14 days. The persistence of fever at 72 hours of treatment or worsening during treatment may be due to acute focal bacterial nephritis, focal suppurative complication, urinary obstruction, papillary necrosis, emphysematous pyelonephritis and an antibiotic resistant microorganism.[41] UTI caused by yeasts in diabetic patients or with indwelling catheters, even asymptomatic, should be treated with antifungal agents (fluconazole, voriconazole, amphotericin B); removal of the catheter is usually necessary to eliminate the source of infection.

Once the treatment is finished and after 48 hours, it is advisable to perform a control culture to detect recurrent infections due to therapeutic failure. Subsequent infections should be considered for long-term treatment (reinfections) or the study of possible pyelonephritic lesions or urological pathology (relapses).[41,42]

In the case of multiresistant microorganisms, the use of fosfomycin has proven to be useful in blocking the first step of the synthesis of the bacterial wall of a variety of both Gram-positive and Gram-negative microorganisms, and exerting synergy with other antimicrobials.[43]

Vaccination in UTI

Vaccines for recurrent UTI are intended to reduce the frequent use of antibiotics, adverse events, and bacterial resistance, prolonging the interval

Table 4. Guidelines for the treatment of UTIs in CKD.

Urinary tract infection (complicated by definition in CKD)	
Usual treatment for 7 days (except with fosfomycin): Fosfomycin-trometamol 3 g in a single dose Nitrofurantoin (Only if eGFR > 40 ml / min) Amoxicillin clavulanate 500/125 mg every 8 h Ciprofloxacin 250-500 mg/12 h (only if low local resistances) Levofloxacin 500 mg/24 h (only if low local resistances)	
Acute pyelonephritis Treatment 10 to 14 days. Intravenous route if there are criteria for admission. Adjust dose to renal function.	
No risk factors for multidrug resistance	
No allergy to beta-lactams	Allergy to beta-lactams
Cefuroxime 3rd generation cephalosporin	Fosfomycin Aztreonam Aminoglycosides (last option)
With risk factors for multidrug resistance	
No allergy to beta-lactams	Allergy to beta-lactams
Ertapenem Piperacillin-tazobactam	Aztreonam IV Fosfomycin sodium ± amikacin (last option)

between infections or radically reducing their incidence.

In a meta-analysis conducted by Naber *et al*.[44] with the vaginal vaccine SolcoUrovac® and the oral Uro-Vaxom®, it was observed that the number of UTIs was significantly lower in the patients treated with the oral vaccine. The vaginal vaccine was effective when it was administered with a booster cycle (50% of non-recurrence versus 14% with placebo).

The individualized bacterial vaccine Uromune®, which is applied sublingually for a minimum of three months and acts as an immunomodulator for the prevention of recurrent UTI, has been available since 2010. It contains whole bodies of selected inactivated bacteria from the main organisms that cause these infections: *E. coli, Proteus vulgaris, Klebsiella pneumoniae, Enterococcus faecalis, Staphylococcus saprophyticus* and *Proteus mirabilis*.[45]

Lorenzo-Gómez *et al*.[46] retrospectively studied 669 women with recurrent UTI: 339 had taken antibiotic prophylaxis for six months and 360 had received the Uromune® sublingual bacterial vaccine for three months. All patients (100%) treated with antibiotics had at least one episode of UTI during the 12-month follow-up period, with a mean of 19 days free of UTI and a range of 5-300 days, while only 35 patients (9.7%) of the Uromune® group presented it. The reduction of the absolute risk amounted to 90.28% and the number of patients needed to treat was 1.1. The same authors[47] compared Uromune® for 3 months versus prophylaxis with trimethoprim sulfamethoxazole (200/40 mg/day) in 319 women. The 159 patients who received Uromune® experienced a significant reduction in the number of UTIs compared to the 160 who received the antibiotic (0.36 vs. 1.6, respectively, p <0.0001). A significant reduction was also observed at 9 and 15 months (p <0.0001). The number of patients who did not have any UTI at 3, 9 and 15 months were 101, 90 and 55 in the Uromune® group and 9, 4 and 0 in the antibiotic prophylaxis group.

Yang B *et al*.[48] treated with Uromune® for three months 77 women with recurrent UTI, of whom 75 completed the treatment, and they found that 78% of them did not have any UTI episode during the follow-up period, which lasted 12 months.

There are no published studies on the use of the bacterial vaccine in the population with UTI and CKD. In a series of more than 50 patients with recurrent UTI and CKD, treated with the bacterial vaccine in our center, the Hospital La Mancha-Centro de Alcázar de San Juan (Ciudad Real, Spain), It was observed that, after two years, one fifth of the subjects have not had a UTI again and the number of episodes was reduced by two thirds.

However, the results of clinical trials have shown limited efficacy, but they are too few to draw conclusions.[49] More studies are needed in the population with CKD to assess the benefits of sublingual vaccination to prevent UTI and the efficacy of extending the duration of vaccination to six months, due to predisposing and concomitant factors for the appearance of UTI and the decreased response to other vaccines in these patients.[50]

Other treatments for UTI

The fruit and the leaves of the red cranberry (*Vaccinium macrocarpon*) have been used for the prevention of UTI (cystitis and urethritis) due to their antioxidant effect. Due to bacterial resistances and the frequency of recurrent UTI, there is a growing interest in its use, but the studies carried out do not show sufficient evidence due to the high rate of treatment abandonment because of its low long-term acceptability.[37-39]

Conclusions

The population with CKD has a high prevalence of risk factors for UTI, which appears more frequently the more advanced the stage of kidney disease, which in turn contributes to its progression. When establishing the treatment, the need to adjust the dose of antibiotics to glomerular filtration, the use of non-nephrotoxic alternatives and the higher frequency of enterobacteria and multiresistant microorganisms in this population group must be

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taken into account. Specific studies are required to verify the efficacy and safety of alternative treatments and vaccines that minimize the use of antibiotic therapy and thereby, the problem of multidrug resistance in this type of patients.

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Conflict of interest

The authors declare no conflict of interest.

Ethical responsibilities

Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

Data confidentiality

The authors declare that patient data do not appear in this article.

Right of privacy and informed consent

The authors declare that patient data do not appear in this article.

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Review article

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Aquapheresis: Does it work?

Utilidad de la terapia de acuaféresis

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Abstract

The therapy of Aquapheresis has been studied as a therapeutic tool for patients with volume overload refractory to treatment with loop diuretics, whose main objective is to mitigate the clinical impact therein in patients with decompensated heart failure and cardiorenal syndrome, recognizing positive cumulative balances in critically ill patients as an independent factor for mortality. A search was made in the main scientific databases for review articles, and studies that included the Acuapheresis strategy. Bibliographic references were found in databases from 2005 to 2017. Aquapheresis therapy is a patented ultrafiltration therapy aimed at improving refractory overload in patients with congestive heart failure. There are gaps in knowledge regarding cost-effectiveness therapy, serious adverse events attributable to it and candidates who will benefit, and we believe that more quality studies are required to reach solid conclusions. So far there is no compelling evidence to support aquapheresis therapy to implement its routine use in the ICU.
Key words: Ultrafiltration, heart failure, fluid overload, cardiorenal syndrome, acute kidney injury, dialysis, extracorporeal, critical care.

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Resumen

La terapia de acuaféresis ha sido estudiada como una herramienta terapéutica para pacientes con sobrecarga de volumen refractaria al tratamiento con diuréticos de asa. Su objetivo principal es mitigar el impacto clínico de esta sobrecarga en los pacientes con insuficiencia cardiaca descompensada y SCR, reconociendo de esta manera los balances acumulados positivos en los pacientes críticamente enfermos como un factor independiente de mortalidad. Se realizó una búsqueda en las principales bases de datos científicas sobre la terapia de acuaféresis. Se incluyeron guías de manejo, ensayos clínicos controlados, revisiones sistemáticas y metaanálisis. Las bases bibliográficas que arrojaron resultados relevantes fueron Web of Sciences, Scopus, PubMed y SciELO y en total se encontraron 47 referencias bibliográficas publicadas entre 2005 y 2017. La acuaféresis es una terapia de ultrafiltración patentada que mejora la sobrecarga refractaria en pacientes con insuficiencia cardiaca congestiva. Hay brechas en el conocimiento en relación a su costo-efectividad, a los eventos adversos graves que se le atribuyen y a los candidatos que beneficia, por tanto, se requieren más estudios de calidad para llegar a conclusiones sólidas. Hasta el momento no hay evidencia contundente que respalde el uso sistemático y rutinario de la terapia de acuaféresis en las unidades de cuidado intensivo.
Palabras clave: ultrafiltración, falla cardiaca, sobrecarga fluidos, síndrome cardiorrenal, injuria renal aguda, diálisis, terapia extracorpórea, cuidado crítico.

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Introduction

Aquapheresis is an ultrafiltration (UF) therapy designed to eliminate fluid overload. In patients with congestive heart failure and cardiorenal syndrome (CRS) it has been studied as a therapeutic strategy to restore balance; achieve euvolemia in a safe, effective, and predictable manner, and reduce hospital stay and readmissions for acute decompensation and mortality. Likewise, it has been compared with conventional pharmacological measures, mainly with loop diuretics, to determine its efficacy in these aspects.

A compilation of the currently available medical literature is performed in this article in order to analyze the benefits and limitations of aquapheresis therapy.

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Materials and methods

A search was conducted in the main scientific databases on aquapheresis therapy. Management guidelines, controlled clinical trials, systematic reviews and meta-analyses were included. All the articles in which UF strategies for the management of fluid overload were mentioned and those that implemented aquapheresis therapy in adult patients were included. Articles related to the pediatric and obstetric population were excluded.

Results

The bibliographic databases that yielded relevant results were Web of Sciences, Scopus, PubMed and SciELO, and a total of 47 bibliographic references published between 2005 and 2017 were found.

Epidemiology

The incidence of acute kidney injury (AKI) depends on the definition used; however, this is a condition that can reach rates of 44% in hospitalized patients[1] and that in intensive care units (ICUs) can rise to 60%, being septic shock (50%) and sepsis (20%) the main causes.

About 6% of patients with sepsis who develop ARF require some type of renal support therapy, which constitutes an event with a high risk of morbidity and mortality and poor results in the short and long term.[2,3] Likewise, it is estimated that the mortality rates associated with ARF in patients with septic shock who undergo dialysis therapy ascend to 80%.[4]

On the other hand, more than 1 million hospitalizations per year for congestive heart failure (CHF) are recorded in the United States,[5] finding that 82% of patients hospitalized for this cause have some degree of kidney dysfunction in the first 48 hours after admission, which demonstrates that there is a complex crossover dialogue between the two organs.[6,7]

Cardiorenal syndrome

The term "cardiorenal syndrome" was proposed in the 1940s to describe the bidirectional interactions between the heart and the kidney,[8] it is defined as a state of advanced deregulation between these two organs and is mediated by compensation mechanisms that become insufficient and deleterious and generate systemic repercussions.[9]

In 2008, the Acute Dialysis Quality Initiative Group held a conference to define the CRS; in which this pathology was classified into five types according to the time and the primary organ affected[10]: type 1, acute CRS; type 2, chronic CRS; type 3, acute renocardiac syndrome; type 4, chronic renocardiac syndrome, and type 5, secondary CRS. Some examples of the latter are diabetes *mellitus* and sepsis, which simultaneously produce heart and kidney dysfunction. As a demonstration of the significant interaction between the heart and the kidneys, the dysfunction or injury of one organ often contributes to the dysfunction or injury of the other.[11]

Pathophysiology of CRS

From the pathophysiological point of view, CRS is the product of the connection of complex pathways, although the conventional explanation for its development in the context of a primary cardiocentric movement focuses on the inability of the defective heart to maintain an adequate cardiac output, which results in pre-renal hypoperfusion.[11] In this sense, the inadequate renal affeent flow activates the renin-angiotensin-aldosterone system (RAAS) and the autonomous nervous system through upregulation of the sympathetic system and secretion of arginine-vasopressin, leading to fluid retention and the subsequent increase in preload defined as the factor that has the greatest impact on the worsening of kidney function and heart pump.[12] In this context, the increased central venous pressure leads to renal venous hypertension and intrarenal blood flow insufficiency as well as increased renal resistance, which ostensibly affects the glomerular filtration rate.[12-14]

There are other mechanisms responsible for the development of CRS, for example, the activation of the neurohumoral axis increases sodium and water reabsorption in the proximal tubule, which maintains effective plasma volumes and eventually results in oliguria and makes congestion worse.[11]

There are two cardiovascular mechanisms that have a direct effect on the development and outcome of CRS and therefore affect renal hemodynamics: the right ventricular dysfunction (which generates a decrease in the preload of the left atrium and consequently of the left ventricle, with the subsequent drop in cardiac output) and interventricular asynchrony (which affects the cardiac cycle and the biventricular interaction). It is described in the literature that there are phenomena of biventricular interdependence (what happens in one ventricle consequently affects the other), but the tricompartmental model, which includes the heart, the pericardium and the interventricular septum is also proposed. In this way, the proper cardiac function will depend on the integrity of the interventricular septum, the intrapericardial changes and the transmural pressure of the heart. The alteration in these mechanisms greatly affects stroke volume, cardiac output, and renal hemodynamics.[15]

Among the non-hemodynamic pathways that aggravate the cardiac or kidney injury, chronic inflammation, the imbalance in the proportion of oxygen reactive species and/or production of nitric oxide and the persistent activation of the RAAS axis are fundamental for the activation of the sympathetic nervous system.[16] In experimental models, it has been found an elevation in the levels of tumor necrosis factor ? (TNF-?), interleukin-1 (IL-1) and interleukin-6 (IL-6) that has direct cardiodepressive effects, which result in a reduction of the left ventricle ejection fraction (LVEF). On the other hand, the so-called uremic nephropathy is characterized by the development of myocardial remodeling, with a significant burden of left ventricular hypertrophy, in which it has been demonstrated that the fibroblast growth factor-23 (FGF-23) has an independent causal effect.[17]

Since left ventricle hypertrophy is associated with a reduction in capillary density in the central endocardium, it is possible that microvascular ischemia plays a role in the progression of uremic cardiopathy. Meanwhile, peripheral venous congestion causes an endothelial tightening, which generates the conversion of the vascular endothelium of a proinflammatory phenotype into an inactive one and highlights the importance of decongestion in the natural history of the CRS, beyond its hemodynamic effects.[11]

Finally, they are data suggesting that dendritic cells play a role in the activation of adaptive immune responses in the context of the CRS. The reported data may represent a useful tool in future studies that allow to better understand the different mechanisms underlying the pathophysiological presentation of the syndrome and, in this way, develop alternatives to shorten the course of the chronic CRS.[18]

Impact of fluid overload

Fluid overload has been described as a factor of mortality in critically ill patients,[19-24] but it also has an important impact on the hospital readmissions of patients with congestive heart failure, since it has been estimated that about 90% of those who are admitted through the emergency department have signs and symptoms related to this overload and, once they are discharged, it is estimated that 25% are readmitted within the first 30 days and 50% within the first 60 days due to related symptomatology.[25]

Several studies have reported that volume overload is directly related to a lower probability of recovery of renal function, with a greater probability of the need to start renal support therapy, and the development of adverse events in almost all organs and systems. The study conducted by Shen *et al.*,[20] published in 2017 and derived from the analysis of a database of multiparameter intelligent monitoring in ICU, included 2,068 patients and found that the more negative the cumulative fluid balance and the lower the fluid intake were, the better the results were in terms of mortality with statistical significance, which is in consistent with the literature.

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Management of the overload

In order to mitigate the volume overload, diuretics have been considered the cornerstone of treatment in patients with heart failure; in the European guidelines to treat this condition their use is a recommendation in the management of this overload.[26] However, it has been found that such drugs have certain disadvantages in their routine use, since the changes in the intravascular volume they produce are unpredictable; likewise, it has been widely recognized that loop diuretics in the setting of ARF are related to a worsening of renal function associated with hypovolemia, which leads to an exponential increase in neurohormonal activation with the implications that this entails within the cycle.[11]

The use of high-dose diuretics is also related with hydroelectrolitic and acid-base imbalance, and with a reduced efficiency because about 40 % of patients may have diuretic resistance, defined as failure to achieve reduction of edema despite a full dose of loop diuretic (essentially 240 mg of furosemide or maximum dose of its equivalents), a fractional excretion of sodium (FeNa) <100 mmol/24 hours or an amount of excreted sodium as percentage of filtrate <0.2 %.[11]

The multiple causes of diuretic resistance include poor adherence to drug therapy, dietary restrictions, pharmacokinetic problems, and compensatory increases in sodium reabsorption in the nephron sites that are not blocked by the diuretic. [11] Felker *et al*.[27] report that patients who have already been chronically taking loop diuretics require doses 2.5-fold higher for the management of their acute condition.

Likewise, there is a series of direct and indirect pathophysiological events that explain this diuretic resistance and in relation to this risk, algorithms have been developed to mitigate it[28,29]; however, the high percentage of patients who do not respond to this therapy has raised the need to develop other therapeutic tools such as UF.

According to the guidelines for the management of heart failure, the UF can be considered for patients with refractory congestion who do not respond to diuretic treatments (IIB: *weak recommendation, moderate quality of evidence*) and renal replacement therapy should be considered for patients with refractory volume overload and acute renal failure (IIA: *weak recommendation, high-quality of evidence*).[26]

Considering the unmet need for the management of the overload, in a review of extracorporeal UF therapies, Constanzo *et al*.[30] include the studies that have used the aquapheresis therapy to improve the volume overload, and they state that, in contrast to diuretics, UF may be associated with more effective decongestion and fewer cardiovascular events; however, the essential aspects of UF are still poorly defined and it is clear that the adjustment of UF rates to the vital signs (systolic blood pressure) and the renal function of the patients is required.[30]

Ultrafiltration and aquapheresis

The principle that governs aquapheresis therapy is the convective transport, which explains that UF occurs in response to a transmembrane pressure gradient and depends directly on factors such as the permeability coefficient, the transmembrane pressure, the hydrostatic pressure of the blood, the ultrafiltrate and the oncotic pressure.[31] The convective principle governs the slow continuous ultrafiltration (SCUF) which shares technical characteristics with aquapheresis; the difference lies mainly in the pump flows and in the possibility of initiating aquapheresis therapy with a peripheral venous access, which suggests that it can be used in settings outside the ICU. There are some studies of SCUF in volume overload of CHF patients with disappointing results.[32]

Aquapheresis is an UF therapy designed to eliminate fluid overload with which balance is restored and euvolemia is achieved in a safe, effective and predictable manner. In a simplified approach of UF called the Aquadex Flexflow® System by its manufacturer, this therapy is approved by the Food and Drug Administration and is characterized by being a therapy that works with a

small, portable machine: it consists of a console that has friendly features for its programming and, although it requires trained personnel, it is relatively easy to use with a tentative programming time of less than 10 minutes. The amount and velocity of UF can be specified and adjusted in the programming console with pump flows (Qb) of 40 cc/min and gradual increments of 5 mL/min, which generates a gradual reduction of the overload with no significant clinical impact on hemodynamics or in the electrolyte balance.

Aquapheresis therapy has an important advantage that consists in that it can be connected to a peripheral venous access cannulating the basilic vein as the preferred route, followed by the external jugular vein or the antecubital vein; however, this generates reasonable doubt about the need of admission to the ICU and whether it would eventually have some interference on possible outcomes in relation to complications derived from the treatment in this unit. Aquapheresis can also be used by central line in the usual accesses.[33]

This system was designed to improve the symptoms and the clinical outcomes of the patients and can be implemented in temporary (up to 8 hours) or long term basis (> 8 hours) according to the degree of overload and the clinical indications, taking into account that the half-life of the filter is 24 hours.[33]

According to the manufacturer's characteristics, the volume of the extracorporeal circuit is 22 mL, the ultrafiltration range fluctuates between 0 and 500 mL/h, (increments of 10 mL/hour), with a priming volume of 50 mL and a reduced contact surface between the blood and the system, which ensures a minimal blood loss if the circuit coagulates and reduces the required doses of heparin. The standard dose of unfractionated heparin is 10-20 U/kg with monitoring guided by activated clotting time for targets of 180-220 seconds.[33]

During this therapy, the machine draws the blood of the patient and is directed to the system passing through a pump and a volume sensor, to reach later the hemofilter, which consists of a semipermeable membrane that allows the extraction of the plasma volume thanks to the hydrostatic pressure gradient; this generates the elimination of the isotonic fluid and subsequently the ultrafiltered blood returns to the patient.[30,33]

This machine also has a hematocrit sensor, which is optional, and is used to monitor and adjust the UF. On-line hematocrit sensors allow the continuous estimation of the changes in the blood volume during the UF and can be programmed to stop the fluid extraction if the hematocrit exceeds a threshold established by the physician (for example, 5% to 7%) and restart the therapy when the hematocrit value falls below the prespecified limit, which indicates an adequate filling of the intravascular volume from the interstitial space.

However, given that many factors such as changes in the position of the patient may alter the hematocrit values, physical, laboratory and hemodynamic variables should be assessed concomitantly to determine the appropriate UF rates and the amount of fluid to be removed.[30]

Objectives of fluid removal and monitoring of UF therapy

As a general recommendation, it is important that once the initial UF rate is chosen, to perform a clinical and, if possible, paraclinical monitoring and to make the pertinent adjustments in relation to slowing down the UF rate or stopping the therapy, given that the capillary filling of the interstitium decreases as the fluid is removed and it could have unfavorable outcomes in the hemodynamics of the patient.[34] Although the optimal rate and duration of UF must be individualized, UF rates >250 mL/h are not recommended in critically ill patients.[33]

Patients with predominantly right heart failure or with heart failure with preserved LVEF (>50 %) are more susceptible to intravascular volume depletion and they only can tolerate low UF rates (50-100 mL/h).[26] In addition, the clinical experience teaches that fluid removal with methods of

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extracorporeal dialysis is better tolerated when it is carried out with low UF rates and during prolonged periods.[33]

Indications for aquapheresis

The current indications for the use of aquapheresis therapy are volume overloads (defined as the presence of more than two peripheral edemas, ascites, pulmonary edema, jugular venous distention >7 cm or an increase by more than 5 kg), overloads that meet criteria for refractoriness to standard therapy (defined by the criteria of diuretic resistance) and patients with CRS and those in whom chronic renal failure has not been documented.

Aquapheresis therapy should be avoided in special conditions such as the need for renal replacement therapy for other causes in addition to overload, hemodynamic instability or hemoconcentration (Hematocrit > 53 %).[30,33]

It is worth mentioning that it is necessary to perform monitoring of the UF that includes clinical and paraclinical assessment of the response to therapy. Taking into account the low sensitivity and specificity of the physical examination in contrast with other techniques such as ultrasound or bioimpedance, joint assessment methods should be implemented, while recognizing that all the tools mentioned have evidenced limitations and are outside the scope of this review.[19,30]

Clinical evidence of aquapheresis

Although there is a record of previous pilot studies and case series, it was not until 2005 when the first articles that used the Aquadex 100® system were published; the last study was published in 2016:

The study conducted by Constanzo *et al.*,[34] published in 2005, included 20 patients and it result was in favor of UF (after receiving doses of diuretics) in relation to hospital readmissions for symptoms of CHF. In the same year, Bart *et al.*[35] published the RAPID-HF, a multicenter randomized clinical trial (RCT) conducted in 6 hospitals of the United States with a total of 40 patients diagnosed with CHF (defined as the presence or more than two edemas and one congestive symptom); in this research, the patients were randomly distributed into two groups of 20 subjects: in the first, the participants were assigned to the usual treatment, receiving a mean dose of 160 mg of furosemide with an outcome of removed volume of 2838 mL, and in the second, they were assigned to UF therapy and underwent a single session of 8 hours, receiving a mean dose of 80 mg of furosemide with a secondary outcome of total volume removed of 4650 mL. The primary outcome was the weight loss at 24-48 hours. In the results, a more marked volume removed was found in the patients who received UF, but in terms of the primary outcome, weight loss after 24 hours was 2.5 kg in those treated with UF and 1.86 kg in the groups treated with pharmacological therapy, without reaching statistical significance (p=0.240).

In 2007, Constanzo *et al.*[36] published an RCT conducted in 200 patients, that compared the safety and efficacy of UF versus loop diuretics using the Aquadex 100® system and where the mean elimination rate was 241 mL/h during 12 hours. The patients received diuretics intravenously during 24 hours, twice the daily oral dose they received before the hospitalization. The primary outcome was the weight loss and the improvement in the dyspnea assessment scale at 48 hours. The secondary outcomes were: net fluid loss at 48 hours, decline in functional capacity (assessed by 6-minute walk test, New York Heart Association functional class scale and Minnesota Living with Heart Failure scale at 30 and 90 days) and hospital readmissions for CHF at 90 days. It was also found that patients undergoing UF therapy had, on the one hand, fewer hospital readmissions as a result of volume overload and, on the other hand, an improvement in weight, but without significant changes in the dyspnea scale and with deterioration in kidney function.

By the year 2012, Bart *et al.*[37] published a study that again sought to evaluate the differences between UF therapy and diuretics in relation to the creatinine level and body weight at 96 hours; for this, a follow-up was carried out during 60 days. This was a

multicenter RCT that included 22 hospitals in the US and Canada, with an initial number of enrolled patients of 15,871, that is, up to that point it was the largest study regarding aquapheresis therapy in the clinical setting of management of fluid overload in patients with CHF. However, it only was possible to recruit 1.18 % of the sample (188 patients) due to the interruption futility and adverse events. The patients had a CRS, defined as CHF with two or more signs of congestion and acute kidney injury categorized as KDIGO I. It is necessary to mention that 77% of the participants had been hospitalized for CHF during the previous year and that in the baseline characteristics the patients in the UF group had lower LVEF and a higher level of N-terminal pro-brain natriuretic peptide (NTproBNP) than the group of pharmacological therapy with loop diuretics.

The patients treated with UF were programmed at a fixed rate of 200 mL/min/1.73 m^2 with a mean duration of 40 hours, which could be unfavorable for those who were more dependent on the preload to maintain the hemodynamic stability. Pharmacological therapy was staggered to obtain a target diuresis of 3 to 5 L/day, with a mean dose of furosemide of 120 mg/day and a mean duration of 92 hours.[37]

The results of Bart *et al*.[37] evidenced a significant increase in creatinine levels with the UF therapy in the first 7 days, but there was no significant difference in weight loss at 96 hours. In the light of the findings, only 10 % of the patients had an adequate improvement in the signs of fluid overload at 96 hours and 43 % of the patients died or were readmitted for CHF within the 60 days of study; in the same period the mortality was higher in the patients who underwent UF therapy (17 %) than in those treated with diuretics (14 %) (p=0.4651).

Among the adverse events of this study,[37] it is described that 72% of the patients in the UF group presented problems with the catheter, acute functional renal failure or gastrointestinal bleeding (p=0.033). However, the analysis of these results obliges to consider that 39 % of the patients received concomitantly diuretics, which affects the adjudication of the events to one or other therapy. The conclusions of the research indicate that in the UF therapy there were more costs and a worse renal function, furthermore, there were no significant changes in terms of improvement of the congestion.

In 2013, Wen *et al*.[38] published a systematic review that included 5 RCTs, with a total of 477 patients, and they found in the primary outcome a greater weight loss at 48 hours and a greater net volume removal in patients treated with UF therapy, although the first outcome presented a heterogeneity index (I^2) of 51 %. In this review, the adverse events did not show statistically significant differences.

One year later, Barkoudah *et al*.[39] published a meta-analysis which included 9 RCTs, with a total of 613 patients, and they found an advantage in favor of the UF in the outcome of the mean weight loss, with an I^2=66.8 % and without differences in the outcomes of changes in creatinine and mortality from all causes. The significant heterogeneity of this meta-analysis is due to the fact that within the studies assessed there were differences in the type of therapies; likewise, continuous veno-venous hemodiafiltration, intermittent hemodiafiltration and aquapheresis were included, and different machines were used, which makes it difficult the correct interpretation of the results.

Finally, in 2016, Constanzo *et al*.[40] published a multicentric RCT conducted in the United States, with an initial number of 810 patients with a diagnosis of CHF. The study was discontinued unilaterally and prematurely by the sponsor, which was justified by a slow recruitment when only 27.5% of the initial sample had been reached. However, 224 patients were randomized into two groups, one of 110 patients who were assigned to a UF session adjustable to renal function and systolic blood pressure, and another of 114 patients who were assigned to drug therapy. The primary outcome was the development of CHF symptoms within 90 days and cardiovascular events.

The mean UF rate in this study was 138 mL/h and it was administered during a longer period (70 hours). Among the secondary outcomes, it was found a trend towards a longer time until the presentation of the

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first event of heart failure within 90 days and less cardiovascular events in the UF group, which was attributed to the fact that the UF restored the patient's response to the diuretic agent as key mechanism to delay the recurrence of CHF events.[40]

However, it is not encouraging that the primary outcome did not present statistical significance due to the limitation of the incomplete statistical analysis of the data given the sample size, which was insufficient to reach a power of 90% with the Log-Rank test.

On the other hand, adverse events occurred in 31 % of UF patients, 14% being recognized as serious, which include cardiovascular disorders such as acute myocardial infarction, cardiac arrest and, paradoxically, increased heart failure and cardiogenic shock, in addition to the complications derived from the procedure. The analysis of mortality derived from one or the other therapy did not show a statistical difference and it was found that 70% of all the cases of death were due to cardiovascular causes.

In the literature, there are two more studies conducted in Italy: the ULTRADISCO,[41] which included 30 patients who received UF therapy with the PRISMA® machine and in which clinical, biohumoral and hemodynamic variables were evaluated at 36 hours, and it was found that the UF was associated with a greater reduction of body weight, improvement in the signs and symptoms of CHF, decrease in the aldosterone and NT-proBNP levels and systemic vascular resistance, which results in improvement in the objective cardiac output measurements; and the CUORE,[42] conducted in 56 patients with the Dedyca Device® machine and that reported in its primary outcome that patients under UF therapy had less hospital readmissions for heart failure in the 1-year follow up.

In terms of costs, which is a matter of current concern, there is a limited evidence: Bart *et al*.[37] concluded that the UF therapy was more expensive, and Constanzo *et al*.[43] published a study of cost analysis of UF versus diuretic therapy for patients with heart failure from the hospital perspective in which they reported a cost saving of USD$3,975 by reduction of readmissions at 90 days in the patients who received UF therapy.

Discussion

It has been suggested that there is a direct relationship between volume overload and mortality, hence the need to use therapeutic strategies that reduce this overload and improve the clinical outcomes of the patients by reducing the body weight (in terms of overload), the hospital readmission rates and the number of cardiovascular events.

Taking into account the principle of diuretic resistance, aquapheresis therapy has been presented as a tool that allows the removal of fluid and improves clinical outcomes, but requires to be individualized due to the risk of instability and complications associated with the procedure. Since the year 2004, studies comparing this therapy with conventional pharmacological management have been published in order to evaluate efficacy and safety. However, in the initial studies there are limitations derived mainly from the small samples and low follow-up, while in the large studies published later the limitations are due to premature discontinuation, either due to futility, adverse events or slow recruitment, which makes it very difficult to draw strong conclusions.

In this sense, so far there is no convincing evidence to support the systematic use of acuapheresis therapy in patients with volume overload. A possible explanation would be that it is not clear to which extent the clinically established overload of the patients corresponds to extravascular water, which translates into a lack of knowledge as to whether, despite the edema, the effective intravascular volume is contracted and would largely explain the failure of therapy.

Given the panorama, it is clear that there is a clinical challenge in the creation of diagnostic tools that allow the objective measurement of the volume status, as well as gaps in knowledge regarding the cost-effectiveness of therapy, the actual relationship

of serious adverse events attributed to it and the candidates who would benefit from the intervention. Therefore, the authors consider that more high-quality studies are required to reach solid conclusions.

Conclusions

There is a directly proportional relationship between the volume overload and mortality, being the diuretics the cornerstone of treatment to mitigate it. However, there are a non-negligible percentage of patients who present diuretic resistance of multifactorial etiology. Such resistance makes UF an attractive therapeutic tool; however it requires to be adjusted and individualized in order to improve the clinical impact in patients with refractory overload.

The clinical evidence yields promising results in relation to the tendency to reduce the body weight in terms of overload to lessen hospital readmission rates and the occurrence of cardiovascular events, with a subsequent decrease in total costs of care. However, both the initial studies and the large research published later have limitations in the analysis of results derived from premature discontinuation, either due to futility, adverse events or slow recruitment, which makes it very difficult to draw firm conclusions about the benefit of aquapheresis therapy as superior to pharmacological treatment with loop diuretics. The incomplete statistical analysis of the data due to insufficient sample size to reach a power of 90 % with the *Log-Rank* test allows to evaluate trends, but not to establish solid conclusions.

From the pathophysiological point of view, if the problem is overload, the question arises as to why aquapheresis therapy, despite reducing the weight by water extraction, has no relevant clinical impact on the outcomes. A reasonable analysis could be that it is not clear to what extent the clinically established overload in patients corresponds to extravascular water, resulting in a lack of knowledge as to whether, despite the edema, the effective intravascular volume is contracted; this would explain to a great extent the failure of the therapy. In this way, it is recognized that there is a clinical challenge in the creation of diagnostic tools that allow the objective measurement of the volume status.

On the other hand, there are gaps in the knowledge of the cost-effectiveness of aquapheresis therapy, the real relationship of serious adverse events attributable to it, and the candidates who would benefit from the intervention. In this sense, more high-quality studies are required to reach solid conclusions, since up to now there is no conclusive evidence to support the systematic and routine use of this therapy in the ICU. There is currently a study which is waiting the results on the topic of aquapheresis[44] and two studies in recruitment process,[46] which will surely make important contributions to the critical analysis of the evidence for this therapeutic tool.

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Ethical responsibilities

Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

Data confidentiality

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

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Right of privacy and informed consent

The authors declare that patient data do not appear in this article.

Contribution of the authors

Diana Ávila: Conception and design of the article, literature search, reading of articles, analysis and processing of information, writing and sending of the manuscript.

Andrés Bernal: Conception and design of the article, reading of the articles, analysis and processing of information, scientific and methodological advice on the design of the article and scientific terminology

Conception and design of the article, reading of articles, analysis and processing of information, scientific and methodological advice, editorial corrections

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Clinical case

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Distal renal tubular acidosis: case series report and literature review

Acidosis tubular renal distal. Serie de casos y revisión narrativa

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Abstract

The distal renal tubular acidosis presents due to a defect in the excretion of hydrogen ions at the distal tubular level, causing an increase in the pH of the urine and a decrease in the plasma pH, with several associated clinical manifestations. This article makes a thorough review of distal renal tubular acidosis and presents the case of three siblings with the entity, two men and one woman, this being one of the first family cases reported in Colombia. All three received the diagnosis during the lactation period, presented nephrocalcinosis and good response to the alkali therapy started early, eventually achieving their suspension. Interestingly, one of them also presented mevalonate-kinase deficiency with hiperinmunoglobulinemia D, alteration not previously described. This association and the apparent lack of need for continued management with alkali are atypical in the light of current knowledge, deserving special consideration.

Key words: Acidosis, renal tubular, nephrocalcinosis, genetics, kidney tubules, distal, rare diseases.

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Resumen

La acidosis tubular renal distal es causada por un defecto en la excreción de iones de hidrogeno a nivel tubular distal, lo que aumenta el pH de la orina y disminuye el pH plasmático; esta es una enfermedad con varias manifestaciones clínicas asociadas. En este artículo se hace una revisión profunda sobre la acidosis tubular renal distal y se presenta el caso de tres hermanos (dos hombres y una mujer) con la entidad, siendo este uno de los primeros casos familiares reportados en Colombia. Los tres pacientes recibieron el diagnóstico durante el período de lactancia, presentaron nefrocalcinosis y tuvieron buena respuesta a la terapia con álcali iniciada de forma temprana, logrando eventualmente su suspensión.

De manera curiosa, uno de los pacientes también presentó deficiencia de mevalonato quinasa con hiperinmunoglobulinemia D, una alteración no descrita con anterioridad. Esta asociación y la aparente falta de necesidad de continuar el manejo con álcali son atípicas a la luz del conocimiento actual, mereciendo especial consideración.

Palabras clave: acidosis tubular renal, nefrocalcinosis, genética, túbulos renales distales, enfermedades raras.

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Introduction

Renal tubular acidosis refers to a heterogeneous group of diseases in which, despite having a relatively normal glomerular filtration rate (GFR), metabolic acidosis occurs due to a defect in the renal tubules, which alters their regulatory capacity of the normal acid-base status.[1] In this group of diseases, metabolic acidosis with normal (hyperchloremic) anion gap (AG) occurs, which is secondary to losses of bicarbonate, mainly in the proximal tubules, or due to defects in the excretion of hydrogen chloride or of some salts that are metabolized to hydrogen chloride (such as ammonium chloride) distal to the nephron.[1,2] This disorder can be primary, secondary, acquired or hereditary, and is sometimes associated with other systemic diseases.[3-8]

Three main forms of renal tubular acidosis have been defined: distal (type 1), proximal (type 2), and hyperkalemic (type 4); type 3 corresponds to a mixed distal and proximal form.[9-11]

In type 1 renal tubular acidosis (RTA1), the excretion of acid in the distal tubule is altered[12] and in the absence of alkalizing therapy, a progressive accumulation of hydrogen in plasma is generated, that leads to a decrease in plasma pH and is accompanied by urine pH> 5.5.[5,6,12] Likewise, RTA1 can be accompanied by hypokalemia secondary to potassium loss due to the acidemia.[13] In Colombia its incidence is unknown due to the lack of records, but in Spain, with a population of about 45 million inhabitants, 50 cases of hereditary RTA1 have been registered in Renaltube; of these, only 20 are Spanish[5,6,9]; likewise, in most European countries the prevalence is low[5,6,11]; in England and France, genetic studies estimate a ratio of 1 case per million inhabitants.[1,3,8] According to several investigations, the population with RTA1 is concentrated in immigrants of Arab origin.[8,9,13]

This article presents one of the first reports of RTA1 with family commitment in Colombia; three siblings with this pathology and with a typical autosomal recessive presentation are identified here. Given the importance of the issue, a review of the literature on this disease is also made.

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Presentation of case 1

A male patient who was admitted for the first time to a hospital of third level of complexity when he was 12 years old. His mother brought an extra-institutional medical history that showed a diagnosis of RTA1 and reported that she had two other children, both minors, who had the disease.

The child had a history of pyloric hyperplasia during his first days of life, for which he required surgical management before reaching his first month of age. Later he developed gastroesophageal reflux disease (GERD), for which he received medical management during the following years. When he arrived at the institution, he was taking antiemetic and antisecretory drugs.

At 10 months of age, the gastroenterology service referred him to nephrology for suspected kidney disease due to persistent emesis and evidence of altered renal function. After some studies, nephrology diagnosed RTA1 and established a management and follow-up plan. At the age of 16 months, nephrocalcinosis was detected and by audiometries performed at 4 and 12 years of age, hearing alterations were ruled out.

Likewise, in their first extra-institutional evaluations, the child had a growth deficit that was corrected with alkalizing therapy. He arrived at the hospital of third level of complexity being managed with polyethylene glycol (PEG) 7 g/day for chronic constipation; otherwise he had adequate symptomatic control.

At the time of his first assessment at the intra-institutional pediatric nephrology service, the patient was being managed with Shohl's solution (1 liter = citric acid 140 g + sodium citrate 70 g + potassium citrate 70 g) 5 cm^3 orally every 8 hours and was asymptomatic. The physical examination showed a weight of 40 kg (41st percentile), height of 144 cm (14th percentile), and vital signs within normal limits for age. The mother delivered paraclinical tests taken 1 month before at the altitude of Bogota, Colombia, which showed venous gases (VG) with pH: 7.383; PCO_2: 38.4; HCO_3: 22.4; BE: -2.3; BUN: 8.7;

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creatinine: 0.45 (GFR: 176 mL/min/1.73 m^2), calciuria: 70.9 mg/day (1.7 mg/kg/day) and urinalysis with pH=6, with the rest of parameters normal. Likewise she brought a ultrasound scan of the same date which showed a right kidney of 100x37 mm and a left kidney of 87x46 mm (Hodson index 10.8), without other alterations.

Subsequently, the patient was evaluated by the genetics service, which requested an international consultation for genetic mapping. This study was carried out by Renaltube (Spain) and its results ruled out the presence of mutations of ATP6V0A4, the most frequently associated with RTA1, without being able to rule out other mutations that are not described in the literature.

In one of the institutional controls by pediatric nephrology, it was evidenced that the mother had suspended treatment with citrate solution one month earlier; however, the patient had totally normal blood gases at the altitude of Bogota, serum electrolytes and urinalysis. Therefore, a possible remission was considered, management was not continued and follow-up exams were requested. In the last control, 8 months later, the child was asymptomatic with normal vital signs and physical examination and the paraclinical tests requested showed VG with pH: 7.381;PCO_2: 47; HCO_3: 21: BE: 3, urianalysis with pH=6 y electrolytes within normal ranges. With this, it was corroborated that he overcame the RTA1 and it was decided to continue without alkaline therapy.

Presentation of case 2

A male patient with an extra-institutional medical history which evidenced that, in addition to ATR1, he had a diagnosis of mevalonate kinase deficiency associated with hyperimmunoglobulinemia D.

During his first two years of life, he presented recurrent bronchoobstructive symptoms for which he required intrahospital management on multiple occasions, eventually receiving a diagnosis of asthma.

In one of his bronchoobstructive episodes at 10 months of age, the patient required hospitalization and management with corticosteroids; on that occasion, through paraclinical results, a persistent hydroelectrolytic deficit was evidenced. Taking into account these electrolyte alterations and the recent diagnosis, at that time, of RTA1 in his older brother, a diagnosis of renal tubular acidosis was suspected. Therefore, at discharge the child was referred to the extrainstitutional pediatric nephrology service with a request for extension studies. At one year of age he was assessed, confirming the diagnosis of RTA1 with pertinent studies. Since then, this service established management with citrate solution and follow-up, which was progressively adjusted to achieve therapeutic goals. However, repeated emetic episodes were evident.

The child was assessed by the extra-institutional pediatric gastroenterology service where a diagnosis of GERD was established and occasional antisecretory management was given with symptomatic improvement. Likewise, at 7 years of age, nephrocalcinosis was detected and hearing alterations were ruled out by audiometry. Like his older sibling, this patient also had short stature during his first extra-institutional evaluations, which was corrected, and did not present additional repercussions during extra-institutional follow-ups for about a year and a half more.

Since the patient was 6 years old he began to have multiple episodes of fever, arthralgia, sporadic headache, appearance of aphthae and asthenia, for which he received different diagnoses and treatments for 6 months, until finally superimposed immunodeficiency was suspected, for which he was referred to extra-institutional pediatric rheumatology and infectious diseases, who carried out extension studies and corroborated the diagnosis of mevalonate kinase deficiency associated with hyperimmunoglobulinemia D when he was 8 years old. Since then, management with lovastatin and colchicine was started to modulate the inflammatory process and prevent the development of renal amyloidosis.

At 9 years of age, he was taken for the first time to the institution for multidisciplinary management, being initially assessed by pediatric nephrology. The patient was being managed with Shohl's solution 5

cm^3 orally every 12 hours, lovastatin and colchicine. The physical examination showed a weight of 28 kg (37^{th} percentile), height of 128 cm (13^{th} percentile), and vital signs within normal limits for age. The last paraclinical tests that the mother brought showed VG (at the altitude of Bogota) with pH: 7.363; PCO_2 41.9; HCO_3: 23.3; BE: -2.1, BUN: 6-7, creatinine: 0.4 (GFR: 132 mL/min/1.73 m^2), calciuria: 55.6 mg/day (1.98 mg/kg/day) and serum calcium in 9.35. She also brought an ultrasound scan performed one week before the control in which a right kidney of 98x40 mm and a left kidney of 98x45mm were evidenced (Hodson Index 9.9), without additional positive findings.

Subsequently, the child was assessed by the institutional pediatric rheumatology service, which considered that the patient could benefit from biological therapy with etanercept for mevalonate kinase deficiency associated with hyperimmunoglobulinemia D. Later, the genetics service requested sequencing of the MVK gene due to the risk of retinitis pigmentosa given the described autoinflammatory condition and sent samples for genetic mapping in search of ATP6V0A4 mutations compatible with RTA1, whose result was not known at the time of writing this article.

The mother discontinued the citrate solution one month before the control by nephrology. The control paraclinical tests reported VG (at the altitude of Bogota) with pH: 7.356; PCO_2: 44: HCO_3: 23.2; and serum electrolytes and urianalysis within normal limits. She also brought a new ultrasound and an audiometry performed three months before the control which showed no alterations. A possible remission of the disease was considered, so management was not continued and control tests were requested. In his last control, 8 months later, the paraclinical tests showed arterial blood gases (at the altitude of Bogota) with pH: 7.317; PCO_2: 50.9; HCO : 26.1; BE: -0.1; BUN: 19.2, creatinine: 0.62 (GFR: 93.3 mL/min/1.73 m^2), calciuria120 mg/day (3.2 mg/kg/day) and urinalysis with pH=6; a renal ultrasound was also performed in which no lithiasis was found and the electrolytes were normal. The service of nephrology considered stability for RTA1 based in the previous paraclinical tests, the absence of pathological symptoms and signs and the remission of the brother, so the medical management established by rheumatology continued without adding alkalinizing therapy.

Presentation of case 3

A female patient in whose extra-institutional clinical history was evident, like in qher siblings, a diagnosis of RTA1.

This patient had no immediate complications during her first days of life. However, the mother, taking into account the diagnosis of RTA1 in her first two children, decided to take her to an extra-institutional pediatric nephrology evaluation at one month of age to rule out the presence of this disease. The paraclinical tests performed revealed alterations compatible with tubulopathy similar to those of her brothers. Subsequently, the diagnosis of RTA1 was confirmed and follow-up was established without introducing alkaline supplementation therapy initially. However, during the following 6 months, she presented recurrent emetic episodes and paraclinical control tests with alterations regarding the initial ones, for which management with citrate solution was initiated.

During the follow-ups, nephrocalcinosis was detected by renal ultrasound scans performed in her nursing nperiod and at 5 and 6 years of age. Likewise, hearing alterations were ruled out with normal audiometries at 3 and 8 years of age. Due to the detection of nephrocalcinosis, her management was progressively adjusted to meet therapeutic objectives. Her height was constantly below 1 standard deviation for age, without being short stature as such.

This patient received extra-institutional assessment by the genetics service, who, taking into account the clinical context and family history, requested a specific genetic study, which, like in the older sibling, was performed in Renaltube and did not show any usual ATP6V0A4 gene mutations compatible with RTA1, again without being able to exclude other mutations. Gastrointestinal symptoms persisted and she was subsequently diagnosed with

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GERD and chronic constipation, with adequate symptomatic control for the latter.

In her first evaluation by the institutional pediatric nephrology service, the girl was being managed with Shohl's solution 13 cm^3 orally every 8 hours and presented gastrointestinal symptoms given by burning epigastric abdominal pain, heartburn, dysphagia and rumination. The physical examination showed a weight of 25 kg (49^{th} percentile), a height of 123 cm (26^{th} percentile), and vital signs within normal limits for age. The mother brought paraclinical tests that had been taken 1 week before and that showed VG (at the altitude of Bogota) with pH: 7.432; PCO_2: 31.1; HCO_3: 20.3; BE: -2.8; BUN: 6.4; creatinine: 0.37 (GFR: 137 mL/min/1.73 m^2), calciuria: 248.5 mg/day (9.7 mg/kg/day), as well as an ultrasound scan of the same date that showed a right kidney measuring 93x33 mm and a left kidney measuring 91x43 mm (Hodson index 9.6), without other alterations. Therefore, the therapy was adjusted by increasing citrate solution 15 cm^3 every 8 hours and trying management with low sodium diet and restriction of calcium intake.

Subsequently, the patient was evaluated by the pediatric gastroenterology service, who considered an exacerbation of GERD symptoms and uncontrolled constipation, for which they requested extension studies and adjusted management with PEG 15 g per day and indicated an increase in oral fluid intake.

During a year and a half of follow-up, pediatric nephrology adjusted the management with alkaline therapy and dietary measures and one month before the follow-up appointment the mother of the patient suspended the treatment. The results of the paraclinical tests without medication were VG (at the altitude of Bogota) with pH: 7.344; PCO_2 : 43; HCO_3: 23; BE: -2.5 and normal serum electrolytes and urianalysis. As with her siblings, it was considered a possible RTA1 that has been overcome, so management was not continued and control tests were requested.

Eight months later, in the last control, the girl was asymptomatic, with adequate development and with VG (at the altitude of Bogota) with pH: 7.24; PCO_2: 63; HCO_3: 27; BE: -1.6, electrolytes without alterations and urine test with pH 5. However, as in her sibling, RTA1 was considered stable, urine with adequate acidification and concentration, so it was decided to continue without management until the next control to evaluate evolution.

It is important to mention that none of the three siblings had significant additional antecedents, that neither the pregnancies nor the deliveries had complications and that all were born full-term. The family is of mixed race, natural and coming from Duitama (Boyacá) and has always lived in adequate economic conditions in a home with all the basic services. The parents, who did not undergo genetic extension studies, were apparently healthy, denied consanguinity, did not have low weight or stature in a constitutional way, did not have significant antecedents, and have not presented pathological conditions suggesting renal alterations such as those observed in their children.

Type 1 renal tubular acidosis (distal)

Pathophysiology

In the distal tubule, the excretion of hydrogen ions into the tubular lumen is carried out by intercalated cells (type A), which are present in the final section of the distal convoluted tubule and in the collecting tubule (Figure 1).[13] Intracellular H_2O dissociates into H+ and OH- ions; the former are secreted into the tubular lumen by means of the H+-ATPase and H+-K+- ATPase pumps and the latter are combined with CO_2 to form HCO_3 - in a reaction catalyzed by carbonic anhydrase II (CAII). The HCO_3 - passes to the peritubular space through the anion exchanger (AE1), which allows the entry of Cl- through a counter-transport mechanism with HCO_3-.

Thus, in the distal RTA1, the decrease in H+ secretion can be caused by a decrease in the net activity of the proton pump or by an increase in the permeability of the luminal membrane to H+.[13-16]

The decrease in the net activity of the proton pump is the main mechanism that produces RTA1 and may

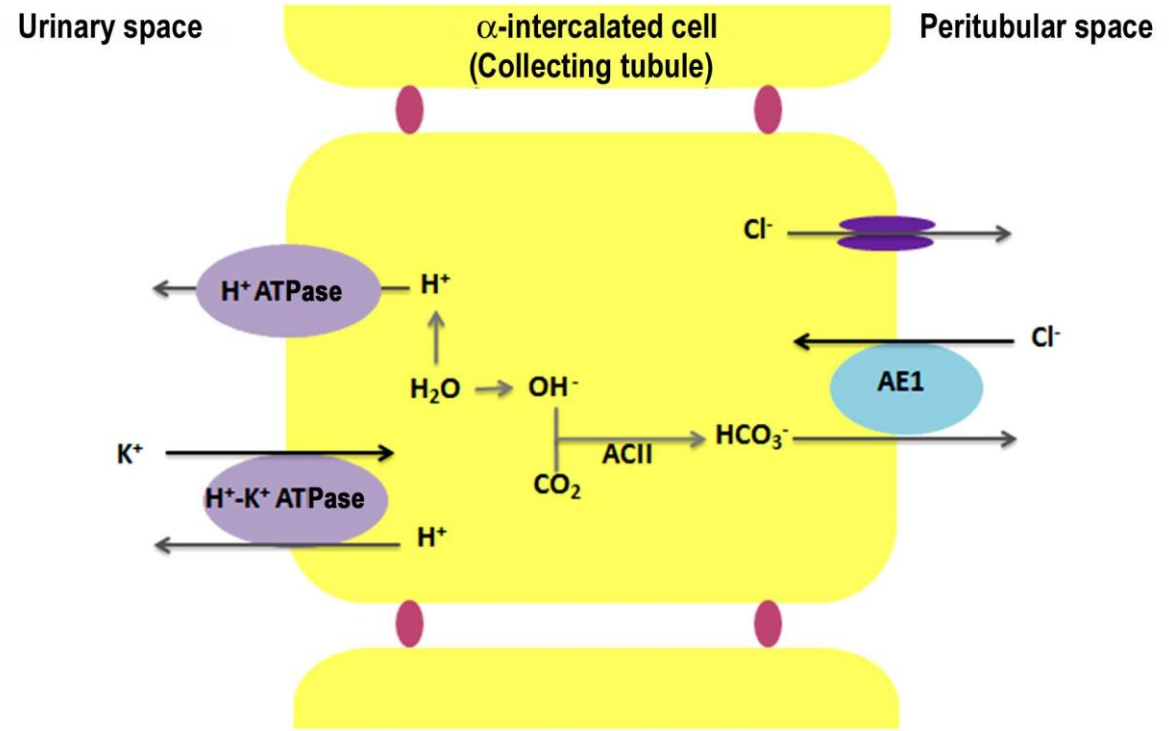

Figure 1. Role of the α-intercalated cell in the maintenance of the acid-base balance. Source: Elaboration based on Batlle & Haque.[6]

be due to several alterations that affect it directly or indirectly.[16-18] For example, several mutations have been found in genes that encode subunits of the H+-ATPase pump and that lead to a loss in their function of proton secretion.[8,19,20] On the other hand, in Sjögren's syndrome (SS) with RTA1 it has been evidenced a complete absence of the H+-ATPase pump, which occurs due to poorly understood immunological mechanisms.[21,22] Likewise, high titers of autoantibodies against CAII that decrease its activity, the generation of H+ ions in the intercalated cell, and its secretion by the proton pump have been identified in this syndrome.[23] Finally, mutations in AE1 have been identified in several families with hereditary forms of RTA1, which by decreasing the activity of this transporter would lead to the accumulation of HCO_3- in the cell A with a consequent decrease in the generation of intracellular H+.[24-28]

A less frequent mechanism of production of RTA1 is related to the permeability of the luminal membrane to H+. Since in many occasions the concentration of H+ is higher in the urine than in the extracellular space, this membrane must be relatively impermeable to prevent these ions from returning to the tubular cells and subsequently to the systemic circulation. When the permeability of this membrane decreases, as occurs in nephrotoxicity associated with the use of amphotericin B, these ions tend to return to the extracellular space, leading to hyperchloremic metabolic acidosis.[29,30]

Etiology

In children, RTA1 almost always has a primary origin, being identified several genetic mutations that are transmitted in an autosomal dominant or autosomal recessive manner. However, in about 20% of cases, no known mutation can be identified.[1,5,19,31] The three main genetic forms of primary RTA1 are distinguished in Table 1.

In addition to the genetic disorders described, Ehlers-Danlos syndrome and sickle cell anemia can

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Table 1. Classification of primary distal renal tubular acidosis

Classification	Type 1a RTA	Type 1b RTA	Type 1c RTA
Compromised gene	SLC4A1	ATP6V1B1	ATP6V0A4
Locus	17q21-22	2p13	7q33-34
Defective transporter	AE1	B1 subunit of the H+-ATPase	A4 subunit of the proton pump
Clinic	It can coexist with hereditary spherocytosis and Southeast Asian ovalocytosis	Alteration in endolymphatic homeostasis of the pH and cilia cell function with associated deafness. Acidification on semen maturation occurs.	Renal or ear involvement is generated, even leading to late deafness.

Source: Elaborated based on[31-42].

also be a genetic etiology of RTA1, although of secondary type.[43,44]

Some acquired secondary causes and less frequent in children are the consumption of some medications and autoimmune disorders. Among the former stands out amphotericin B, which can produce irreversible RTA1[29,30]; lithium, which can generate an incomplete form of RTA1 in which there is a decrease in acidification of the urine despite the plasma pH being normal,[45] and isophosphamide.[46] SS and systemic lupus erythematosus has been reported as associated autoimmune disorders, which can cause this disorder by immunological mechanisms still unknown.[21-23,47,48]

Clinical manifestations

The manifestations vary considerably depending on the etiology. In the case of the primary forms of RTA1, more stereotyped clinical pictures appear at more characteristic ages.

Recessive RTA1 is the most frequent and severe; it courses with severe hyperchloremic metabolic acidosis and moderate to severe hypokalemia.[19,49-51] Therefore, its manifestations usually appear early and the diagnosis is generally established earlier in relation to the dominant form of the disease.[19,49,50,52]

Figure 2 summarizes the clinical manifestations of RTA1 according to the involved organ systems, being present mainly in the recessive form of the disease.

Patients with the recessive form of RTA1 present with abdominal or lumbar pain secondary to nephrocalcinosis and/or renal litiasis[7,50] which are explained by the alkaline urine that favors the precipitation of calcium phosphate crystals.[54] On the other hand, there is a decrease in the concentration of urinary citrate (a powerful inhibitor of the formation of calcium stones), which favors the precipitation of this last mineral.[55,56] In addition, the acidemia promotes hypercalciuria by increasing the release of calcium phosphate from the bone by the bone buffer system and by directly decreasing the tubular reabsorption of these minerals.[57,58]

These alterations are frequent in patients with RTA1 in such a way that a late diagnosis can compromise the size of the kidneys or even lead to end-stage renal failure, for which it is recommended

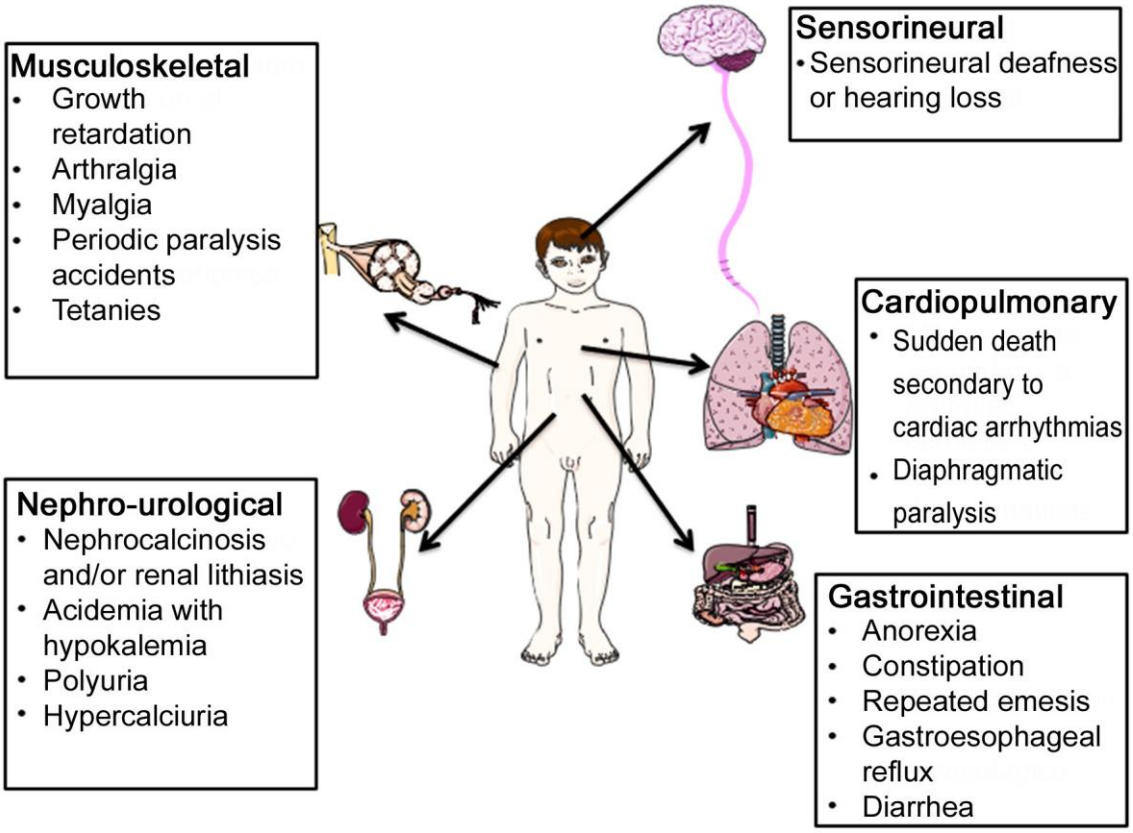

Figure 2. Clinical manifestations of distal renal tubular acidosis according to compromised organ systems. Source: Elaborated based on[53-66].

to perform renal ultrasonography annually during follow-up.[6,59]

On the other hand, sensorineural hearing alterations occur exclusively in the recessive form of RTA1.[37,42,49] However, the recessive forms of RTA1 are not necessarily accompanied by deafness, in addition, the associated hearing alterations exhibit considerable phenotypic heterogeneity.[20,41,42] In situations where genetic studies are available, the hearing status of the patient should not influence *a priori* a decision about which genes to study, and the finding of mutations associated with sensorineural hearing alterations obliges to perform periodic hearing tests.[20,37,49,60]

In the case of RTA1 of dominant inheritance, the manifestations are usually mild, being nephrocalcinosis and renal lithiasis the most frequent,[7,50] and can occur with mild or without metabolic acidosis (incomplete RTA1), as well as with normokalemia or mild to moderate hypokalemia.[25,50] Bone diseases or growth retardation occur rarely[25,50] and other alterations described for the recessive RTA1 are not common. Therefore, the dominant form of RTA1 is usually discovered late, even in adulthood.[50,67]

Diagnosis

Figure 3 illustrates the initial approach upon the clinical suspicion of renal tubular acidosis.

To diagnose a possible case of RTA1 is important to evaluate the urinary excretion of NH4+, which due to a decrease in the secretion of H+ to the tubular lumen in RTA1 is always decreased (<20-40 mEq/day).[17,69,74] This measure is of particular relevance in the differential diagnosis of metabolic acidosis secondary to inhalation of toluene, which,

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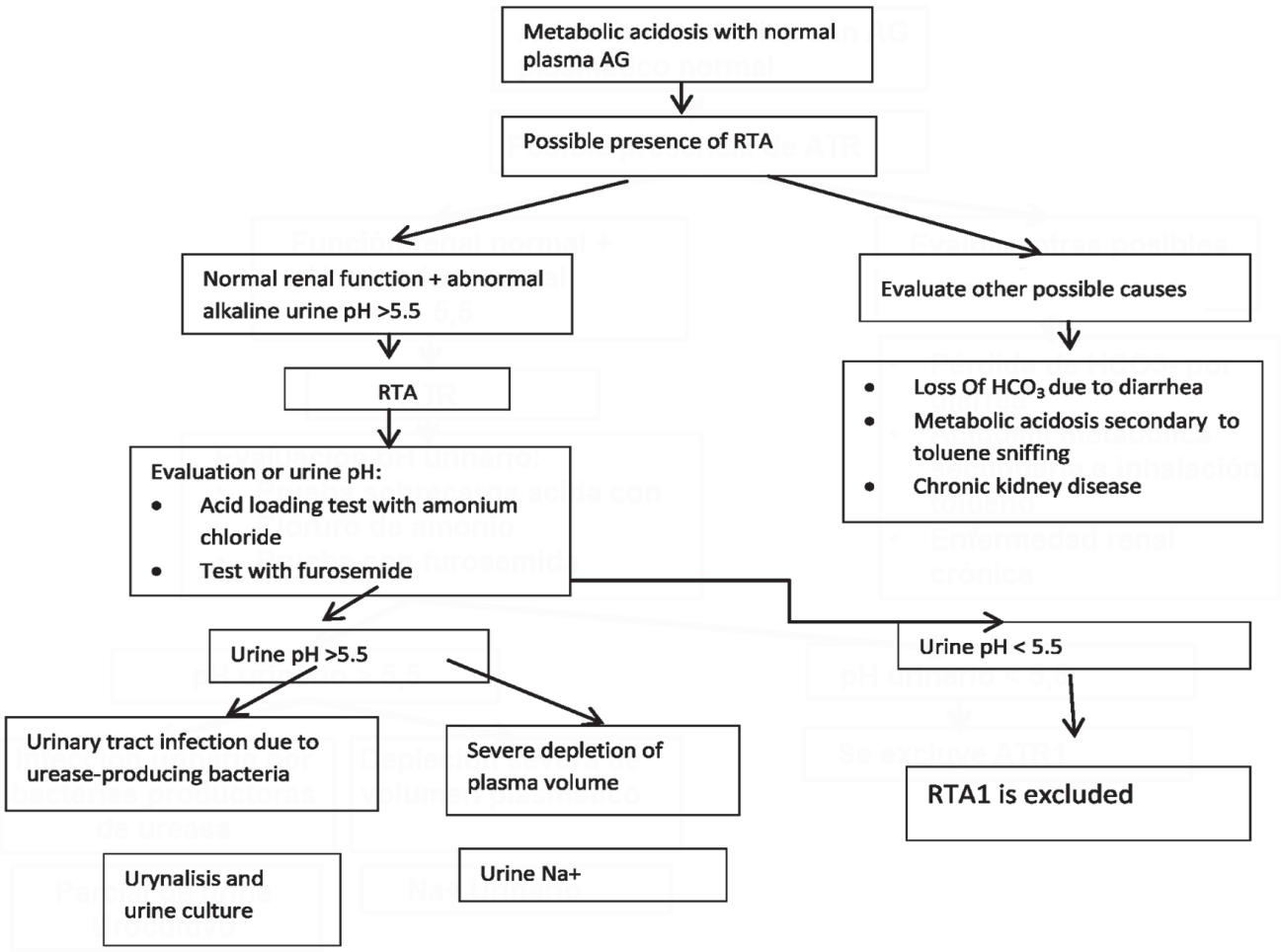

Figure 3. Diagnostic approach to renal tubular acidosis. Source: Elaborated based on[68-73]

although it presents normal AG and hypokalemia as in RTA1, it occurs with normal or elevated ammonium excretion (> 40 mEq/day).[75] Since very few laboratories can directly measure ammonium, urinary AG (uAG) has emerged as an indirect measure of NH4+ in urine.[74] Figure 4 illustrates concepts for understanding the use of uAG.

According to this, the uAG would become more negative as the concentration of NH4+ increases, which would simultaneously increase the Cl. The relationship between uAG and the urinary concentration of NH4+ was evaluated in some studies, finding an inverse linear relationship and developing the formula [NH4+ = -0.8 uAG + 82] for the estimation of NH4+.[74,76]

Likewise, in these studies the uAG of individuals with normal tubular function was averaged between -20 and -50 mEq/L and higher values (less negative) were observed in patients with low excretion of NH4+.[74,76] Therefore, in RTA1 it will be found an increased uAG, usually positive, and a decreased NH4+, either estimated or measured directly.[17,69]

Treatment

Correction of acidemia has demonstrated great efficacy in RTA1, as it reduces renal potassium loss, restores normal growth, delays nephrocalcinosis and urolithiasis, prevents progression to chronic renal failure and even reduces bone alterations associated with this

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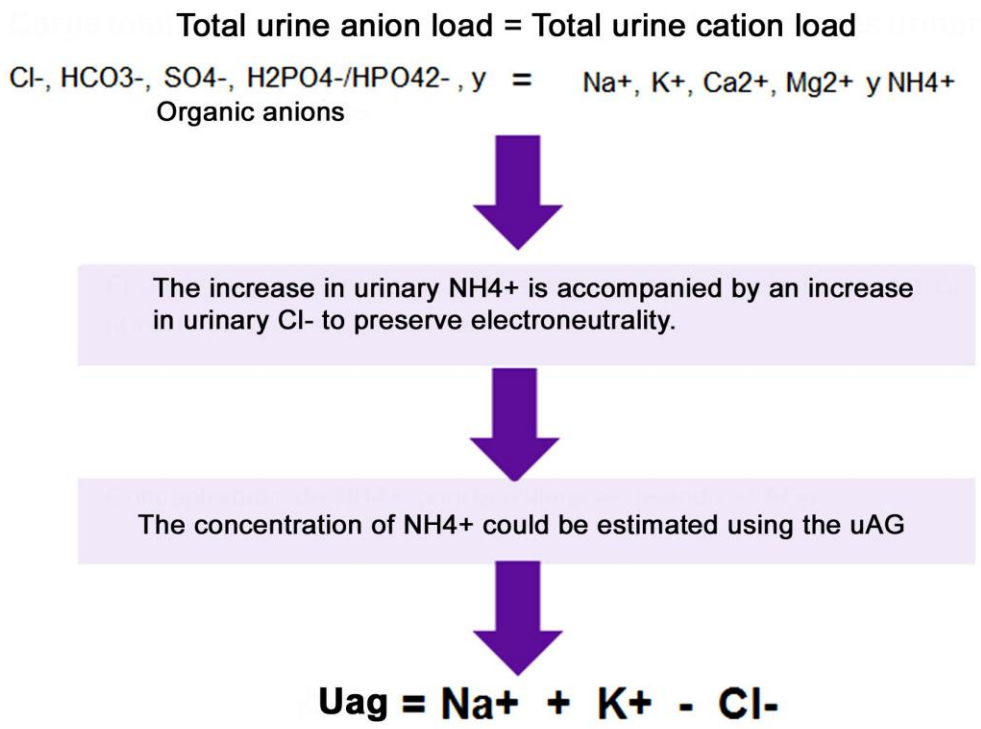

Figure 4. Basic concepts about the urine anion gap. Source: Elaborated based on[74-76]

disease.[77-80] Alkalinizing therapy is therefore the indicated management for RTA1, since it seeks to achieve relatively normal plasma levels of bicarbonate.

Sodium bicarbonate and sodium citrate are viable alternatives; however, the first occasionally generates digestive intolerance, which is one of the main obstacles.[81] The required doses in children can reach up to 4-8 mEq/kg/day, while in adults 1-2 mEq/kg/day are usually sufficient.[1,82] Potassium citrate is also an excellent alternative, mainly due to its usefulness for the replacement of K+ and its tolerability[83]; furthermore, the citrate provided when it is filtered in the kidney can directly increase the urinary excretion of citrate, although the main mechanism for this increase is the decrease in acidemia, which causes increased tubular reabsorption of citrate in RTA1.[55,56,78,79]

RTA1 is almost always a permanent disease, which is why alkali therapy must be continued lifelong.[84] When diagnosed early, the patients may have fewer complications and their prognosis will improve.[1,85] Likewise, a low sodium diet could have beneficial effects, due to mild volume depletion, increasing the reabsorption of Na+ at the proximal tubule and, secondarily, of HCO_3-.[86, 87]

Discussion

Some characteristics of the clinical picture presented in the three patients draw attention and deserve to be analyzed in the light of current knowledge about RTA1:

The three siblings presented different comorbidities since the first months of life; however, the initial manifestation of RTA1 in the three siblings consisted in refractory emetic syndrome at a young age, which is frequently reported in the literature on RTA1.[7,88,89] The patients also had early development of nephrocalcinosis and short stature, although the younger sister only had measurements within the risk range of short stature, all of which were common clinical findings.[6,7,11,50] These cases also coincided with that is reported in the literature regarding clinical

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alterations that manifest at a very young age in recessive hereditary presentations of RTA1.[19,49,50,52]

As mentioned above, early therapy usually leads to an excellent prognosis,[1] which was reflected in the adequate evolution and development of these patients. Thus, as previously reported,[77-80] both nephrocalcinosis and short stature improved with proper management.

Although a control renal ultrasound scan was not performed annually, as recommended,[6,59] at least four renal ultrasound scan were made during follow-up, which evidenced the remission of the nephrocalcinosis. On the other hand, calciuria, arterial gases and serum potassium improved during the follow-ups with alkalizing treatment, which coincides with what has been described in the literature.[77-80]

It is highlighted that none of the patients had hearing impairment, which is compatible with RTA1 type 1c.[8] Nevertheless, the studies carried out by Renaltube were not able to identify the main mutations of the ATP6V0A4 gene that are compatible with this presentation. This does not rule out the diagnosis, since it is probably a mutation not described so far in the international literature. This is not unusual taking into account that, although the main cause of RTA1 in the pediatric population is genetic, in up to 20% of primary RTA1 cases in children the underlying mutation cannot be identified.[1,5,19,31] The description of these mutations is not the main objective of this publication, however, their report can be the basis for future studies.[19,20,37,41,42]

It is curious that in one of the siblings there was a concomitant presence of mevalonate kinase deficiency associated with hyperimmunoglobulinemia D, a metabolic disease that definitely alters the prognosis and the evolution of the patient. The association between congenital RTA1 and metabolic diseases has not been clearly described in the literature, so it is worth reporting this event in order that in future studies and case reports some type of relationship will be determined.

Something that also attracted attention was the persistence of clinical improvement in the three patients after the discontinuation of alkalizing therapy and that within the biochemical alterations derived from this disease they only presented a decrease in pH to clear ranges of acidemia, but with normal urinalysis, serum electrolytes and urinary calcium. The main goal in management was achieved in the three patients: correction of symptoms associated with RTA1, remission of nephrocalcinosis, and avoiding permanent kidney damage.[1] The main goal in management was achieved in the three patients: correction of symptoms associated with RTA1, remission of nephrocalcinosis, and avoiding permanent kidney damage.[1] The caveat should be made that the follow-ups are still continuing and that future studies and evaluations will define whether the alkaline therapy requirements will indeed not be necessary again. Another possibility is that the needs for alkaline therapy have decreased without disappearing completely, as has been clearly described as patients with RTA1 grow older,[82] which will also be confirmed with the follow-up.

Conclusions

Although the clinical manifestations of the cases presented are in concordance with that is reported in the literature on RTA1, this publication highlights some uncommon facts that merit to be taken into account in future research. On the one hand, the association of one of the cases with mevalonate kinase deficiency with hyperimmunoglobulinemia D and, on the other, the disappearance of the need for alkalinizing therapy, particularly in the first case, which is not usual according to current knowledge about RTA1.

The study of relatives of patients affected by this pathology is important, since there are different genetic mutations with various forms of transmission and associated clinical manifestations. An active search should then be carried out in relatives, evaluating the risk factors previously described. Even though at this moment there are no protocols validated with an adequate scientific methodology for cost-effectiveness analysis for this type of study, its possibility is something that should be contemplated and investigated in future studies.

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It is striking that mutations previously associated with RTA1 have not been evidenced in these patients. However, there is a possibility that they have had undescribed mutations that should be studied in the future.

This type of pathology in pediatrics must be studied and managed in a multidisciplinary way by pediatric nephrology, general pediatrics, genetics, pediatric endocrinology and even nutrition, and it must be established a periodic follow-up plan that includes genetic counseling when indicated by the results of the studies.

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None declared by the authors.

Conflict of interest

None declared by the authors.

Ethical responsibilities

For the preparation of this case report, informed consent was obtained from the legal guardian of the patients.

Contribution of the author

JSFO summarized the case and conducted the search of scientific literature. JAUD and JSFO reviewed the content of the articles found and created a preliminary version of this article. CJLT and GLM reviewed, completed and corrected this version.

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Clinical case

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Cytomegalovirus colitis in kidney transplant recipients: presentation of two cases

Colitis por cytomegalovirus en trasplante renal: Presentación de 2 casos

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Abstract

Cytomegalovirus infection is a latent risk among immunocompromised kidney transplant recipients and is associated with increased risk of allograft failure and death. CMV infection can manifest as active infection or as CMV disease (divided into CMV syndrome and CMV tissue-invasive disease). We present two cases of tissue invasive CMV disease, presenting within 7 months after kidney transplantation. Both cases were D+/R-, received lymphocyte-depleting agents and mycophenolate, and both received CMV prophylaxis according to General Practice Guidelines. CMV disease criteria included detectable viral replication in blood, classical endoscopic findings and histopathological confirmation. We emphasize the need of categorical identification of CMV infection risk factors among kidney transplantation recipients, specially CMV donor/recipient serostatus and immunosuppressive medication. Although clinical practice guidelines suggest 1 to 3 months of CMV prophylaxis in high-risk cases, extended prophylaxis and immunosuppressive medication adjustment should be considered.

Key words: Kidney transplantation, cytomegalovirus infections.

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Resumen

La infección por citomegalovirus (CMV) es un riesgo latente en pacientes inmunocomprometidos por trasplante renal, asociándose con aumento del riesgo de rechazo del injerto y muerte. La infección por CMV puede manifestarse como infección activa o enfermedad por CMV (dividida en síndrome por CMV y enfermedad tisular invasiva por CMV). Presentamos dos casos de enfermedad tisular invasiva por CMV, la cual se presentó entre los primeros siete meses posteriores al trasplante. Ambos casos eran D+/R-; recibieron agentes depletores de linfocitos y micofenolato y profilaxis para CMV de acuerdo con las guías de práctica clínica. Los criterios para enfermedad por CMV incluyeron replicación viral detectable en sangre, hallazgos endoscópicos clásicos y confirmación histopatológica. Hacemos énfasis en la necesidad de identificar los factores de riesgo para la infección por CMV en pacientes con trasplante renal, especialmente el seroestatus donador/receptor y los medicamentos inmunosupresores. Aun cuando las guías de práctica clínica sugieren de uno a tres meses de profilaxis para CMV en casos de alto riesgo, debería considerarse la profilaxis extendida y el ajuste de los medicamentos inmunosupresores.

Palabras clave: trasplante de riñón, infecciones por citomegalovirus.

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Introduction

Cytomegalovirus infection frequently affects kidney transplant recipients, being associated with an increased risk of rejection and mortality.[1] The infection in kidney transplant recipients occurs as an active infection (evidence of CMV replication in blood regardless compatible signs and symptoms) or as CMV disease, which is divided into CMV syndrome (viral detection in blood with nonspecific signs and symptoms and absence of tissue invasion) and CMV tissue-invasive disease (CMV infection with signs and symptoms of specific organ damage).[2,3]

Gastrointestinal disease is the most common clinical manifestation of the tissue-invasive CMV disease, presenting nausea, vomiting, diarrhea and/or abdominal pain; erythematous erosions, localized ulcers and less frequently plaques, nodules and polyps are found in the endoscopic studies.[4]

We present two cases of CMV tissue-invasive disease, making emphasis on the risk factors associated with the infection and with proposals regarding the duration of prophylaxis and the adjustment of the immunosuppressive treatment.

Presentation of case 1

A 30-year-old male patient with a history of trisomy 21 and G5 chronic kidney disease without requiring replacement therapy before transplant. In January, 2018, he received a living related-donor kidney transplant. Immunosuppression was induced with methylprednisolone 500 mg and thymoglobulin 50 mg, and was maintained with tacrolimus 2 mg every 12 hours, mycophenolic acid 720 mg every 12 hours, and prednisone 30 mg every 24 hours.

The serostatus of the patient for CMV was negative before the transplant (IgG 4.3 AU/ml, IgM 0.08 AU/ml); however, his donor had IgG 135 IU/ml (0-14) and IgM 5 IU/ml (0-22). Prophylaxis was given with valganciclovir 450 mg every 12 hours during one month after the transplant.

The patient was hospitalized five months later due to bloody diarrhea, nausea and vomiting of gastric contents for one week, with a blood pressure of 100/80 mmHg, heart rate 86 bpm, respiratory rate 18 bpm, and temperature 36.4 ºC. biochemical analysis with hemoglobin of 7.4 g/dl, hematocrit 23.48%, platelets 72x10^3/µl, leukocytes 3.03x10^3/µl, glucose 114 mg/dl, urea 58 mg/dl, creatinine 1.5 mg/dl, Na 144 mmol/L, K 4.5 mmol/L, Cl 108 mmol/L, Ca 9.1 mg/dl, Mg 1.5 mg/dl, P 3.9 mg/dl.

A colonoscopy was performed, finding nonspecific colitis with erosions of aphthous "shirt button" appearance (Figures 1 and 2). The histopathological

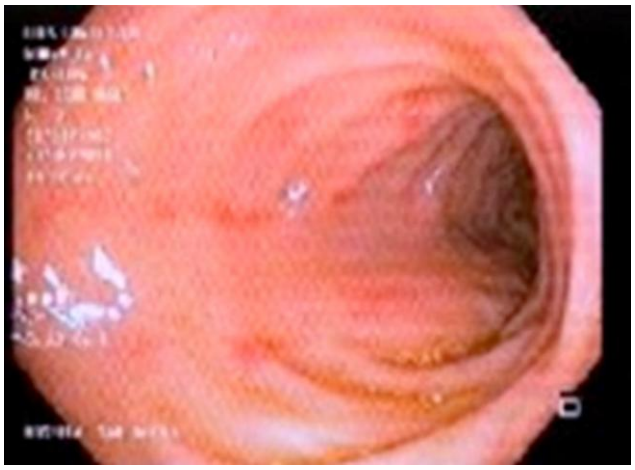

Figure 1. Multiple linear erosions in the left colon

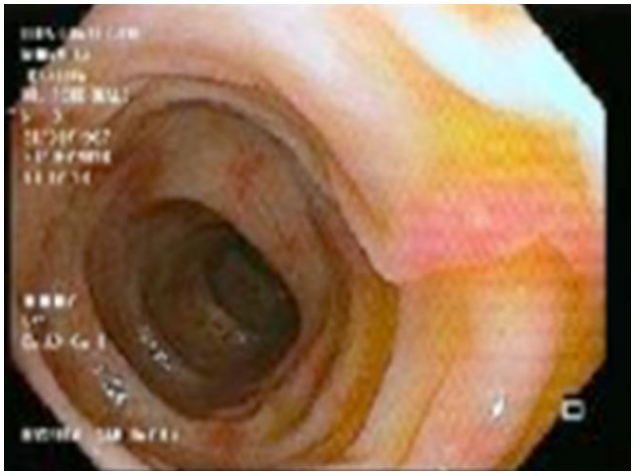

Figure 2. Erosions of aphthous "shirt button" appearance.

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study reported slightly edematous and congestive supporting stroma, mixed inflammatory infiltrate predominantly lymphoid and hemorrhage without involvement of glandular structures and lining mucosa. Mucosal endothelial cells with prominent intranuclear basophilic inclusions, consistent with CMV infection, were identified (Figures 3 and 4). A viral load test was performed in the first weeks after diagnosis, with a result of 1.724 copies/ml (< 200).

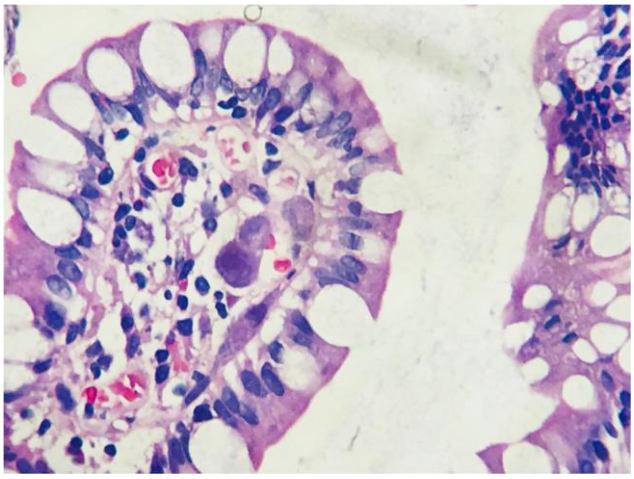

Figure 3. Terminal ileum with mucosal endothelial cells with intranuclear basophilic inclusions.

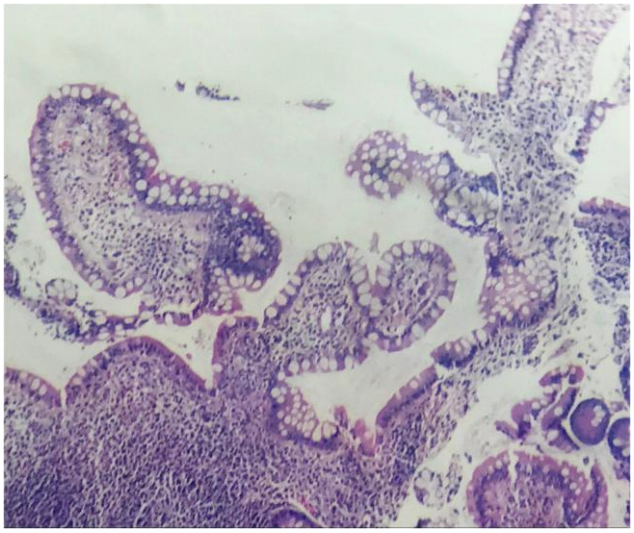

Figure 4. Terminal ileum with edematous and congestive supporting stroma, with inflammatory infiltrate of lymphoid predominance.

CMV tissue-invasive disease was considered as diagnosis. It was treated with intravenous ganciclovir 350 mg every 12 hours for 2 days and subsequently with oral valganciclovir 450 mg every 48 hours for 3 months, with improvement of symptoms. Latest studies: urea 55.9 mg/dl, BUN 26 mg/dl, creatinine 1.2 mg/dl.

Case 2

A 23-year-old male patient with G5 chronic kidney disease of 2 years of evolution, on renal replacement therapy with hemodialysis for 5 months prior to kidney transplantation from a related living donor in October, 2017. The induction of immunosuppression was carried out with methylprednisolone 500 mg and basiliximab 20 mg, and it was maintained with prednisone 40 mg every 24 hours, tacrolimus 3 mg every 12 hours and mycophenolic acid 720 mg every 12 hours.

Before the transplant the CMV serostatus of the patient was negative (IgG < 5 IU/ml, IgM < 5 IU/ml), and his donor was positive, with IgG of 250 AU/ml (0-6) and IgM of 0.270 AU/ml (negative < 0.85). He received prophylaxis with valganciclovir 450 mg every 12 hours for 2 months.

Two months after transplantation, the patient was hospitalized due to data compatible with acute graft rejection, corroborated by biopsy with transient acute ischemia, being managed with six doses of thymoglobulin, 1.25 mg/kg, with remission and normalization of nitrogen compounds.

Seven months after transplantation, he presented abdominal pain, diarrheal stools, asthenia and adynamia of 5 days of evolution. Without alteration in his vital signs (blood pressure of 120/74 mmHg, heart rate of 81 bpm, respiratory rate of 16 rpm, and temperature of 36.2 ºC), but urea of 71 mg/dl, creatinine of 2.99 mg/dl, Na 133 mmol/l, K 3.33 mmol/l, hemoglobin 13.5 g/dl, hematocrit 40,5%, leukocytes 3.7 x 10^3/µl, glucose 115 mg/dl and Cl 104 mmol/l.

A colonoscopy was performed, observing isolated ulcerations with a fibrinoid base and raised erythema-

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tous halo in the descending colon, of nearly 1 cm in diameter in the transverse colon and more abundant and of larger size in the ascending colon (Figures 5 and 6). The histopathological study reported slightly edematous and congestive supporting stroma, with a moderate amount of mixed inflammatory infiltrate, predominantly lymphoid, and hemorrhage without affecting the glandular structures and the lining mucosa. Mucosal epithelial and endothelial cells with viral cytopathic changes characterized by prominent intranuclear basophilic inclusions, consistent with

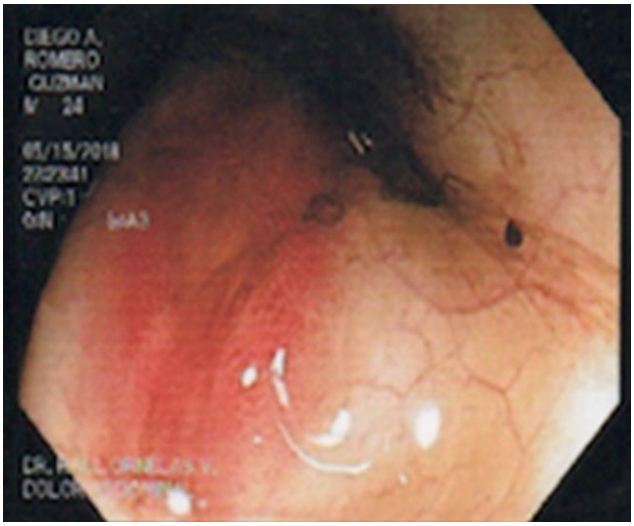

Figure 5. Ulceration with fibrinoid base and erythematous halo.

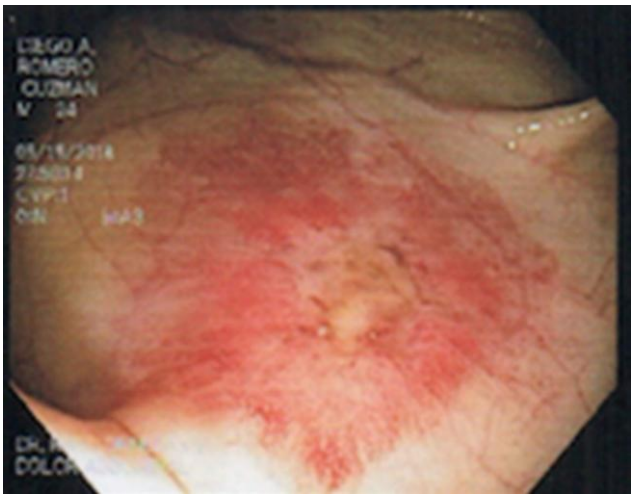

Figure 6. Punched-out lesion with erythematous base.

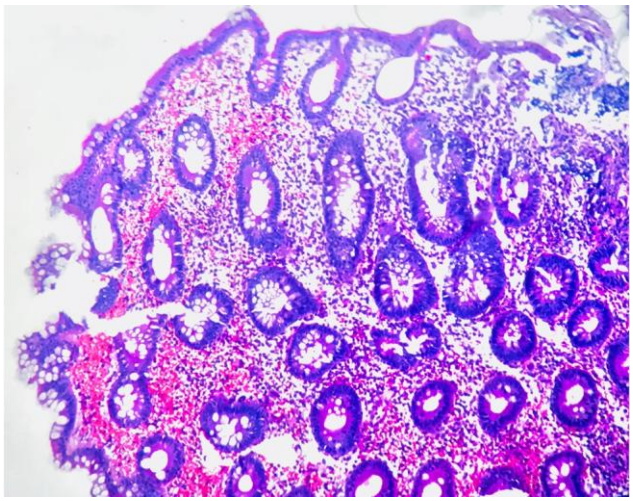

Figure 7. Epithelial mucosa with intranuclear basophilic inclusions.

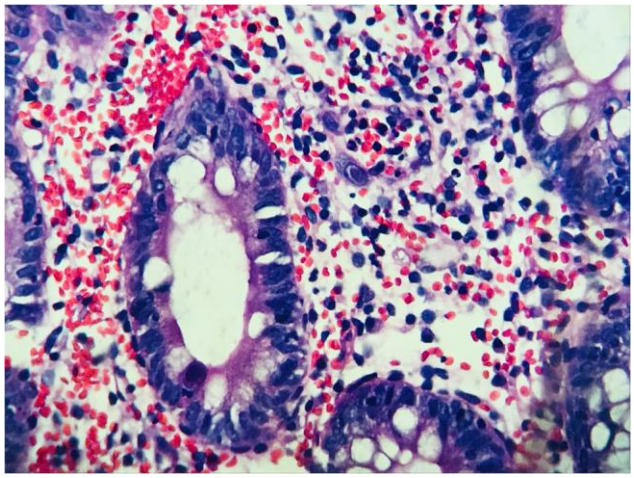

Figure 8. Edema and congestion of supporting stroma.

CMV infection, were identified (Figures 7 and 8). A viral load test was performed with a result of 38.386 copies/ml (< 200).

The patient was treated with ganciclovir 350 mg intravenously every 12 hours for 4 days and subsequently with valganciclovir 450 mg orally every 12 hours until completing 21 days of treatment, with remission of the clinical picture and biochemical improvement (urea 39.2 mg/dl, BUN 18.3 mg/dl, creatinine 2.3 mg/dl). The viral load in the control two months after the onset of the clinical picture was lower than 200 IU/ml.

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Discussion

Cytomegalovirus infection is a latent risk in immunosuppressed kidney transplant patients, with an incidence of CMV disease of 24% in the first 100 days, with a general frequency of infection of 50-80% and of CMV disease of 20-60%.[5-7] It occurs in three forms: primary infection (seronegative recipient and seropositive donor, D+/R-), reactivation of latent CMV (consequence of immunosuppression, even when both the recipient and the donor are seronegative), and reinfection (previously seropositive recipient who becomes infected with another serotype of the virus).[8]

Coinciding with the international reports and other documented cases, both cases presented with gastrointestinal disease, the most common clinical manifestation of invasive CMV disease, characterized by nausea, vomiting, diarrhea and/or abdominal pain, with endoscopic findings of erythematous erosions, localized ulcers and less frequently, plaques, nodules and polyps.[8-11] Other less frequent manifestations are pneumonitis, nephritis, retinitis, pancreatitis and hepatitis.[2]

The main risk factors for the development of the infection are the following:

- The donor/recipient serostatus:
  - Positive donor/negative recipient (D+/R-): the highest risk, without prophylaxis 69% can develop infection and 56%, CMV disease.
  - Positive recipient (R+): lower risk of CMV disease without prophylaxis (20%), but up to 67% risk of reinfection.
  - Negative donor/recipient (D-/R-): low risk, less than 5% develop infection without prophylaxis.
- Induction of immunosuppression with lymphocyte depleting agents such as thymoglobulin.
- Maintenance of immunosuppression with mycophenolate.
- Use of lymp hocyte depleting agents or high doses of glucocorticoids to treat an acute rejection.[1,3,7]

As it can be seen, the two cases presented shared all the risk factors mentioned. Both were D+/R- and the immunosuppression with mycophenolate was maintained. In case 1, immunosuppression was induced with a lymphocyte depleting agent and in case 2 a lymphocyte depleting agent was used as a treatment for the acute rejection that occurred; therefore, they are considered high risk.

For 20 years, there has been a grade A recommendation for the prophylaxis of CMV in seronegative recipients with a seropositive donor and immunosuppression with a lymphocyte depleting agent, as well as in seropositive recipients who use immunosuppression with a lymphocyte depleting agent regardless of the donor's serostatus.

In cases of a seronegative recipient with a seropositive donor and immunosuppression without lymphocyte depletion, the recommendation is grade B. In the seropositive recipient with immunosuppression without lymphocyte depleting agent, regardless of the donor's serostatus, the recommendation is grade C, and when both donor and recipient have negative serostatus, regardless of the immunosuppression regimen, prophylaxis is not recommended.[12,13] Even so, the serostatus prior to transplantation, the identification of high- or low-risk recipients, and the standardized use of prophylaxis against CMV in high-risk cases are not generally reported in other publications.[9]

Even though a grade C recommendation is considered, in the experience of a center with D+/R+ serostatus in all cases, the universal use of prophylaxis for CMV reduced the incidence of CMV disease by 14.2%.[7]

In the absence of prophylaxis, viral replication appears between the first and the sixth month after transplantation, coinciding with the period of maximum immunosuppression.[8] However, since the publication of the clinical practice guidelines for the prevention of CMV disease 20 years ago, until now,

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the duration of the prophylaxis for CMV has not been standardized (its administration for 1 to 3 months is recommended in some bibliography,[12-14] while in another is already recommended for up to 6 months, especially in high-risk patients).[1,15] In our cases presented, the patients received prophylaxis with valganciclovir 450 mg every 12 hours, one during one month and the other during two months, despite both are considered of high risk. The cause for suspension was the presence of adverse events (leukopenia).

It has been found that the risk of CMV disease persists even after the completion of the prophylaxis. The IMPACT study, conducted with 326 high-risk patients, compared the time of prophylaxis with valganciclovir for 100 vs. for 200 days, finding a decrease in the rate of late disease in the group of 200 days (16 vs. 37%, respectively).[16] In addition, a systematic review that analyzed the benefits and risks of antiviral drugs found that prophylaxis for CMV reduces the risk of herpes simplex disease, herpes zoster, pneumocystosis and bacterial infection, acute rejection and loss of the graft.[8] It is considered that prolonged prophylaxis is a measure to reduce the infection rate.[16] Therefore, extended prophylaxis in high-risk patients, with an emphasis on risk-benefit and cost-benefit, is a topic of high impact to be included in clinical trials and clinical practice guidelines. Despite being very common the report of adverse events, most of them are mild and without major repercussion (91%), especially gastrointestinal (diarrhea). Regarding the hematological effects (mainly leukopenia), although they occurred more frequently in patients receiving extended prophylaxis (38 vs. 26%), the average leukocyte count, the incidence of febrile neutropenia, agranulocytosis, anemia , thrombocytopenia and pancytopenia were similar in standard (100 days) and extended (200 days) prophylaxis, as well as the requirement of granulocyte colony stimulating factor (14 vs. 13% respectively).[16]

The adjustment of the dosage of valganciclovir is recommended depending on the renal function (estimated with the Cockroft-Gault or MDRD formulas), as it follows: eGFR >60ml/min = 900 mg/day, 40-59 ml/min = 450 mg/day, 25-39 ml/min = 450 mg every 48 hours, 10-24ml/min = 450 mg twice a week, its use is not recommended in case of eGFR <10ml/min.[15]

Another controversial aspect lies in the adjustment of immunosuppression once the CMV has been documented. In addition to the specific treatment with intravenous ganciclovir or oral valganciclovir, some authors recommend reducing or discontinuing the antimetabolite (mycophenolate or azathioprine), under the concept that the infection is a manifestation of excessive immunosuppression (recommendation grade 2D).[13] However, there is another theory that proposes an increase in the dose of immunosuppressants in patients with CMV disease, since the infectious process is related to an increased risk of graft rejection.[2] In the cases presented, the dose of mycophenolate of case 1 was decreased and that of case 2 was increased. Both cases had a favorable evolution; however, more evidence is required to issue a strong recommendation on the adjustment of the immunosuppression.

Conclusion

CMV infection is a latent risk in kidney transplant recipients. We emphasize the need to identify the risk factors for CMV infection in kidney transplant recipients, especially the donor/recipient serostatus and the immunosuppressive drugs. It is proposed that future clinical trials include extended prophylaxis in high-risk cases, as well as immunosuppression adjustment once the CMV infection is detected.

Conflict of interest

There is no conflict of interest on the part of the authors.

Ethical responsibilities

Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

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Right of privacy and informed consent

The authors declare that patient data do not appear in this article.

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Contribution of the authors

Claudia Alejandra Aceves Quintero: Collection of data from files, search for articles and writing of the work.

Juan Carlos Corona Meléndez: Search for articles and writing of the work.

Gonzalo Agustín García y Otero: Search for articles and writing of the work

Marco Antonio Amaya Carreño: Collection of data from files and endoscopic and histopathological images.

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Clinical case

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Magnesium depletion secondary to hypercalcemic nephropathy during pregnancy: Case report and literature review.

Depleción corporal de magnesio durante el embarazo por nefropatía hipercalcemica. Reporte de caso y revisión de la literatura

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Abstract

Serum magnesium is the «forgotten ion» in medical practice. Most of the times it is not taken into account in clinical studies, its alterations tend to be ignored and its therapeutic approach is not well defined. The symptomatology produced by hypomagnesemia is nonspecific and its diagnostic approach is complex. We present the case of a pregnant patient with symptomatic hypomagnesemia secondary to renal damage due to hypercalcemia.

Keywords: hyperparathyroidism, hypercalcemic nephropathy, nephrogenic diabetes insipidus, pregnancy, hypomagnesemia.

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Resumen

El magnesio sérico es el "ion olvidado" en la práctica médica: la mayoría de veces no se tiene en cuenta en los estudios clínicos, sus alteraciones tienden a ser ignoradas y su aproximación terapéutica no está definida de forma adecuada. La sintomatología producto de la hipomagnesemia es inespecífica y su aproximación diagnostica es compleja. Se presenta el caso de una paciente con hipomagnesemia sintomática severa asociada a daño renal por hipercalcemia durante la gestación.

Palabras clave: hiperparatiroidismo, nefropatía hipercalcemica, diabetes insípida nefrogénica, embarazo, hipomagnesemia.

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Introduction

Hypercalcemia is a frequent electrolyte disturbance that usually arises due to cancer or alterations in parathyroid hormone.[1,2] In acute or chronic presentations, it affects the renal concentrating ability, being a reversible cause of diabetes insípida.[2,3] Primary hyperparathyroidism is the third most frequent endocrine disorder in the general population.[4]

Magnesium, unlike calcium, can be considered as the «forgotten ion»; this is due to the infrequency with which alterations in its serum concentration are investigated in clinical practice[5] or to the number of articles published regarding the other electrolytes.[6] Hypomagnesemia is observed in 10% of hospitalized patients,[7] being often asymptomatic or with manifestations overshadowed by alterations of other electrolytes[7,8]; its main etiology are kidney losses associated with increased glomerular filtration, polyuria, decreased tubular absorption of magnesium and hypercalcemia.[7,9]

Below we present the case of a young pregnant woman who presented neuromuscular symptoms due to body depletion of magnesium secondary to hypercalcemic nephropathy due to primary hyperparathyroidism which required surgery and chronic oral magnesium oxide replacement, with which the correction of the symptoms and resolution of the electrolyte disorder were achieved.

Case presentation

A 24-year-old female patient, 27.4 weeks pregnant without prenatal controls at the time of admission, consulted for a process of tachycardia and chest pain of one month of evolution. The woman was assessed by the obstetrics service, where it was performed an electrocardiogram, which evidenced a sinus rhythm; the medical history, the physical examination and the tests did not suggest an infectious process, which is why a concept from internal medicine was requested.

As an obstetric antecedent, the patient stated that she had had two pregnancies that required cesarean section due to persistent tachycardia during pregnancy, although these episodes occurred suddenly and were self-limited during the last six years. The woman reported intermittent low back pain with a finding of left renal lithiasis of 5 mm in outpatient ultrasound scan, and a bowel habit every four days for four years despite the consumption of a high-fiber diet.

In the initial assessment by internal medicine, the electrocardiogram confirmed sinus tachycardia associated with a short QT interval, and for this reason an electrolyte disorder was suspected. The laboratories confirmed hypercalcemia of 16.5 mg/dL (calcium corrected for albumin, reference value [RV] 8.2-10.4 mg/dL) and hypophosphatemia (Table 1 and Figure 1A). A study of hypercalcemia was started with a report of intact parathyroid hormone (iPTH) of 524 pg/mL (RV 16-46 pg/mL) and 24-hour urine calcium of 1066 mg with a urine volume of 7,085 mL, which configured the diagnosis of primary hyperparathyroidism. Treatment with intravenous crystalloids, prednisone, and furosemide was indicated due to the limitation for the use of bisphosphonates during pregnancy and the unavailability of calcitonin. The nephrology service proposed to perform hemodialysis to reduce the serum calcium levels and be able to control the polyuria and reduce the cardiovascular and fetal toxic effects, prior to the parathyroidectomy.

On the fifth day of hospital stay, the patient persisted with severely elevated calcium despite two hemodialysis sessions and pharmacological management (Figure 1A), therefore, a cervical surgical exploration procedure was performed, with a finding of a parathyroid mass dependent of the right lower lobe of the thyroid, requiring a right partial thyroidectomy with a subsequent pathology report of parathyroid adenoma. The surgical procedure had no maternal or fetal complications and allowed the discontinuation of hemodialysis and the withdrawal of pharmacological management for hypercalcemia. 24 hours after the procedure, an iPTH control test was performed, with a result of 7.63 pg/mL. On the sixth day of hospitalization, the woman presented abnormal uterine activity, associated with hypomagnesemia of 1.0 mg/dL (RV: 1.6-2.6 mg/dL), and the

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Table 1. Reference laboratories during hospitalizations.

Test		First hospitalization		Second hospitalization	
		Entry	Egress	Entry	Egress
Serum/Blood.	Sodium (135-145 mEq/L)	134	138	134	137
	Potassium (3,5-4,5 mEq/L)	4,2	4,2	3,8	4,1
	Calcium corrected for albumin (8.2-10.4 mg/dL)	15	9,3	8,8	10,5
	Magnesium 1.6-2.6 mg/dL)	0,7	2,8	1	2,4
	Creatinine (0.5-0.95 mg/dL)	0,8	0,8	0,7	0,6
	Urea nitrogen (8-23 mg/dL)	13,7	15	12,8	15,6
	Osmolality * (275-300 mOsm/kg)	276			
	iPTH (16-46 pg/mL)	524	7,6	57	60,4
	Vitamin D25 (>30 ng/mL)	27,6			
Urine.	Urinalysis	pH: 6.5; density: 1.015. Negative red blood cells, leukocytes. Calcium oxalate crystals.		pH: 6.5; density: 1.010. Negative red blood cells, leukocytes, proteins.	
	Osmolality ** (390-1093 mOsm/kg)	525		350	
	24-hour volume (600-1600 mL/24h)	7085	3720		
	24 hours calciuria (<250 mg/24 h)	1066	84,4		
	Spot urine calcium (mg/dL)	15	2,27		
	Spot urine creatinine (mg/dL)	16,3		35	
	Spot urine calcium/creatinine ratio(<0.2 mg/mg)	0,92			
	Spot urine magnesium (mg/dL)			20	
	FeMg (%)			37	

* Calculated serum osmolality: 2Na+(Glucose/18)+BUN/2.8.
** Calculated urine osmolality: (Urine density of the patient - 1000)*35.
iPTH: intact parathyroid hormo

obstetrics service indicated intravenous infusion of magnesium 2 g per hour for 24 hours. On the eighth day, hospital discharge was authorized with oral calcium and vitamin D supplementation.

After 14 days of hospital discharge, the patient consulted again due to generalized muscle weakness, walking difficulty and facial paresthesias of four days of evolution. In the emergency service, the woman who was 30 weeks pregnant, presented normal vital signs, but bilateral palpebral ptosis and generalized hyperreflexia associated with positive Trousseau's sign at 90 seconds. A diagnostic impression of hypocalcemia due to the antecedent of partial thyroidectomy with resection of parathyroid adenoma was made and intravenous calcium replacement was started after obtaining samples for laboratory testing. The results ruled out hypocalcemia and evidenced a calcium corrected for albumin of 8.8 mg/dL and severe hypomagnesemia of 1.0 mg/dL, for this reason, a concept of the endocrinology service was requested, which indicated infusion with intravenous magnesium sulfate 1 g every hour (Table 1). A collection of magnesium in spontaneous urine

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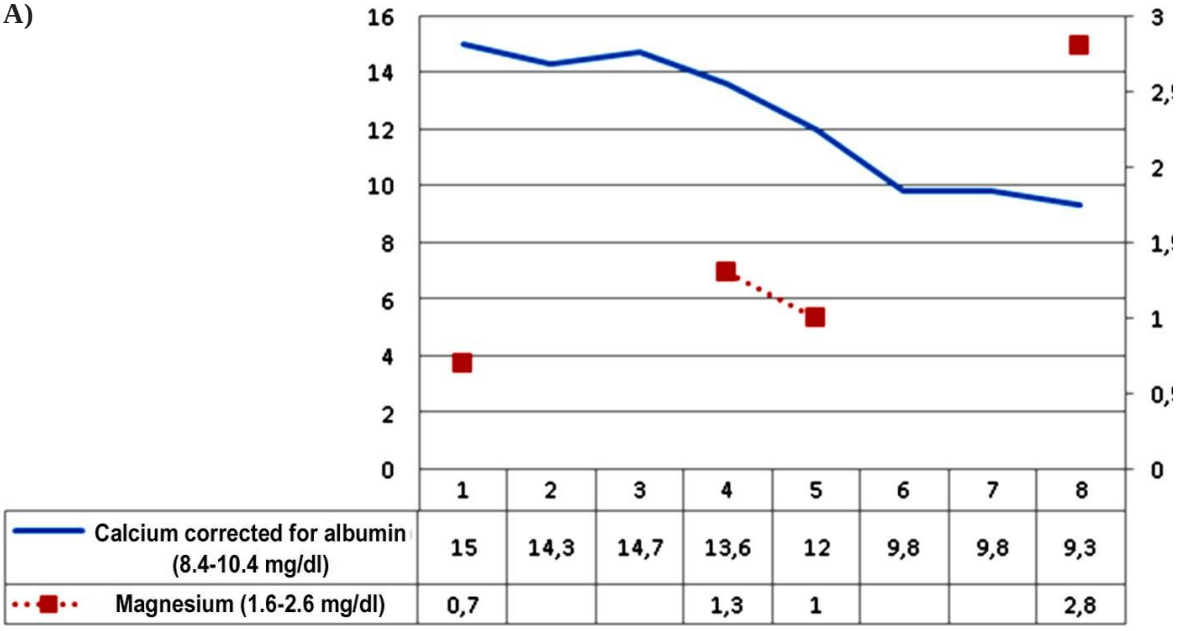
A)



B)

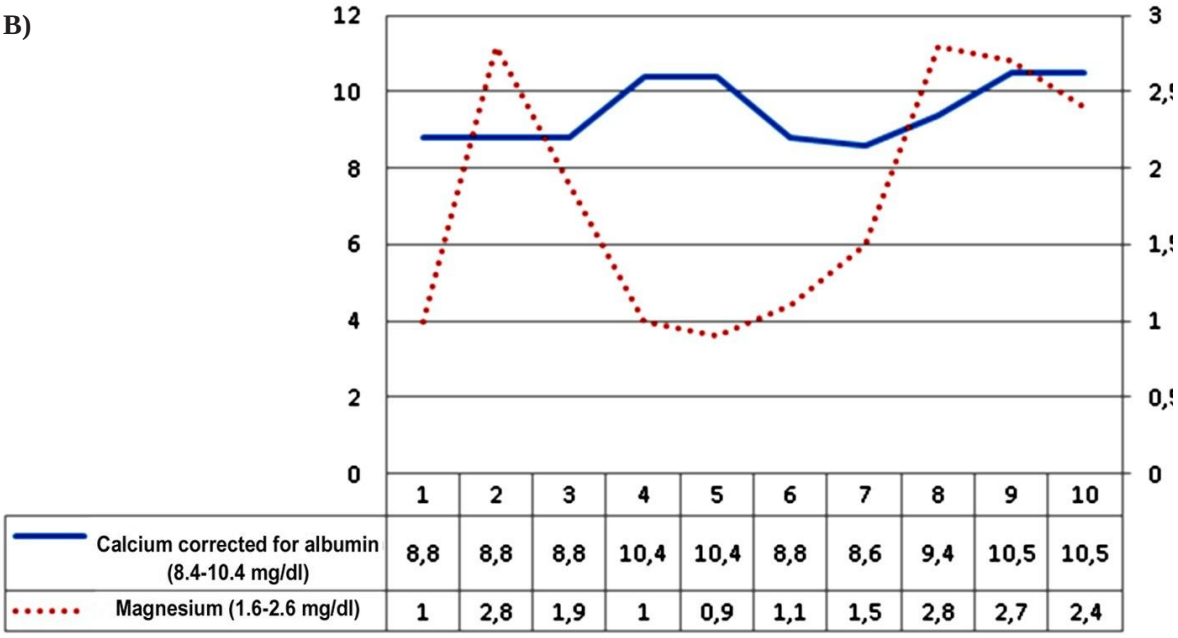


Figure 1. A) Electrolyte profile with calcium corrected for albumin and magnesium during the first hospitalization. **B)** Electrolyte profile with calcium corrected for albumin and magnesium during the second hospitalization. Source: Own elaboration

was made, which confirmed renal losses by a fractional excretion of magnesium (FeMg) of 37%.

The patient was admitted to the intensive care unit to be continuously monitored for the risk of ventilatory failure with an infusion of magnesium sulfate 24 g/day. On the second day of the new hospital stay, her serum magnesium levels were corrected (Figure 1B) with resolution of the palpebral ptosis, normalization of the osteotendinous

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reflexes and positive Trousseau's sign at 2:20 minutes.

After five days of intravenous supplementation of magnesium sulfate, the hypomagnesemia was corrected, and having a negative Trousseau's sign at five minutes, progressive withdrawal of the replacement was started, until leaving an infusion of magnesium sulfate of 6 g/day. Due to the dependence of magnesium supplementation, magnesium oxide was prescribed in one capsule of 50 mg of elemental magnesium orally per day (Figure 2), with which it was possible to achieve normal serum magnesium levels and absence of neurological symptoms on the tenth day of hospital stay, and the infusion was withdrawn. The patient was discharged from the hospital with oral supplementation of magnesium oxide, calcium carbonate, calcitriol and vitamin D25.

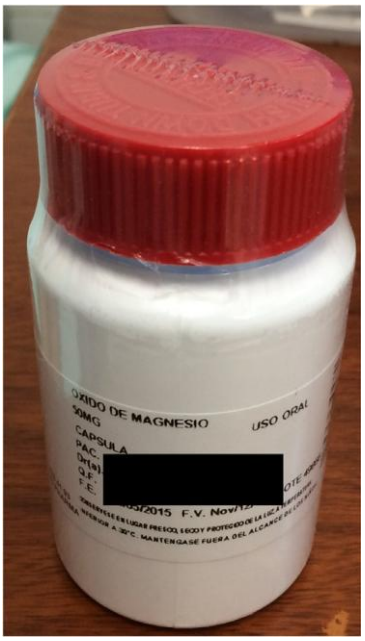

Figure 2. Presentation of Magnesium Oxide. Photograph of the bottle indicated for outpatient oral magnesium supplementation. Source: Original photograph of the author.

Discussion

Calcium and magnesium are essential minerals for multiple physiological processes in humans[9,10] and their serum concentrations are a poor reflection of the body deposits: only 0.1% of calcium and 1% of the total magnesium are present in the extracellular fluid.[9] Physiological changes associated with pregnancy, such as renal hyperfiltration and dilution of serum albumin, can affect the interpretation of the measurement of these electrolytes in serum[4,11]; in addition, due to their nonspecificity, the symptoms resulting from the alteration of the body concentration can be overshadowed or confused.[4,10,11] It is also important to mention that the clinical practice guidelines do not require the evaluation of serum calcium during pregnancy[4] and physicians rarely request the measurement of serum magnesium during the study of patients.[5]

Primary hyperparathyroidism has a prevalence between 0.4% and 1.4% in the general population, but in the case of pregnant patients the incidence is unknown, with less than 200 cases reported.[4] The detection and correction of hypercalcemia during pregnancy are of utmost importance, since it can cause maternal mortality of up to 30% associated with neonatal complications.[4,11,12] Due to the limitation of pharmacological options for treatment, in the present case the use of hemodialysis prior to partial parathyroidectomy was necessary; it was also interesting the renal involvement manifested by polyuria syndrome with preserved urine osmolality (Table 1).

Diabetes insipidus during pregnancy has a prevalence of 4 cases per 100,000 pregnancies.[13] In the case of nephrogenic diabetes insipidus, the ability to produce hypertonic urine is usually preserved, despite the alteration in the maximum urine concentrating ability[14]; it is usually acquired and its etiologies include hypercalcemia,[13,14] which both in acute and chronic elevations can alter the expression of aquaporins in the collecting tubule and in the Na-K-2Cl (NKCC2) pump in the thick ascending limb of the loop of Henle.[2,3] Neurogenic diabetes insipidus is reversible with the correction of serum calcium levels, however, it has not been described in the literature how long it may take the normalization of renal tubular functions.

The hypomagnesemia was documented since the first admission to the hospital (Table 1), but only until

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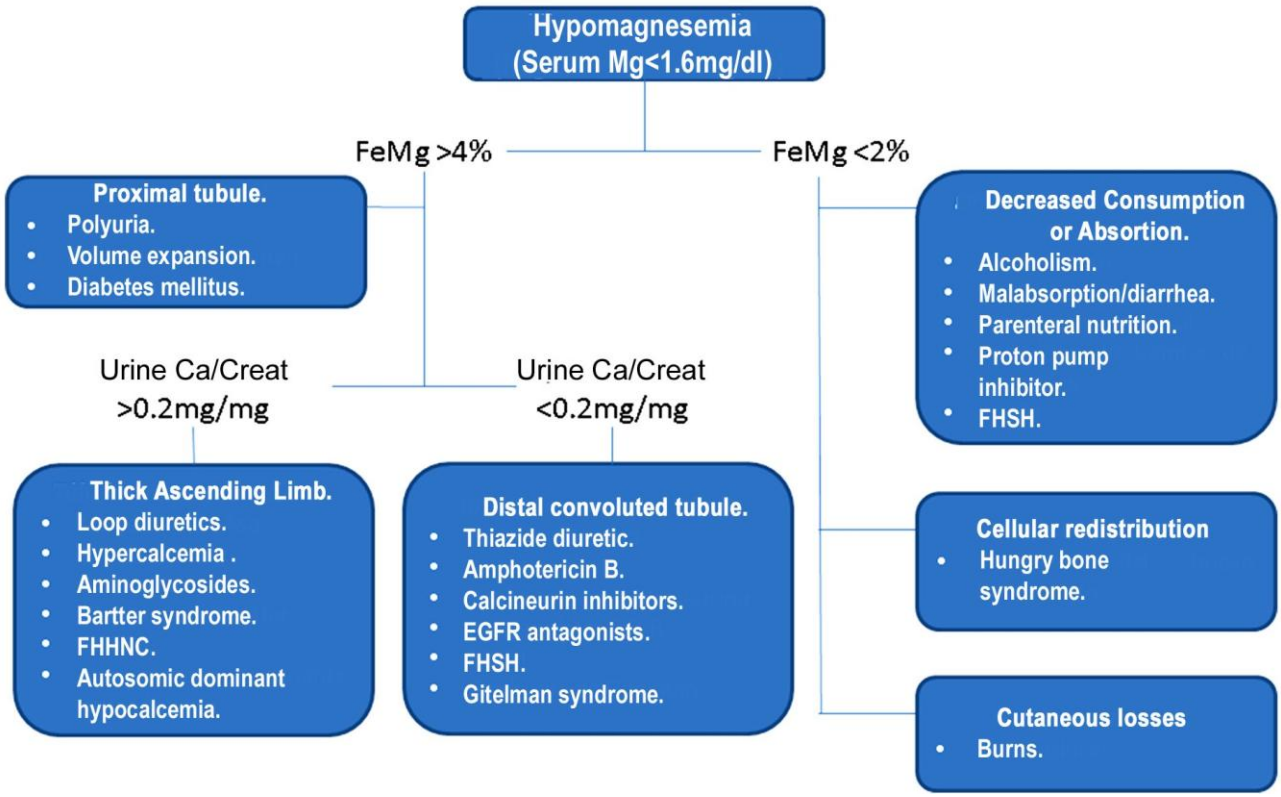
it was symptomatic it was considered a problem that required etiological diagnosis and treatment.

Magnesium is usually overlooked in clinical practice, as reported by Whang & Ryder,[5] who conducted, in an observational study, an active screening for the presence of hypomagnesemia in serum samples in which electrolyte alterations were investigated; of the 1,033 samples analyzed by the authors, only in 8.7% the treating physician requested serum magnesium levels, despite the fact that 53% of the total had hypomagnesemia.[5] Since other methods that evaluate the total body magnesium are only experimental, the magnesium levels are assessed by measuring of the total or ionized serum magnesium, being the total measurement the main method.[15]

The diagnostic approach to the patient with hypomagnesemia lies in differentiating intestinal absorption disorders from renal losses,[7,9] which can be performed by measuring the FeMg and the random urinary calcium/creatinine ratio.[6,8] (Figure 3) The reported patient had a FeMg >4%, a figure that in a subject with normal renal function indicates renal magnesium losses,[16] and a calcium/creatinine ratio in spontaneous urine >0.2mg/mg, indicating hypercalciuria and dysfunction of the thick ascending tubule of the Loop of Henle,[2,6,8,9,17] and a lesion secondary to hypercalcemic nephropathy.[2,3]

The symptoms of hypomagnesemia are mainly manifested when the values are <1.2 mg/dL[8,15] and are characterized by muscle weakness and excitability of the nervous system (Trousseau´s sign, Chevostek sign and tetany).[18] However, the manifestations can be overshadowed by those of other associated electrolyte disorders such as hypokalemia (10%), hyponatremia (6%) and hypocalcemia (Not reported).[5]



Mg: magnesium; FeMG: fractional excretion of magnesium; urine Ca/Creat: spot urine calcium/creatinine ratio; FHSH: familial hypomagnesemia with secondary hypocalcemia; FHHNC: familial hypomagnesemia with hypercalciuria and nephrocalcinosis; EGFR: epithelial growth factor receptor.

Figure 3. Diagnostic flowchart for hypomagnesemia. Source: Own elaboration.

Although the initial presentation of the reported clinical case was the association of hypomagnesemia with hypercalcemia, which was not observed in two studies that analyzed the biochemical alterations along with serum magnesium disorders.[5,19] In the research conducted by Ahmad *et al.*,[1] the symptoms of hypomagnesemia appeared after the correction of the hypercalcemia, being associated with depression of the central nervous system. When trying to compare the clinical presentation of the patient, we found two case reports of women with hypomagnesemia and hypercalcemia secondary to hyperparathyroidism, but with hypokalemia and metabolic alkalosis due to Gitelman syndrome[20,21]; the reported patient did not present hypokalemic metabolic alkalosis (Table 1), in addition, neurological findings were not reported in these cases.

In the same way, it is important to highlight the association between serum magnesium levels and iPTH secretion, since extreme variations in the concentration of the former can dramatically affect the secretion of the latter,[22] being that chronic hypomagnesemia is associated with a reduction in the secretion of iPTH when developing functional hypoparathyroidism and hypocalcemia.[22]

Nevertheless, in the present case, despite the hypomagnesemia, the iPTH levels were elevated at the beginning due to the parathyroid adenoma and decreased after the parathyroidectomy (Table 1 and Figure 1A). In this way, its elevation with normal serum calcium levels was documented again in the second hospitalization and its rise with the correction of the magnesium deficiency. Due to the pregnancy status of the patient, it was not possible to perform a parathyroid gland scintigraphy to rule out whether she had more than one parathyroid adenoma, present in up to 1- 15% of cases of hyperparathyroidism.[23] The patient developed a tertiary hyperparathyroidism by generating a sustained response of secretion of iPTH despite the hypomagnesemia and the vitamin D25 deficiency (Table 1). Unfortunately, this doubt could not be clarified given that after pregnancy the woman did not continue with the medical controls.

The treatment of hypomagnesemia is complex, since, except for specific clinical indications (pre-eclampsia/eclampsia and cardiovascular surgery), there are no clinical studies that guide its correction.[15,24] The recommendation in symptomatic patients without ventricular arrhythmia is to administer 8-12 g of magnesium sulfate in the first 24 hours and continue at 4-6 g per day for three days until the body deficit is replaced.[24]

It should be highlighted that the presented patient required up to 24 g of magnesium sulfate per day and after six days of infusion, she presented decreases when it was discontinued. The intravenous magnesium reposition is slow to balance with the tissue deposits[8,24] and normal serum levels do not indicate a replenishment of the deposits,[24] which is why oral supplementation of magnesium salts is recommended in patients that are already asymptomatic. Although the literature refers multiple options in the market,[6,24] in the present case it was necessary to get a pharmaceutical laboratory that prepared the capsules of magnesium oxide to ensure the withdrawal of the intravenous supplementation.

Conclusion

Hypomagnesemia is a frequent electrolyte disorder, but ignored by physicians, that has significant systemic repercussions. Although there is no scientific evidence on its treatment, the adequate diagnostic approach allows a rapid correction and prevention of complications. In this sense, in this case we must highlight the presence of hypercalcemia due to hyperparathyroidism with damage of renal tubular function and hypercalcemic nephropathy that generated depletion of body magnesium which required oral supplementation to achieve hospital discharge.

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None declared by the authors.

Conflict of interest

None declared by the authors.

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Contribution of the authors

The clinical case was initially treated by the internist José García Habeych, who during the clinical research requested a concept from the Endocrinology service, where doctors Lina Pradilla and Rafael Castellanos assisted to guide the etiological study.

Ethical responsibilities

Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

Data confidentiality

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

Right of privacy and informed consent

The authors declare that patient data do not appear in this article.

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Clinical case

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Presence of reactive renal tubular cells in patients with chronic kidney disease

Presencia de células tubulares renales reactivas en pacientes con enfermedad renal crónica

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Abstract

In patients with kidney disease, the presence of reactive renal cells has been reported. These cells show severe morphological alterations that difficult their classification and interpretation. Therefore, the knowledge of their morphological characteristics and sediment patterns where they can be found will be helpful for their correct management by medical departments. Here, we reported the presence of renal cells grouped in acinus with abundant cytoplasm, caryomegaly, irregular nuclear contours and prominent nucleoli, accompanied with cylindruria and fatty oval bodies in the urinary sediment of two patients with Diabetes Mellitus, these cells were named as reactive renal cells.

Key words: Urine, chronic kidney disease, diabetes mellitus, proteinuria, hematuria, epithelial cells.

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Resumen

En pacientes con enfermedad renal se ha reportado la presencia de células renales reactivas, cuyas alteraciones morfológicas severas dificultan su clasificación e interpretación. El conocimiento de las características morfológicas y los patrones de sedimentos en donde se presentan pueden ser de ayuda para su manejo en los departamentos médicos correspondientes. Aquí, nosotros reportamos la presencia de células agrupadas en acinos, con abundante citoplasma, cariomegalia, contornos nucleares irregulares y nucléolos prominentes, acompañados de cilindruria y cuerpos ovales grasos en el sedimento urinario de dos pacientes con diabetes mellitus, las cuales fueron sugestivas de células renales reactivas.

Palabras clave: orina, insuficiencia renal crónica, diabetes mellitus, proteinuria, hematuria, células epiteliales.

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Introduction

The urinary tract is lined by a great variety of epithelia among which are the cuboidal epithelium and the squamous and columnar urothelium.[1] The urothelium is located from the minor calyces, which form the largest calyces, passing through the ureters and the bladder to the proximal urethra (prostatic in men) and its main function is to form an impermeable barrier against the toxic urine,[2,3] while the cuboidal epithelium is located in the renal tubules (proximal, distal and collecting) and is essential in the exchange of nutrients and toxins between the urine and the blood.[1] However, the presence of renal cells in the urinary sediment has been associated with tubular and glomerular diseases and in some cases with diabetic nephropathy, severe dehydration and hepatitis.[4] These cells have spherical, cubic and even cylindrical morphology, with a size of 9 to 25 µm and granular cytoplasm; their nucleus is spherical, located centrally or eccentrically with nucleoli.[5] On the other hand, the «reactive renal cells » reach sizes up to 100 µm, with karyomegaly, prominent nucleoli, irregular nuclear membrane and presence of acinar groups. The presence of these cells is erroneously interpreted as a neoplastic process due to the morphological alterations they present; this is mainly caused by the scarce information about them. Therefore, the objective of this article is the diffusion of knowledge

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among the healthcare personnel about the presence of these cells in patients with chronic diseases.[6,7]

Clinical case 1

A 52-year-old male patient with a history of uncontrolled diabetes mellitus, hospitalized for diabetic foot surgery. Preoperative laboratory studies were requested. The results of the blood chemistry tests were: glucose 203 mg/dl, urea 62.5 mg/dl, creatinine 1.9 mg/dl, BUN 29 mg/dl, uric acid 9.8 mg/dl and total cholesterol 160 mg/dl; regarding the hematic cytometry it was found an hemoglobin of 10.7 g/dl, erythrocytes $4.16x10^6$/µl, hematocrit 33.9%, leukocytes $12.06x10^3$/µl and platelets $288x10^3$/µl. The chemical examination of the urinalysis revealed the presence of hemoglobinuria (80 erythrocytes/ml), proteinuria (>300 mg/dl), a pH of 6.5 and a density of 1,020. In the urine sediment it was found microhematuria: 5-10 erythrocytes/field in a strong dry lens, of which 40% were dysmorphic; oval fat bodies (Figure 1, panel d) and cylindruria (hyaline, erythrocytic and lipid) were also observed. In addition, we found spherical cells with granular cytoplasm, a spherical nucleus located eccentrically and a regular or slightly irregular contour, and with one or two nucleoli (Figure 1, panel a, b and c). These cells were found in groups of up to 30 cells of acinar appearance and were classified as reactive renal cells based on the literature consulted.[6,7]

Clinical case 2

A 76-year-old female patient arrived to the emergency department with a hyperglycemic clinical picture. The blood chemistry revealed a glucose of 311 mg/dl, urea 197 mg/dl, BUN 92 mg/dl, creatinine 5.8 mg/dl, uric acid 7.2 mg/dl and total cholesterol of 361 mg/dl; the hematic cytometry showed an hemoglobin of 11.6 g/dl, erythrocytes $4.22x10^6$/µl, hematocrit 35.7%, leukocytes $5.28x10^3$/µl and platelets $205x10^3$/µl. In the chemical examination of the urinalysis it was observed a pH of 7.0 and a density of 1,020, as well as glycosuria (250 mg/dl), hematuria (80 erythrocytes/µl), proteinuria (greater than 300 mg/dl) and leukocyturia (70 leukocytes/µl). These results were corroborated in the urine sediment, where leukocyturia (30-40 leukocytes/field in strong dry lens), cylindruria (waxy and granular) and oval fat bodies were observed (Figure 1, panel h). The chemical analyst (first author) carried out the identification of renal cells with atypical morphology, based on morphological characteristics such as karyomegaly, irregular nuclear contour, presence of prominent nucleoli, nuclei of eccentric or central location, some of them pleomorphic with slightly thick chromatin and increased nucleus-to-cytoplasm ratio. They also presented cytoplasmic vacuolization and acinar groups of up to seven cells; most of them were viable cells (not stained by the Sternheimer-Malbin stain). In both cases the cells were classified based on the morphology and the characteristics of the sediment: presence of casts, microscopic hematuria and oval fat bodies (Figure 1, panel e, f and g).

Discussion

Chronic degenerative diseases such as type 2 diabetes *mellitus* are a major cause of nephropathy that can lead to loss of kidney function.[8] These conditions affect glomerular function and as a consequence, the renal tubules, causing detachment of renal tubular cells and formation of urinary casts.[9] The morphology of renal cells in the urinary sediment of patients with renal diseases tends to be homogeneous; however, in some cases it can be drastically modified and cause false positives for a carcinoma. Reactive or reparative changes in renal cells have been observed in glomerular diseases, drug-induced tubular toxicity, ischemia, and severe tubular damage.[6] Renal cells with abundant vacuolated cytoplasm, poorly defined borders, large oval nuclei, with varying degrees of pleomorphism, chromatin agglutination, and prominent nucleoli were observed in both patients. These cells appeared isolated or in cohesive groups of 7 to 30 and showed an acinar configuration, which is consistent with the characteristics of the reactive renal cells as described by Nguyen & Smith in 2004.[6] This type of cells, due to the morphological alterations they present, are frequently misclassified as urothelial cells of low-grade neoplasms, renal carcinoma and

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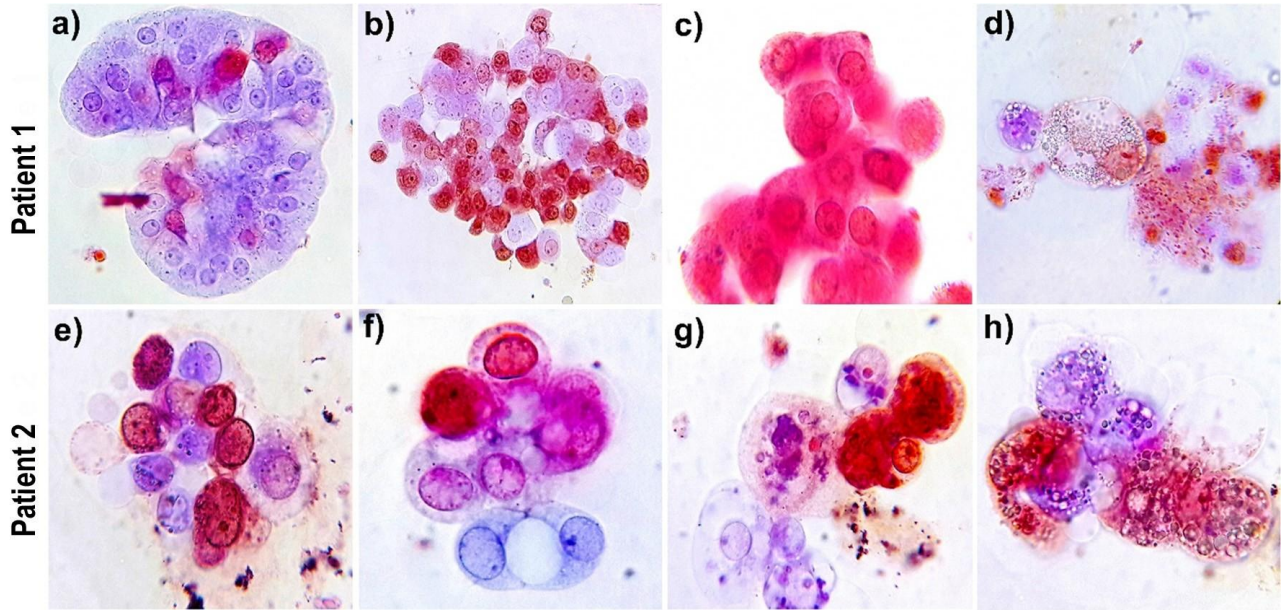

Figure 1. Reactive renal cells in patients with diabetic nephropathy. Patient 1: groups or acinar cells (a) and of large size (b and c) with cells of eccentric nuclei, prominent nucleuli, karyomegaly and granular cytoplasm and oval fat bodies with their birefringent intracytoplasmic lipids (d). Patient 2: acinar groups of cells with karyomegaly, eccentric nuclei and slight nuclear pleomorphism with slightly thick granular chromatin and cytoplasmic vacuolization (e, f and g) and presence of oval fat bodies with a large amount of intracytoplasmic lipids (h). Bright field microscopy, 40x objective, Sternheimer-Malbin stain. Source: Own elaboration.

adenocarcinomas. For the differential diagnosis between the reactive renal cells and the carcinoma cells, is important to look for the presence of renal casts associated with the tubular alterations generated by the glomerular disease and the dysmorphic microhematuria, which support the renal origin of the cells, in contrast with the neoplastic processes in which isomorphic hematuria is found.[6,7,10-12] Casts were found in both patients and in one dysmorphic microhematuria of 40%. In 2008, Fogazzi *et al*. established that dysmorphic hematuria greater than 40% is associated with glomerular diorders.[13] In addition, we reported the presence of fatty oval bodies in both subjects, which are an unequivocal sign of severe kidney disease and are frequently associated with nephrotic syndrome.[5,14]

The confirmation of the presence of reactive renal cells can be carried out by a positive immunocytochemical staining for the vimentin protein, in contrast with the urothelial cells of low-grade tumors. However, the immunocytochemical staining has the disadvantage of not being able to differentiate between a renal carcinoma and reactive renal cells, which can be done based on the type of hematuria and the presence or absence of casts.[7,15] Due to the aforementioned, a series of morphological criteria has been proposed to give greater importance to cytological interpretation in order to be able to differentiate these types of pathological processes based on these criteria.[7]

Conclusion

Reactive renal cells are present in diseases that severely affect the renal tubules; the knowledge of their morphology and their adequate interpretation can guide the clinical diagnosis of kidney disease or neoplastic processes, with which they are commonly confused. This article describes the presence of these cells in patients with type 2 diabetes *mellitus*; but it is still necessary to continue analyzing the importance of the presence of these cells in the diag-

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nosis and prognosis of chronic diseases, as well as the establishment of morphological patterns that can be used by the clinical analyst.

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Conflict of interest

The authors did not declare conflict of interest.

Ethical responsibilities

Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

Data confidentiality

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

Right of privacy and informed consent

The authors declare that patient data do not appear in this article.

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Contribution of the authors

All authors contributed to the analysis, literature research, writing and revision of this work.

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Clinical case

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Early cannulation of native arteriovenous fistulas in hemodialysis. Case reports and literature review

Canulación temprana de fístulas arteriovenosas nativas en hemodiálisis. Serie de casos y revisión de la literatura

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Abstract

The native arteriovenous fistula (nAVF) is the ideal access in patients in hemodialysis, however, traditionally requires a period of maturation from its surgical construction that usually takes more than 8 weeks, exposing patients to a longer time with catheters; In this article, we describe 4 cases of early cannulation (<3 weeks) based on nursing staff expertise and ultrasound criteria.

Keywords: Vascular access, arteriovenous fistula, maturation, cannulation, renal insufficiency, ultrasound.

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Resumen

La fístula arteriovenosa nativa (FAVn) constituye el acceso ideal en los pacientes de hemodiálisis, sin embargo, necesita un periodo de maduración desde su construcción quirúrgica; en este periodo, que suele tardar más de 8 semanas, se expone a los pacientes a un tiempo mayor con catéteres. El presente artículo describe cuatro casos de canulación temprana (<3 semanas) que se llevaron a cabo con base en la experticia del personal de enfermería y algunos criterios ecográficos.

Palabras clave: acceso vascular, fístula arteriovenosa, maduración, canulación, insuficiencia renal crónica, ultrasonido.

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Introduction

Patients with end-stage chronic kidney disease on hemodialysis require adequate vascular access that guarantees an optimal blood flow and allows to obtain an appropriate dialysis; native arteriovenous fistula (nAVF) is considered the ideal access in this group of patients due to its high survival rate and lower risk of complications compared with other types of access such as grafts and catheters.[1] The use of nAVFs is also an indicator for measuring the performance and quality improvement in dialysis centers.[2]

Despite there are guidelines that recommend the use of nAVF,[3,4] a very significant percentage of patients have a catheter as a vascular access. One of the multiple reasons for this situation is the late initiation of cannulation of the nAVF, since important differences in the initiation of the first cannulation have been found worldwide: in Japan the mean time is 10 days; in Europe and New Zealand, 46 days, and in the United States, 82 days.[5] This statistics in Colombia and Latin America is unknown.

Although nAVF is the ideal access, the optimal time to start its cannulation after its construction is relatively long and varies in different dialysis centers: from week 6 until week 10 or 12, depending, among many factors, on the expertise of the nursing staff and other aspects that have shown that 20-40% fail to mature,[2,6-9] with which hemodialysis patients are exposed to a longer permanence of the catheter; this implies greater risks of associated morbidity and

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mortality.[2] Therefore, for a nAVF to be adequate to initiate its cannulation, which is known as "maturation" in dialysis centers, it must have physical characteristics that allow a continuous and safe puncture that guarantees an adequate dialysis.[10,11]

Physical examination by palpation and visualization is the gold standard used in the majority of renal units worldwide, especially in Colombia, to determine when a nAVF can be cannulated to initiate hemodialysis; nevertheless, physical examination by an experienced cannulator predicts clinical maturation (ability to use the nAVF for hemodialysis) accurately by 70-80%,[12] however, this prediction may vary between nursing staffs at different centers depending on their expertise. Therefore, the timely and accurate evaluation of the maturation of this type of access is essential to minimize the prolonged time and the use of the catheter in the renal units.

In recent years, imaging aids such as ultrasound have become an excellent diagnostic tool to evaluate the nAVF and to facilitate its cannulation; moreover, they are non-invasive, easily accessible and inexpensive procedures. A postoperative ultrasound evaluation can provide objective measurements to predict the early use of the nAVF, and even to guide early interventions and evaluate those which are delayed in maturation.[12,13]

For several years, some criteria based on the use of ultrasound have been proposed to assess the maturation of the nAVF; among these are those of the National Kidney Foundation/Diseases Outcomes Quality Initiative. The most commonly used worldwide are known as the rule of six, which indicates that a fistula is mature when it has a vein diameter > 6 mm, a maximum depth from the skin of the access of 6 mm, a time of construction > 6 weeks and a vascular access blood flow> 600 mL/min.[3] Other criteria used are those of the University of Alabama at Birmingham, which require a diameter >4 mm (Figure 1) and a blood flow >500 mL/min.[14,15]

With the idea of reducing the rate of catheters and encouraging the early use of the native fistula with the help of ultrasound, a series of cases of early cannulation of the nAVF using ultrasound criteria and the experience of the nursing staff are presented.

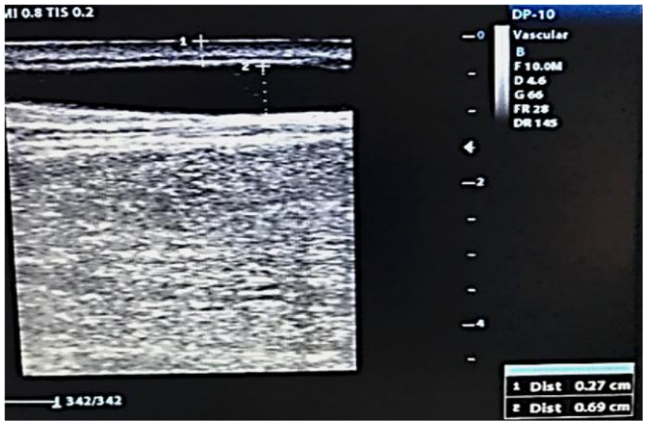

Figure 1. Ultrasound image of a native arteriovenous fistula with a distance from the skin of 0.27 cm and a vein diameter of 0.60 cm. Source. Document obtained during the conduct of the study.

Materials and methods

To assess the inner diameter and the depth of the fistula from the skin, in the reported cases a Mindray DP-10 portable ultrasound machine (Figure 2) with a linear transducer was used. Since a Duplex was not available, blood flow was not measured.

The cannulation of the nAVF was performed by expert nursing personnel (known as master cannulators), with high experience and certified for

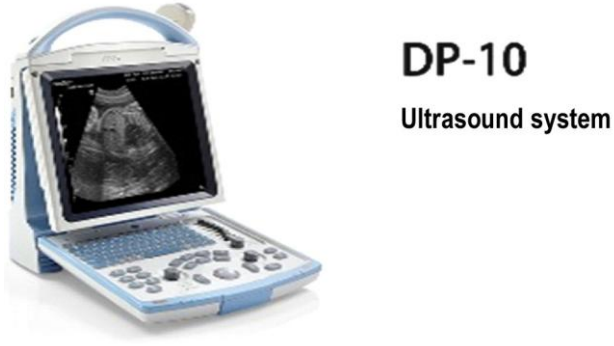

Figure 2. Mindray DP 10 portable ultrasound system used to take ultrasound scans. Source: Document obtained during the conduct of the study.

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these procedures; needles No.17 French (the smaller gauge available) were used in the three first cannulations and No. 15 in the fourth.

The procedure was explained to the patients, along with the pros and cons.

Case presentation

We present the cases of 4 patients who received hemodialysis through an indwelling catheter and whose nAVF was constructed between 2 and 3 weeks before.

Case 1

A 55-year-old male patient with humeral-cephalic arteriovenous fistula (HCAVF) constructed 22 days before (construction date: 01-12-2017, cannulation date: 23-12-2017, inner diameter: 0.4 cm by ultrasound), in whom it was evidenced a catheter dysfunction due to inadequate flow through it, which could not be improved with adequate heparinization and lavage (Figure 3)

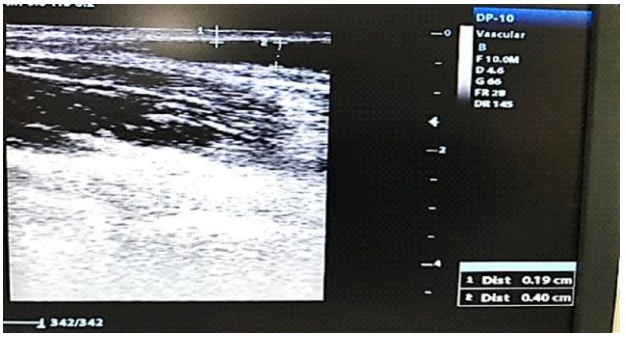

Figure 3. Ultrasound scan of native arteriovenous fistula Patient 1. Source. Document obtained during the conduct of the study.

Case 2

A 48-year-old male patient with nAVF constructed 24 days before (construction date: 29-12-2017, cannulation date: 22-01-2017, venous trajectory diameter: 0.41 cm), who presented accidental dislodgement of the catheter retainer in more than 80% of its length, so it was decided to remove it. An attempt was made to avoid the implantation of a new catheter, so ultrasound was used to verify the largest diameter of the venous traject and decide if the fistula could be cannulated (Figure 4).

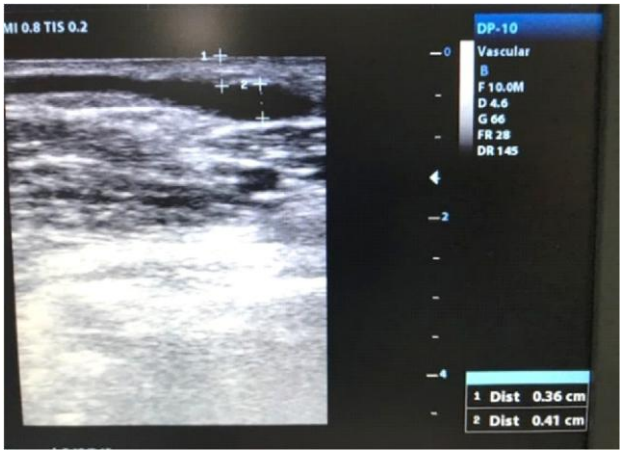

Figure 4. Ultrasound scan of native arteriovenous fistula Patient 2. Source. Document obtained during the conduct of the study.

Case 3

A 56-year-old male patient with radial-cephalic fistula in the left upper limb constructed 15 days before (construction date: 05-10-2018, cannulation date: 20-10-2018). On day 15 of its construction, the nAVF had a depth of 0.36 cm and a venous traject diameter of 0.44cm, so it was cannulated (Figure 5).

Case 4

A 54-year-old male patient with HCAVF constructed 16 days before (construction date: 08-10- 2018, cannulation date: 24-10-2018, venous traject diameter: 0.69 cm) (Figure 6).

Results and discussion

We present 4 cases of male patients who did not suffer from diabetes, who were cannulated with a 17 French needle in their first three hemodialysis sessions without presenting infiltration or hematomas and with a 15 French needle in the fourth session; the pump flow increased from 250 to 300 mL/minute.

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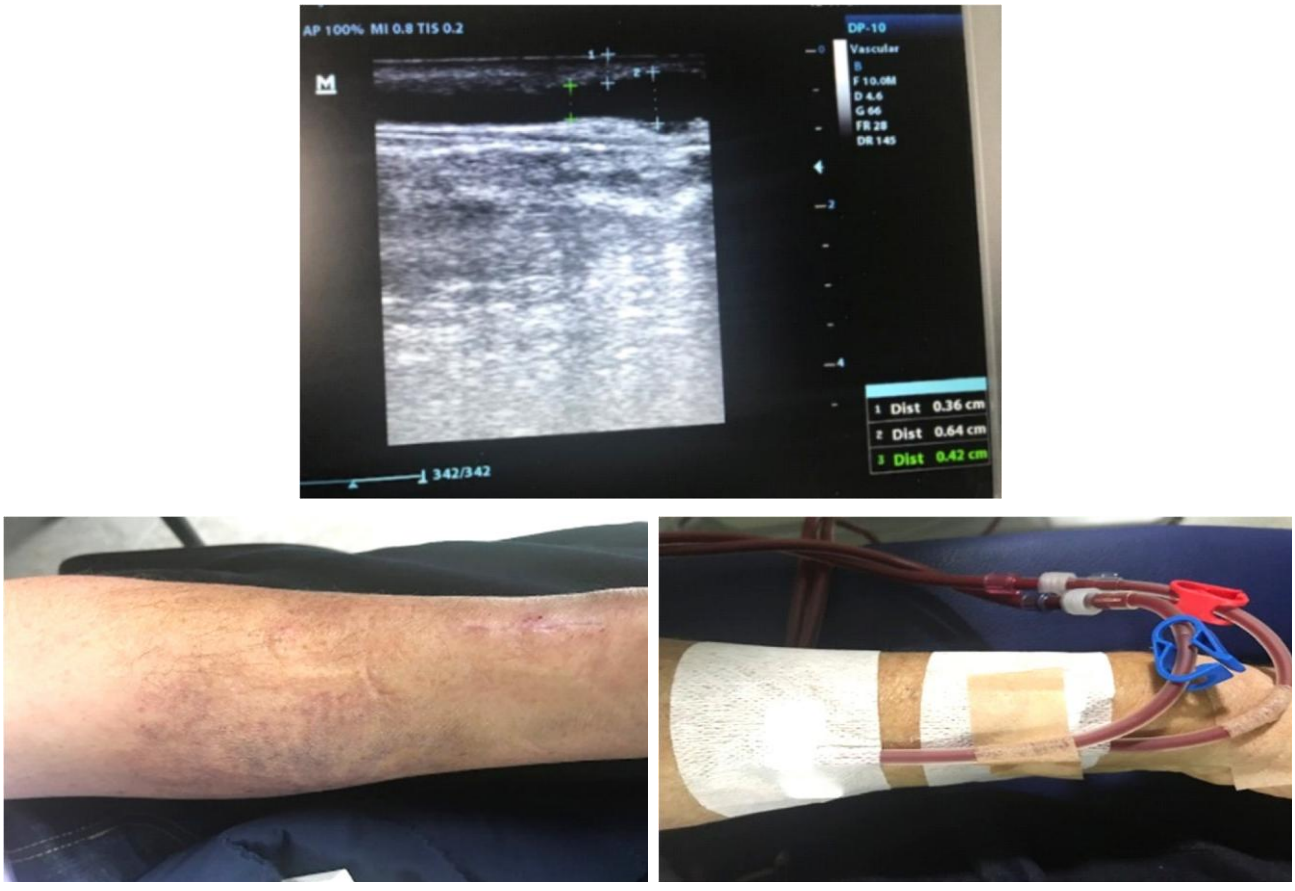

Figure 5. Cannulated radial-cephalic fistula. Source. Document obtained during the conduct of the study.

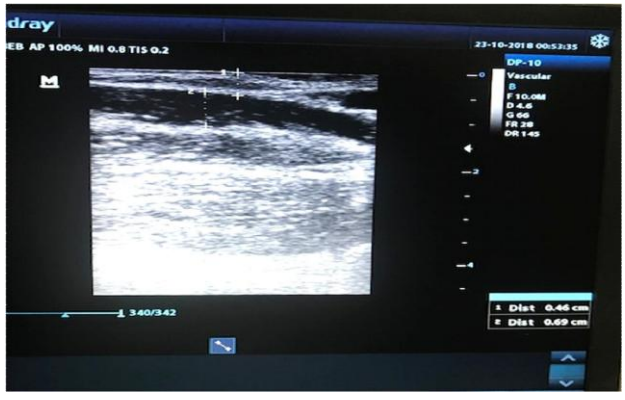

Figure 6. Ultrasound scan of native arteriovenous fistula Patient 4. Source. Document obtained during the conduct of the study.

In the first two cases the cannulations of the n AVF were performed at 22 and 24 days of construction due to catheter dysfunction, while in the other two cases the cannulation was early and was carried out at 16 days of construction upon the initiative and mutual agreement of the nursing staff (Table 1).

While it is true that clinical practice guidelines for hemodialysis recommend a rate lower than 10% at day 90, worldwide there are figures that estimate that 81% of patients start hemodialysis through a catheter.[1]

In clinical practice in dialysis centers, especially in the Western Hemisphere, they have been using the recommendations of the K-DOQI Guidelines,[3] which suggest to wait at least 4 to 6 weeks for the first cannulation, but in clinical practice this time is extended until 8-10 weeks according to expert opinion; in this way the dependence of the patient to the catheter is prolonged with the inherent risks that this implies.[16]

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Tabla 1. Características de los pacientes y de la canulación durante las 3 primeras sesiones de hemodialisis.

Patient	Age (Years)	Gender	Type of fistula	Date of construction	Date of first cannulation	Days after construc-tion	Needle used in the 3 initial sessions	Pump flow in the 3 initial sessions	Compli-cations
1	55	Male	Humeral cephalic fistula	01-12-2017	23-12-2018	22	15 Fr	250 mL/min	None
2	48	Male	Humeral cephalic fistula	29-12-2017	22-01-2018	23	15 Fr	250 mL/min	None
3	56	Male	Left radial-cephalic fistula	05-10-2018	20-10-2018	15	15 Fr	250 mL/min	None
4	54	Male	Right radial-cephalic fistula	08-10-2018	24-10-2018	16	15 Fr	250 mL/min	None

Fr: French
Source: Own elaboration.

An arteriovenous fistula is clinically mature when it is cannulable with two large gauge needles, when it provides sufficient blood flow for adequate dialysis and when an arbitrary time to start cannulation has been chosen for safety after 8 weeks.[12]

The maturation of the fistula is a complex process of vascular remodeling that requires dilation of the vessels and a marked increase in the blood flow rates in the feeding artery and in the draining vein with the respective structural changes in the walls of the vessels.[17] However, there are studies that demonstrate that there is no difference in the failure rate of nAVFs when they are cannulable between days 14 and 28 versus cannulation between days 43 and 84 after their construction, provided that they are clinically and radiologically mature.[18]

Likewise, there are different radiological guidelines to initiate cannulation when the diameter of the venous traject is greater than 4, 5 or 6 mm; however, it has been evidenced that with a diameter > 4 mm, cannulation of the vein using a 17 French needle is already feasible after 14 days of construction. In this sense, the blood flow, the diameter, and the depth of the nAVF predict clinical maturation.[19]

The cannulation of a fistula between days 14 and 28 is feasible and helps avoid the implantation of a new catheter; this decision should be based on an adequate clinical assessment by the nursing, nephrology and vascular surgery staff, furthermore, it is suggested to complement it with ultrasound assistance, which includes the measurement of the diameter of the fistula and, if Doppler is available,

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the measurement of blood flow, with which high rates of conversion of the catheter to nAVF are achieved.[19]

In contrast, early cannulation of the nAVFs before 14 days of constructed has been associated with a greater increase of primary failure of the fistula in the long term, which negatively impacts the survival of the nAVFs.[18]

Early cannulation (before three of four weeks after its construction), is not without risks such as infiltration, thrombosis and loss of access, it will not only constitute a waste of time and investment in the construction of the access, especially in countries such as ours, where the health resources are limited, and in addition, it could negatively affect the patient's perception regarding a new reconstruction procedure.[20]

Despite these risks, the benefit of early cannulation is a reduced amount of time with a catheter, which means less time a patient is exposed to the risk of associated infections and a lower risk of venous access thrombosis when removing the catheter.[20] Taking into account the different practices in different countries such as Japan, where the nAVFs are cannulated 10 days after construction,[21] at the beginning of 2020 we published and suggested a classification according to the time of cannulation or the nAVF after the construction, which is described in Table 2.[22]

Table 2. Time classification of the nAV fistula according to the first cannulation.

- Premature cannulation before 14 days (2 weeks)
- Early cannulation between 15 and 28 days (2 and 4 weeks)
- Late cannulation after 28 days (after 4 weeks)

This classification is based exclusively on the cannulation time of native Arteriovenous Fistulas and could be used as a basis to carry out different comparative and prospective studies to evaluate the safety of cannulation according to time. Likewise, main areas of research are required to identify clinically useful predictive factors in order to ensure successful cannulation of the fistula, as well as to understand the pathophysiology of its maturation.

The *Primum non nocere* principle, attributed to Hippocrates[23] and understood in English as "first, do no harm", has been widely accepted to guide patient care in medical practice and must be taken into account in all aspects of medical practice; therefore, in any medical intervention the risks must be weighed against the benefits it implies. In this sense, vascular access has been rightly referred to as the lifeline of the dialysis patient, and any intervention to create a nAVF or start its cannulation leads to benefits, but there are risks with its creation and use. The knowledge and experience in cannulation by the staff of the renal units along with the use of imaging tools such as ultrasonography improves the success of the procedure and the long-term survival of native fistulas and of the patients themselves.

Conclusion

The purpose of this series is not to promulgate the indiscriminate criterion of early cannulation, especially between the weeks 2 and 4 after the fistula is constructed, nor to put at risk the viability of the nAVF; However, it can be concluded that, despite the limitations of the sample due to the small number of patients and based on the different published studies, with adequate clinical judgment of the nursing staff taking into account an appropriate thrill and/or superficial venous dilation and with the help of ultrasonographic criteria (diameter > 4 mm) it is possible to predict the maturation of a nAVF in order to successfully initiate its early cannulation and avoid the implantation of a catheter or the prolongation of the use thereof.

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Contribution of the authors

Ignacio Villanueva and Mauricio Ruiz M: Attention of cases, literature review and writing of the article.

María de los Ángeles Vélez: writing of the article.

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Case report

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Emphysematous cistitis. A case report

Cistitis enfisematosa. Reporte de un caso

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Abstract

The emphysematous cystitis refers to an uncommon entity generally secondary to low urinary tract infections producing gas around the bladder. It is associated with infections by *E. Coli*, *Enterobacter Aerogenes*, and *Klebsiella* as well as patient risk factors such as advanced age, diabetes and female gender. The diagnosis requires a timely management as well as directed antibiotic and associated comorbidities control. In the following case report a male patient is described in the hospital of San José de Bogotá in whom this pathology is diagnosed. In the following case report we are going to describe etiologies, diagnosis and therapy.

Key words: Cystitis, diabetes mellitus, type 2, urinary tract infections, anti-bacterial agents.

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Resumen

La cistitis enfisematosa hace referencia a una entidad infrecuente, generalmente secundaria a infecciones de vías urinarias bajas, que por diferentes mecanismos producen gas alrededor de la vejiga. Esta patología se asocia a gérmenes (*E. Coli*, *Enterobacter Aerogenes*, y *Klebsiella*, entre otros), y factores de riesgo como género femenino, edad avanzada y diabetes. Este diagnóstico requiere un manejo oportuno, con antibioticoterapia dirigida y control de comorbilidades asociadas; a continuación, se reporta el caso de un paciente masculino de 81 años, en el hospital de San José de Bogotá, a quien se le diagnostica esta patología, con el respectivo aislamiento microbiológico, factores de riesgo, diagnóstico y manejo instaurado.

Palabras clave: cistitis, diabetes mellitus tipo 2, infecciones urinarias, antibacterianos.

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Introduction

Emphysematous cystitis is characterized by the presence of gas between the wall and the lumen of the bladder, it is described as a complication of urinary tract infections.[1] It was initially described in animals by the year 1926[1]; later, by the year 1930, the presence of this pathology is evidenced in autopsy reports of female patients with associated diabetes.[2]

In emphysematous cystitis the most frequent etiologic agents are *E. Coli* and *Klebsiella Pneumoniae*; however, cases have been described with *Enterobacter aerogenes*, *Proteus mirabilis* and *Streptococcus Spp*. The diagnosis is usually difficult since on many occasions its presentation is asymptomatic; however, clinically chills, flank pain, fever, pain on palpation and percussion at the costovertebral angle can occur; it should be highlighted the association of this pathology with glucosuria, complicated urinary tract infections and diabetes, the latter being the most frequent risk factor. In the results of the urinalysis, it is common to find the presence of hematuria, pyuria and bacteriuria, and in the urine culture the associated microorganism; given the importance of demonstrating the presence of gas at the level of the bladder, tomographic images play a vital role in the diagnosis of this entity.[3] For the treatment, the targeted antimicrobial approach and

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bladder catheterization are a fundamental part of the management. Due to the high risk of complications that can be generated by a late diagnosis, it is necessary to include this pathology within the complications of the urinary tract and take it into account as a differential diagnosis, although its incidence is low; hence the importance of the report of this case.

Case presentation

An 81-year-old male patient, with a history of type II diabetes mellitus for 30 years, in outpatient management with glibenclamide, without allergies, or exposure to toxic substances or previous surgical history, who is admitted to the institution for resection of a mass in the right thigh and subsequent histopathological studies. The procedure was performed by plastic surgery, in which intraoperatively was evidenced involvement of deep planes (reaching the muscle) and lymphatic involvement until the base of the testicles, which is why they performed regional radical lymphadenectomy; given the large coverage defect, it was decided to perform a flap in the area. Postoperatively with no additional complications, except for an episode of urinary retention, and for this reason they considered leaving a urinary catheter indefinitely.

One week after the postoperative period, the patient presented clinical signs of a systemic inflammatory response, paraclinically with a leukocyte response and elevation of acute phase reactants, which is why in the search for an infectious focus they documented signs of local infection at the level of the flap, they started empirical antibiotic therapy with first generation cephalosporin (cefazolin), performed secretion cultures and awaited clinical evolution. After three days the clinical response was of torpid evolution; cultures of secretion of the flap and wound were received reporting polymicrobial flora with rescue of *Proteus mirabilis* of usual pattern, *E. coli* with a ESBL (extended-spectrum beta-lactamases) resistance pattern and *pseudomona aureginosa*. In context with the above, Plastic Surgery considered to carry out debridement and surgical lavage, removing the flap. The patient was assessed by the Infectious Diseases service, where they considered that the isolated microorganisms are secondary to hospital stay, indicating antibiotic management with ertapenem and ciprofloxacin for 14 days.

The pathology report was received, which evidenced a Merckel cell neuroendocrine tumor; then was assessed by Oncology, where they indicated to start outpatient chemotherapy, once the patient is discharged from the hospital. One week later the patient presented obvious hematuria and oliguria; the laboratory studies evidenced urinalysis with hematuria, proteinuria in the nephrotic range and active sediment, with renal function within normal parameters. Given the new clinical findings and the antecedent of diabetes, it was decided to request additional studies, and Ophthalmology ruled out diabetic retinopathy; in addition, the Nephrology team ruled out nephrotic syndrome, when evidencing urine of 0.3 g in 24 hours, hypoalbuminemia and normal lipid profile; likewise, globular morphology was found in 60% of eumorphic red blood cells, ruling out glomerulopathies. Investigating the origin of the hematuria, it was complemented with anatomical studies; indeed, starting with urinary tract ultrasound which reported good corticomedular differentiation with preserved kidney size; subsequently, an Uro-CT was requested to observe the lower urinary tract, showing thickening of the bladder wall, perivesical gas as seen in images 1, 2 and 3, and retroperitoneal lymph nodes conglomerates, findings compatible with emphysematous cystitis.

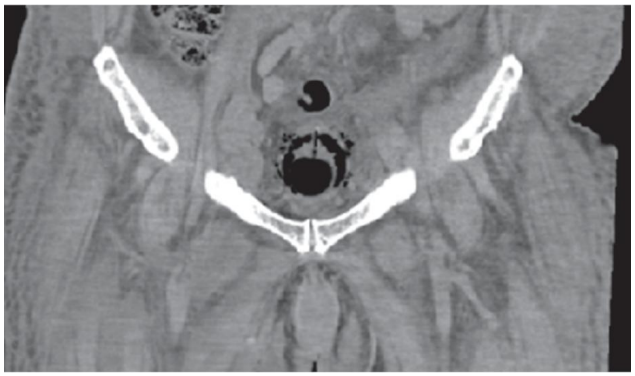

Image 1. Uro-CT in anterior sagittal section evidencing a vesicle reduced in size, with thickening of its walls and perivesical gas.

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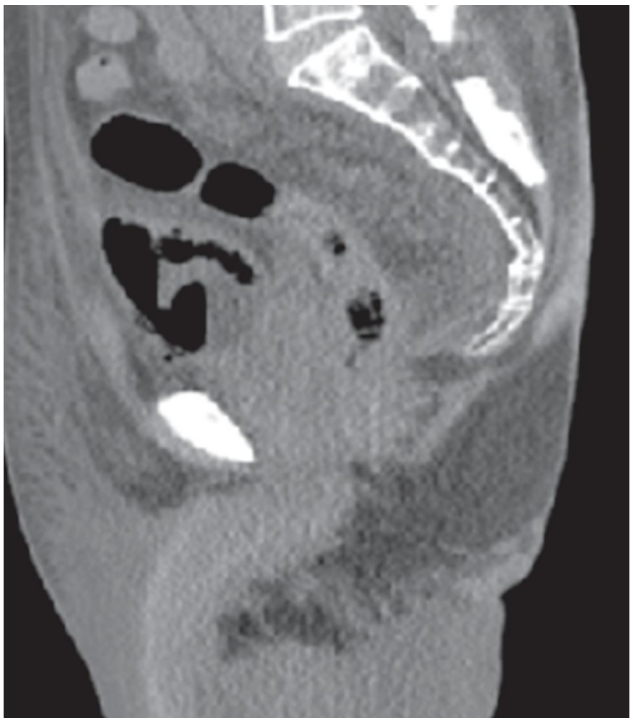

Image 2. Uro-CT in sagittal section evidencing particulate content within the bladder and perivesical gas.

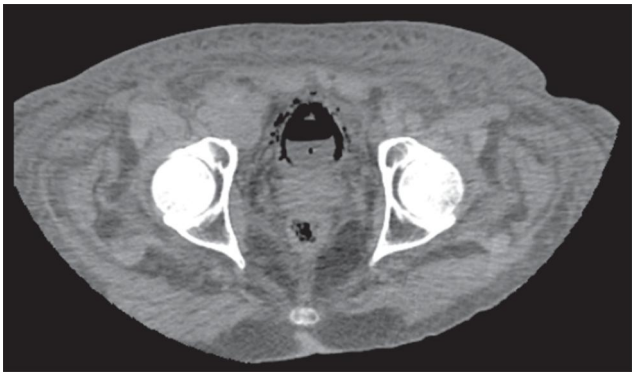

Image 3. Uro-CT in axial section evidencing thickening of the bladder wall and perivesical gas.

Given the above finding, a urine culture and bacilloscopy were requested to determine the etiology, and additionally an evaluation by urology, ruling out an indication for surgical management. The serial urine bacilloscopies were negative and *E. coli* of ESBL pattern was isolated from urine culture; it was indicated to continue antibiotic management with ertapenem for 14 days and to continue with a urinary catheter; later, macroscopic hematuria ceased and the urine output increased. In relation with the lymph node conglomerates described, it was considered a possible tumor compromise for subsequent follow-up by the service of oncology on outpatient basis. See the paraclinical tests chart.

Discussion

Grupper et al. (2007),[4] in a series of 53 cases between 1986 and 2006, describe regarding the emphysematous cystitis that the majority of patients were elderly women with diabetes *mellitus* (62.2%). The classic symptoms of urinary tract infection were present only in 53.3% of the cases. Abdominal tenderness and hematuria were observed in 65.6 and 82.3% of the cases, respectively. The plain abdominal radiography was very sensitive (97.4%), while the abdominal computed tomography was the most sensitive and specific diagnostic tool. A complicated course attributable to emphysematous cystitis was described in 18.8% of the cases. The exact mechanism that contributes to formation of gas in such cases is unknown. Several theories have been suggested, including the fermentation of glucose in urine, with an emphasis on the imbalance between gas formation and elimination.[4]

Even so, multiple risk factors are considered in the pathogenesis of emphysematous cystitis: 1) persistent hyperglycemia, with provides an excess of glucose to bacteria 2) fragility of the defense mechanism against infection due to the hyperglycemia 3) dysuria due to the diabetic nephropathy and 4) obstruction of the lower urinary tract, such as refractory and recurrent urinary tract infection, neurogenic bladder and benign prostatic hyperplasia.[5]

Emphysematous cystitis has a highly variable presentation and course, with considerable potential for complications. Wang (2010)[6] describes that emphysematous cystitis is an unusual infectious disease of the bladder and more than 50% of the cases of emphysematous cystitis have diabetes *mellitus*; Other risk factors include bladder outlet obstruction, neurogenic bladder, and patients receiving immunosuppressive therapy.

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Paraclinical tests chart

Hemogram	Urinalysis	Metabolic	Globular morphology	Nitrogen compounds Electrolytes	Ultrasound	Uro-CT
Leukocytes 5,000 Neutrophils 2,900 Hemoglobin 11.4 Hematocrit 34.2 Platelets 304,000	Density 1020 pH 5 Leukocytes 500 Nitrites positive Sediment Epithelial cells 0-2 x field Bacteria +++ Red blood cells 20-30 x fielld 24 HOUR PROTEINS 0.3 gr/24 hours Volume 500 ml/24 hours	Albúmina 2,5 Albumin 2.5 LDL Cholesterol 50 HDL Cholesterol 43 Triglycerides 115 Total Cholesterol 115	Eumorphic red blood cells 60% Dysmorphic red blood cells 40%	BUN 17 Creatinine 0.7 Sodium 135 Potassium 3.8 Phosphorus 2.2 Calcium 6.9	Both kidneys with good corticomedullary differentiation without focal lesions, right kidney 92*39*48 mm Parenchyma 11 mm and left kidney 90*44*42 mm. Parenchyma of 10 mm, no evidence of hydronephrosis or urolithiasis.	Kidneys of normal size, distended bladder with thickened walls, presence of gas inside, retroperitoneal lymph nodes.

The usual clinical symptoms are fever, chills, diarrhea, dysuria, and lower abdominal pain. In general, pyuria, hematuria, pneumaturia and leukocytosis are also observed. *E. coli* is the causative organism in the majority of cases, but *Klebsiella pneumoniae, Enterobacter aerogenes, Enterobacter cloacae, Citrobacter spp, Proteus mirabilis, Acinetobacter baumannii, Corynebacterium genitalium, Staphylococcus aureus, Aspergillus spp* and *Candida albicans* have also been reported.[7]

The prognosis for this condition is generally favorable; however, there have been reports of complications such as severe necrotizing cystitis requiring cystectomy and with a mortality rate of 20%.[8] Other complications due to late diagnosis can be bladder rupture, sepsis and acute abdomen, and even ascent of the inflammatory process to the upper urinary tract causing emphysematous pyelonephritis, which increases morbidity and mortality.[9]

For the diagnosis of the EC and to rule out differential diagnoses such as vesicocolic fistula, intra-abdominal abscesses, adjacent neoplasms and emphysematous pyelonephritis, it becomes necessary to use imaging methods such as simple conventional abdominal radiography, abdominal ultrasound and computed tomography, where gas in the bladder, and thickening of the bladder walls can be evidenced.[9]

Given that in the majority of cases gram-negative microorganisms are the most commonly associated, the initial empirical antibiotic therapy should be

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addressed to their coverage, using quinolones or cephalosporins, and once the result of the urine culture is obtained, the antibiotic therapy should be modified according to the antibiogram.[10]

In addition, the catheterization of the bladder as therapy is generally successful, with a complication rate lower than 20%[8]; as well as the management of comorbidities such as glycemic control,[11] this strategy reduces mortality without the need for surgical intervention and likewise preserves renal function. In case of complications, there are other rescue procedures such as percutaneous drainage, implantation of a ureteral stent, surgical debridement and cystectomy.[12]

The case reported here correlates with what is found in the literature from the point of view of microbiological isolation that corresponds to *Escherichia coli*, although ours is an *E. Coli* with an extended spectrum beta-lactamase (ESBL) resistance pattern, probably due to the complications noted, such as prior hospitalization for postoperative management of the skin flap and the use of antibiotics in this hospitalization. Also, it correlates with the literature in the presentation of the clinical picture, the history of diabetes as the most associated risk factor, and in the diagnostic approach, in which perivesical air could be documented by means of the Uro-CT, which is the test with higher sensitivity and specificity for the diagnosis of this pathology.

Conflict of interest

The authors state they do not have any conflict of interest.

Ethical responsibilities

Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

Right to privacy and informed consent

The authors declare that patient data do not appear in this article.

Author contributions

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Andrés Lamos, Cristian Rodríguez and Daniela Trujillo Hincapié: structure of the article, writing.

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Consensus

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Recommendations for treatment with recombinant human growth hormone in pediatric patients in Colombia

Recomendaciones para el uso de la hormona de crecimiento humana recombinante en pacientes pediátricos de talla baja en Colombia

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Abstract

In Colombia there are no guidelines for diagnosis and management of patients with short stature and for the use of recombinant human growth hormone, mainly caused by the diversity of training centers in pediatric endocrinology. In response to this situation, the Colombian College Association of Pediatric Endocrinology (*Asociación Colegio Colombiano de Endocrinología Pediátrica*) leds the first Colombian short stature expert committee in order to standardize the use of human recombinant growth hormone. This work had the participation and endorsement of a consortium of clinical experts representing the Colombian Society of Pediatrics (*Sociedad Colombiana de Pediatría*), Bogota Health District Secretariat- Southwestern Health Services Integrated Subnetwork (*Secretaría Distrital de Salud de Bogotá- Subred Integrada de Servicios de Salud Suroccidente*), Sanitas University Foundation (*Fundación Universitaria Sanitas*), University of los Andes (*Universidad de los Andes*) and some public and private health institutions in the country, in addition to the participation of methodological experts from the Keralty Global Institute of Clinical Excellence (*Instituto Global de Excelencia Clínica Keralty).* By reviewing the literature and with the best available evidence, we proposed to unify definitions, a diagnostic algorithm, biochemical and dynamic tests with their reference parameters, a description of the considerations about growth hormone use among the indications approved by regulatory agency for medications and food in Colombia and finally a proposal for an informed consent and a medication fact sheet available for parents and patients.

Keywords: Body height, growth disorders, human growth hormone, endocrine diagnostic techniques, endocrine system diseases, pediatrics.

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Resumen

En Colombia, actualmente no existen parámetros claros para el diagnóstico de pacientes con talla baja, ni sobre el tratamiento de esta población con hormona de crecimiento recombinante humana (somatropina), lo cual se ve favorecido por la diversidad de programas de formación de profesionales en endocrinología pediátrica. En respuesta a esta problemática se realizó el primer acuerdo colombiano de expertos en talla baja liderado por la Asociación Colegio Colombiana de Endocrinología Pediátrica (ACCEP); este trabajo contó con la participación y el aval de expertos clínicos de importantes instituciones de salud públicas y privadas del país, además de expertos metodológicos del instituto Keralty, quienes garantizaron la estandarización del uso de la somatropina. Después de realizar una minuciosa revisión de la literatura, se propone la unificación de definiciones, un algoritmo diagnóstico, los parámetros de referencia de las pruebas bioquímicas y dinámicas, una descripción de las consideraciones de uso de la somatropina para el tratamiento de las patologías con aprobación por la entidad regulatoria de medicamentos y alimentos en Colombia y, por último, un formato de consentimiento informado y de ficha técnica del medicamento.

Palabras clave: estatura, trastornos del crecimiento, hormona de crecimiento humana, técnicas de diagnóstico endocrinológico, enfermedades delsistema endocrino, pediatría.

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Introduction

Short stature (SS) in pediatric age may be a sign of an underlying disorder which requires proper diagnosis and treatment [1,2]; its prevalence ranges between 2.23% and 5.12%, with important differences between the level of socioeconomic development, countries and urban and rural regions.[3,4]

In Colombia, the National Survey of the Nutritional Situation 2015[5] indicates a prevalence of delay in height or in growth of 10.8% in children under 5 years of age, of 7.4% in children between 5 and 12 years and of 9.7% in children between 13 and 17 years.[6] Although the nutritional causes of SS in children do not suppose hormonal treatment, given the socioeconomic conditions or the ethnic origin and the inequity that exists in different regions of the country, it is important to take into account these causes in the diagnostic approach.

Most cases of children with SS correspond to variants of normality, being estimated that only about 20% of cases correspond to children with pathological SS[7-9] Therefore, the challenge is to identify the latter group of patients to facilitate decision-making about the need for specific diagnostic tests and indications for treatment with recombinant human growth hormone (somatropin).

Among the causes of pathological SS are endocrine disorders, which correspond to 5-10% of all cases. The most frequent of these disorders is the growth hormone deficiency (GHD), which affects mainly men with a 4:1 ratio and has a prevalence which may range from 1 case per 3,480 children, up to 1 case per 30,000 children.[9-11] In Colombia, specific data on the frequency of GHD are not known.[12]

Somatropin therapy is the approved treatment for a number of growth-related conditions, the most

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common being GHD. Other indications for this treatment differ depending on the countries and the available formulations of the hormone.[2,13] In Colombia, its use is approved for GHD, Turner syndrome (TS), small for gestational age (SGA) newborn without growth recovery or without catch-up growth, Prader-Willi syndrome (PWS) and chronic kidney disease (CKD) in children under 18 years of age, the last condition being the only one included in the health benefits plan (Annex 1).[14,15]

Just like the European Medicine Agency,[16] the Colombian National Food and Drug Surveillance Institute (INVIMA, *Instituto Nacional de Vigilancia de Medicamentos y Alimentos*), as a regulatory entity in Colombia, has not yet authorized the use of somatropin for patients diagnosed with Idiopatic Short Stature (ISS). There is also no approval for conditions that are authorized in other countries such as deficiency of the Short Stature HOmeboX-containing gene (SHOX),[2,13] or for the management of familial SS or for the increase in muscle mass in high-performance athletes or for aesthetic conditions; in the latter cases there is no certainty that the benefits outweigh the long-term risks.[17-19]

According to the records of the Drug Price Information from Colombia,[20] in 2014 the average cost of the microgram of somatropin was COP$24.83 and according to the analysis of the Institute of Health Technology Assessment, the average annual cost of the treatment per patient for that same year was COP$11,269,325, which is equivalent to USD$2,800 as of April 2020.[21] The above implies a high impact on the use of healthcare system resources and a great responsibility of the medical and scientific community for the adequate prescription of this treatment.

It should be mentioned that the international currents of pediatric endocrinology, which have a healthy heterogeneity, influence medical practice in the Colombian territory, which is why efforts have been made to put these guidelines into practice in the context of the country, such as the initiative of the University of Antioquia to formalize in 2007 the first national postgraduate degree in this specialty. Nevertheless, there are barriers to patients' access to consultation with pediatric endocrinologists and/or to perform specialized laboratory tests and dynamic tests in some regions of the country.

As for the interpretation of the results of the biochemical tests, it is necessary to point out that there is uncertainty around the reference values (especially in those requested to determine GHD), false expectations of patients and relatives and even medical-legal repercussions, which makes the approach to a patient with SS and the requirement of hormonal treatment a complex problem. These and other considerations were taken into account in an analysis of the situation with representatives of scientific societies, Colombian College Association of Pediatric Endocrinology (ACCEP, *Asociación Colegio Colombiano de Endocrinología Pediátrica*), Colombian Society of Pediatrics (SCP, *Sociedad Colombiana de Pediatría*)—, state entities —Bogota Health District Secretariat (*Secretaría Distrital de Salud de Bogotá*), universities —Sanitas University Foundation (*Fundación Universitaria Sanitas*) and Los Andes University (*Universidad de los Andes*)— and clinical experts from some public and private healthcare institutions in the country —*Hospital Infantil Concejo de Medellín*, *University IPS*, *Hospital Pablo Tobón Uribe*, *Hospital Militar Central* and Santa Fe de Bogota Foundation (*Fundación Santa Fe de Bogotá*)— for the identification and prioritization of the scenarios of greater uncertainty that were addressed in this publication.

This work aimed to present the fundamental principles of good clinical practice for the use of somatropin in pediatric patients. In this sense, the most appropriate recommendations established based on the best available evidence are presented in order to facilitate their implementation in the clinical, social and regulatory context of medical practice in Colombia.

Methodology

A study which integrated the best available evidence was carried out in order to inform each of the problems related to the use of somatropin in

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pediatric patients. In a first phase, the leader of the study conducted a SWOT (strenghts, weaknesses, opportunities and threats) analysis to identify and prioritize the scenarios of greatest uncertainty. In the next phase, which lasted about three months, each scenario was addressed in multiple work sessions (virtual and face-to-face) by a base team made up of five people (three pediatric endocrinologists and two epidemiologists). When the nature of the problem allowed, questions were formulated under the PICO structure (population, intervention, comparison, and outcome) to guide the search for relevant literature. In the other cases, and when it was not possible to identify primary or secondary studies, guiding questions were formulated to retrieve full-text documents from government agencies, ministries of health, scientific societies, health technology assessment agencies and sites for collection and development of clinical practice guidelines (CPG).

In a preliminary way, 27 questions of clinical interest were defined and then they were discussed in a face-to-face session with 25 members of the ACEP and three of the SCP, who approved the inclusion of 22 questions through anonymous electronic voting of a single round. Agreement or disagreement was considered if the results were > 70% and partial agreement if they were <70%. Of the total number of questions, four were discarded and it was suggested the revision and rethinking of three. At the end, the inclusion of a new question in the same session and an additional question included during the virtual review phase, were formulated and approved, for a total of 22 clinical questions.

From the search for evidence and the definition of the questions, full text documents were reviewed, extracting and interpreting the most relevant results and conclusions, and analyzing them with the base team of experts taking into account their degree of applicability in the Colombian context. No statistical method was applied for data analysis in this investigation. Subsequently, the recommendations were formulated, supported by the consulted evidence, which were analyzed by clinical experts in pediatrics, pediatric endocrinology, genetics and clinical laboratory in a virtual round of review. After adjusting the document, a second virtual round was required to approve the content of the document with the final recommendations. Subsequently, the recommendations were formulated, supported by the consulted evidence, and then were analyzed by clinical experts in pediatrics, pediatric endocrinology, genetics and clinical laboratory in a virtual round of review. After adjusting the document, a second virtual round was required to approve the content of the document with the final recommendations.

Information search

The search for CPG was performed on the following sites that compile and develop these types of documents: Ministry of Health and Social Protection (MSPS) of Colombia, GuíaSalud Spain, Guidelines International Network, CPG Infobase Canada, National Institute for Health and Care Excellence, Scottish Intercollegiate Guidelines Network, New Zealand Guidelines Group, Ministry of Health of Chile, National Center of Technological Excellence in Health of Mexico (*Centro Nacional de Excelencia Tecnológica en Salud de Mexico*, World Health Organization (WHO) and European Society of Pediatric Endocrinology; the terms *growth, short stature, turner, Prader, small for gestational age, chronic kidney disease* and *clinical practice guideline*, were used for this search, in English or in Spanish, depending on the search site.

We also consulted the medical database Ovid MEDLINE and the Google portal to expand the search of CPG on PWS and CKD using the terms *Prader Willi, chronic kidney disease, growth hormone* and *guidelines.*

In total, 149 articles were identified, of which five[22-26] were selected because they met the selection criteria (evidence-based CPG, addressed to the population under 18 years of age and published in the last 10 years in English or Spanish).

Five agencies for health technology assessments were consulted: Institute of Health Technology Assessment in Colombia (*Instituto de Evaluación Tecnológica en Salud de Colombia*), Health Technology Assessment Network of the Americas

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(*Red de Evaluación de Tecnología en Salud de las Américas*), Spanish Network of Health Technology Assessment Agencies and Benefits of the National Health System (*Red Española de Agencias de Evaluación de Tecnologías Sanitarias y Prestaciones del Sistema Nacional de Salud*), Canadian Agency for Drugs and Technologies in Health and National Institute for Health Research) using the terms *growth hormone* or *somatropin* and their equivalents in Spanish, and 41 documents were identified, of which six were selected[12,13,27-30] because they met the selection criteria (being an evaluation of health technology aimed at a population under 18 years of age, having been published in the last 10 years in English or Spanish and having not been referenced in a more recent health technology assessment).

Subsequently, a non-systematic review of the literature was conducted in the PubMed and Cochrane databases to expand the information on biochemical diagnostic tests, genetic tests and pharmacological management in SS patients with specific diseases and health conditions: TS, PWS, CKD and SGA; the terms *growth, child, turner syndrome, Prader Willi syndrome, chronic kidney disease, mineral and bone disorder, small for gestational age, growth hormone, somatropin, pharmacological tests, stimulation tests, provocative testing*, in articles in English and Spanish, without date limit. The inclusion criteria were: studies in children under 18 years of age on pathologies approved in Colombia for treatment with somatropin.

The searches were conducted between April and September of 2019 and outcomes analyzed with more interest corresponded to diagnostic methods, treatment, safety, efficacy, adverse events, growth and body composition outcomes, final height achieved and other outcomes related to the use of somatropin.

Results

The derived recommendations for each or the 22 questions prioritized by the experts are presented below.

Question 1. What is the definition of SS proposed for Colombia?

SS is defined as a height below -2 standard deviations (SD) or of 2.3 percentile for chronological age and sex of a given patient, and ideally of the same ethnic or racial group.[31-34] It also corresponds to a height that, even though it is between ± 2 SD for the general population, is below the growth lane corresponding to the genetic height.

The literature has defined SS based on the mid-parental height when the patient is between 1 and 1.8 SD below it.[32,34] As there is no unit of auxological criteria in the publications, the recommendation for the Colombian population is to consider SS for mid-parental height when the patient grows at -1 SD ± 5 cm from it. Severe short stature would be the one below -3SD.[31,35]

Question 2. What is the classification of SS proposed for Colombia?

Given the characteristics of the Colombian population and considering the multiple classifications available for SS, the classification proposal is presented in Annex 2, which integrates concepts from the version of the European Society of Pediatric Endocrinology,[36] the one suggested in Argente, Spain[37,38] and the one proposed by Allen & Cuttler.[39]

Question 3. What criteria generate high suspicion to consider that a patient with SS requires treatment with somatropin?

There are pathologies whose auxological outcome is SS, but not all are susceptible to treatment with somatropin, therefore it is considered that the following characteristics merit further studies in order to establish a possible pharmacological treatment in this type of patients.[7,40-42]

- Having SS according to the definition proposed in these recommendations.
- Presenting pathological bone age delay.[43]
- Evidencing alteration in the grow rate (GR) with respect to the height percentile lane (usually -1

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SD) for age and sex documented in periods of at least 6 months and for a cumulative time of 2 to 3 years, or in general, when the GR has deteriorated significantly, even before reaching -2.5 SD.[33]

- Having in the medical history data compatible with the indications for the use of somatropin (dynamic tests suggestive of GHD, karyotype compatible with TS, history of SGA newborn, morbid obesity accompanied by cognitive deficit, pathognomonic phenotypic characteristics and CKD).

- Having ruled out the presence of other causes of SS (genetic, nutritional, organic, metabolic or psychogenic) not susceptible to treatment with somatropin.

Question 4. What are the criteria for referring a patient with SS from pediatrics to pediatric endocrinology?

The pediatrician must refer the patient to the pediatric endocrinologist when:

- A GR below the 25th percentile (or -1 SD) is documented in whom a specific cause of the SS is not detected.[22]

- Being in front of a patient with a history of being born SGA who does not show height recovery at two years of age and in whom no specific cause is detected.[22,44]

- The patient has SS with high weight for height in the range of overweight or obesity and hypothyroidism, glucocorticoid excess or GHD are suspected.[22]

- Discordance between chronological age and sexual maturity according to Tanner stages is detected. [22]

- Delayed bone age is detected and hypothyroidism is suspected in children with postnatal SS. [22]

- Any of the following pathologies is suspected or identified: GHD; dysfunction in the secretion of somatropin secondary to radiotherapy; CKD in conservative treatment, dialysis or hemodialysis; pre and post kidney transplantation; TS; dysmorphism or disproportionate SS, and suspected chromosomal abnormality.[22]

The referral to pediatric endocrinology of patients who grow by their genetic lane, whose target height is included in the population reference and who also have a good GR is not considered a good clinical practice.

Question 5. What are the cut-off points for growth hormone stimulation tests?

The literature refers different cut-off points for growth hormone that vary according to the population studied, as well as in the case of patients diagnosed with obesity and overweight,[45] and according to the methodology used in the laboratory.[46-52] In Colombia there is no information to define or establish these cut-off points, thereby Table 1 presents some studies that report values for the determination of adequate plasma levels of growth hormone that differ according to the type of stimulation test used and the standardization of tests at the local level.

Question 6. What is the usefulness of determining the insulin-like growth factor 1 (IGF-1) in children with SS?

The determination of IGF-1 is a diagnostic aid and a follow-up criterion, since the low values suggest GHD and their elevation during the treatment with growth hormone allows to evaluate the response.[53] However, for children between 3 and 8 years it is recommended to be cautious with the request of this exam and the interpretation of the results, since the values that are considered normal can overlap between patients with an without GHD.[53,54]

In patients under treatment with somatropin, it is suggested to monitor IGF1 levels twice a year and to especially monitor patients with high determinations. Likewise, various authors recommend titrating the dose of this hormone based on the IGF-1 values.[23,25,55]

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Table 1. Cut-off points of growth hormone published in some studies.

Year	Country	Cut-off point	Assay	Reference
1996	Italy	10 µg/l	RIA	47
2006	Argentina	5.4 µg/l	IQL	48
2014	Germany	7.09 µg/l	IQL	49
2016	Brazil	3 µg/l	IQL	50
2016	United Kingdom	6-8 µg/l	IQL	51
2019	Brazil	7 µg/l	IQL	52

RIA: radioimmuunoasay; IQL: immunochemiluminescence. Source: Own elaboration.

Question 7. What reference values of IGF1 are suggested to be used in Colombia?

In Colombia there are no reference values for IGF-1 and these are linked to the platform (equipment) and the processing technique; for this reason, the results may vary between each laboratory. There are different reference values in the literature that can be consulted by the pediatric endocrinologists,[56-59] but given the national panorama it is important that professionals know in which processing platform the test was performed in order to correlate the results with the information available.

Some authors suggest that IGF-1 values vary depending on the age, gender and pubertal development stage, so there are tables that show reference values according to Tanner 's stage of pubertal development.[58,60] Likewise, the results can also be analyzed according to the SD (Z-score) of the reference population for each test and whose values are distributed between +2 SD (97.5 percentile) and -2 SD (2.5 percentile).

Question 8. What somatropin stimulation tests should be requested when GHD is suspected?

It is suggested that dynamic tests with chemical stimulation for the diagnosis of GHD are requested by the pediatric endocrinologist as a last-line study to confirm this diagnosis, the above taking into account that the results are not the single criterion to define the pharmacological treatment and that two dynamic tests with different stimuli are required to confirm GHD following standardized laboratory protocols.[25,52]

The performance of dynamic test implies the compliance with technical requirements, infrastructure and standardized processes, as it implies the administration of drugs with potential risk for the safety of the patient; in this sense, medical surveillance becomes necessary in a service center with the capacity of initial care for possible adverse effects, and hospitalization in cases of difficult management.

Based on the foregoing, in Colombia it is considered a good clinical practice to request the dynamic tests available in the laboratories authorized lin the country with the stimuli of clonidine, insulin, glucagon and levodopa.[8,33,52,61-69]

Question 9. What are the indications for testosterone or estrogen impregnation?

It is the duty of the clinician to make the decision to formulate impregnation with sex steroids before the requested functional tests when GHD is suspected in prepubescent boys >11 years and in prepubescent girls >10 years to prevent unnecessary treatment with somatropin in children with constitutional delay of growth and development.

Regardless of gender, it is recommended to indicate 2 mg of β-estradiol (1 mg for a body weight <20 kg) orally during the two nights before the test. Males can be prepared with intramuscular testoste-

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rone (50-100 mg of a depot formulation administered one week before the test).[25]

Since the availability of sex steroids for impregnation is not constant in some countries, it is suggested to individualize the decision to perform dynamic tests in this way.

Question 10. In which population and with what frequency is indicated to determine the bone age?

It is necessary to determine the bone age through an anteroposterior radiograph of the left hand and wrist (carpogram) in children > 3 years of age in whom an alteration of the GR has been documented[43,46,70,71]; this test is not recommended in children <2 years, in whom the assessment of the bone age is less reliable. In the same way, it is recommended to take special care in obese children, in whom the bone age is typically advanced.[54] There is no certainty about when it should be repeated or perform radiological follow-up, but it is recommended to evaluate the benefit of its performance given the levels of exposure to ionizing radiation to which a child may be subjected in the case of indiscriminately repeating the study.

In general, it is suggested to consider to take a carpogram annually in patients who are being treated with somatropin; in specific conditions such as pubertal development, it may be taken at shorter intervals according to the criterion of the treating physician.

Question 11. What is the dose of somatropin according to the indications approved in Colombia?

In Table 2 are listed the doses of somatropin according to the indications approved so far in Colombia. The literature suggests to titrate the dose based on the IGF-1 values.[23,25,55]

Question 12. What are the molecules and technical specifications of the somatropin most commonly used in Colombia?

In Colombia there are several molecules of somatropin with INVIMA registry, but the most frequently used are listed in Annex 1, along with their technical specifications.

Question 13. What growth curves are suggested to be used in Colombia for the follow-up of children with SS?

It is suggested to follow the recommendations of the CPG of growth and development of the MSPS of Colombia,[74] where two main recommendations are made:

- Use the indicator height-for-age below -2 SD for their age and sex in the growth reference patterns of the WHO to classify children between 0 and 5 years of age as SS for age (delay in height).[74]

Table 2. Growth hormone dose according to the indications approved in Colombia.

Therapeutic indication	Dose µg/kg/day	Dose mg/kg/day	Dose IU/kg/day*	Reference
Growth hormone deficiency	22-35	0.023-0.034	0.07-0.1	25
Turner syndrome	45-50	0.045-0.05	0.14-0.15	23
Prader-Willi syndrome**	35	0.017-0.035	0.05-0.1	24
Chronic kidney disease in <18 years	45-50	0.045-0.05	0.14-0.15	26
Small for gestational age newborn without catch-up growth	35-70	0.035-0.07	0.1-0.2	13.72

* 1 mg of somatropin corresponds to 3IU of somatropin.
** Bakker *et al.*[73] suggest 1 mg/m^2/day of somatropin as a dose for patients with Prader Willi syndrome.
Source: Own elaboration.

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- Use the indicator height-for-age below -2 SD for their age and sex in the Colombian growth curves to classify children between 5 and 10 years of age as SS-for-age (delay in height).[74]

For the clinical diagnosis and follow-up of patients with SS, it is proposed to compare the auxological parameters (height, weight, body mass index and head circumference) with those generated from the Colombian population between 0 and 20 years of age and published by Durán *et al*.[75] in 2015, since the growth dynamics and the final height depend mainly on the genetic load and take into account the substantial effect of the specific environmental factors of each population.

Regarding the GR, it should be considered that while local curves are generated, we must use the reference patterns of the study conducted by Kelly *et al*.[76] published in 2014, which demonstrated statistical superiority compared to those proposed by Tanner & Whitehouse,[77] that were developed with the statistical technique of centralization that can oversize the GR and had an evident bias in the selection of the population for their development. The study by Kelly *et al*.,[76] conducted with the Lambda Mu-Sigma (LMS) mathematical method for the adjustment of anthropometric data, also included Latin population and considered slow, average and rapid maturation profiles.

Question 14. What codes of the 10th edition of the International Classification of Diseases (ICD-10) should be used in Colombia for the unified registry of health conditions related to SS in children?

For the unified registry of health conditions related to SS in children, it is suggested to use the ICD-10 codes presented in Table 3.

It is suggested to use the code E230: hypopituitarism in patients in whom growth hormone deficiency has been confirmed. The R629 code will be used in the patient with short stature on etiological study.

Question 15. What are the criteria for suspension or withdrawal of somatropin?

The decision to interrupt the treatment with somatropin should be made in conjunction with the patient and/or the caregivers, when the epiphyseal

Table 3. Main ICD-10 codes related to short stature in children.

Name of the pathology or health condition		ICD-10 code
Short stature, not classified	**Includes:** NOS (Not otherwise specified) constitutional short stature, Laron-type short stature, psychosocial.	**E34.3**
	Excludes: other specific endocrine disorders (E34.8), congenital malformation syndromes mainly associated with short stature (Q87.1), Immunodeficiency with short-limb dwarfism (D82.2), achondroplastic (Q77.4), delayed development followed by protein and energy malnutrition (E45), hypopituitarism (E23.0), renal osteodystrophy (N25.0)	
Hypopituitarism		**E23.0**
Small for gestational age		**P05.1**
Congenital malformation syndromes mainly associated with short stature		**Q87.1**
Turner syndrome, unspecified		**Q96.9**
Lack of expected normal physiological development, unspecified		**R62.9**
Chronic renal failure, unspecified		**N18.9**

Source: Own elaboration.

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closure is demonstrated[26]; when the patient is within the genetic range of target height and has a GR <2 cm of total growth in one year,[13] and when there are insuperable problems of adherence to treatment.[13] It should also be discontinued in patients with bone age >16 years when they are boys and >15 when they are girls.

Having reached a high within the range of the family height calculated according to Tanner's formula[78,79] should also be considered as an event to interrupt treatment. Somatropin should be discontinued in patients with CKD and persistent severe secondary hyperparathyroidism (Parathyroid hormone [PTH] > 500 pg/ml), but it can be re-established when the levels return to the desired target range of PTH.[26] This treatment should also be discontinued when any serious adverse event appears (avascular necrosis of the femoral head or epiphysiolysis of the femoral head)[26] and/or reported in the technical data sheet of the drug. (See Annex 1). Finally, if the patient does not respond adequately to treatment despite optimal nutritional and metabolic control, it should be postponed.[26,80]

Question 16. Is the use of an Informed Consent to start treatment with somatropin suggested in Colombia?

It is suggested that informed consent is part of the medical history of the patient as a document that evidences the process of participation in making informed decisions by the patient and their caregivers, both to accept and to reject the initiation of treatment (Annexes 3 and 4).

Question 17. What are the considerations related to the use of somatropin in patients with and without GHD?

According to the CPG of *Grimberg et al.*,[25] the following considerations are proposed regarding the use of somatropin in patients with or without GHD:

- The diagnosis of GHD does not require provocation tests when the following three conditions are met: auxological criteria, some hypothalamic-pituitary defect (malformation, neoplasm or radiation) and deficiency of at least one additional pituitary hormone.[25]

- GHD due to congenital hypopituitarism does not require somatropin provocation tests in a newborn with hypoglycemia who does not reach a serum concentration of this hormone above 5 µg/L and has a deficiency of at least one additional pituitary hormone and/or the classic imaging triad (ectopic posterior pituitary and pituitary hypoplasia with abnormal stem).[25]

- Given the substantial number of healthy children with normal growth and tests below the accepted limits, an inadequate response to two provocation tests with different stimuli is required for the diagnosis of GHD.[25]

- Given the big discrepancies between trials with somatropin, it is recommended that institutions request that laboratories provide harmonized trials on this hormone using the standard (IRP IS 98/574, 22k rhGH isoform) as recommended by the consensus statements of 2006 and 2011 and the published commutability standards.[25,81]

- It is not useful to request basal growth hormone levels to confirm the diagnosis of GHD in a clinical setting,[25] so dynamic tests are used for this purpose.

- In Colombia it is no necessary to carry out dynamic tests for other approved indications for the use of somatropin (other than GHD), whenever they are documented with the respective studies for each diagnosis (TS, PWS, CKD, SGA).[23,24,26,82]

- It is recommendable to perform a nuclear magnetic resonance imaging with contrast of the sella turcica and the suprasellar region, once the diagnosis of GHD is confirmed and before starting treatment with somatropin,[34] as well as to evaluate the other pituitary hormones.

- The adrenal and thyroid axes should be reassessed after initiation of the therapy with somatropin in patients whose GHD is associated

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with possible multiple pituitary hormone deficiencies (panhypopituitarism).[25]

- Some conditions have an increased intrinsic risk of malignancy (neurofibromatosis-1, Down syndrome, Bloom syndrome, Fanconi anemia, Noonan syndrome and Diamond-Blackfan anemia), and therefore the prescription of somatropin is not recommended in these patients.[25]

Question 18. What are the considerations related to the use of somatropin in patients with TS?

According with the CPG of Gravholt *et al*.[23] the following considerations are proposed:

- It is recommended to make a kariotype to every girl who has come to supra-specialized consultation (pediatric endocrinology or genetics) for SS without an apparent cause).[23]
- In women with TS, somatropin treatment should be started early (around 4 to 6 years of age), when there is evidence of a decrease in GR below the 50th percentile and sustained in this way for 6 months; in the absence of another treatable cause of growth deficit; when there is a high probability of SS due to parents with short stature or predicted adult SS, and when the patient is at a population age of puberty at the time of diagnosis of TS.[23]
- The treatment with somatropin should be monitored in women with TS by measuring height every 4-6 months during the first year of treatment and every 6 months thereafter.[23]
- The safety of somatropin therapy should be monitored by measuring IGF-1 at least once a year; if the values are above +3 SD of the mean for the age, a reduction of the dose of the hormone is justified, but for values between +2

  SD and +3 SD, clinical judgment should guide the selection of the dose.[23]
- Screening for hypothyroidism should be performed at the time of diagnosis and then annually with measurements of free T4 and TSH

beginning in early childhood and during the whole life.[23]

- It is necessary to request an annual measurement of HbA1c lifelong with or without fasting glycemia. [23]
- Clinical evaluation for scoliosis every 6 months is recommended during somatropin therapy until growth is completed; if the evaluation is done in another way, it must be annual.[23]
- It is suggested not to add routinely very-low dose estrogen supplements in prepubertal patients to promote growth[23] and that pubertal induction with estrogens between 11 and 12 years of bone age is a mimetic effect of the pubertal growth spurt.[23]

Question 19. What are the considerations related to the use of somatropin in patients with PWS?

According to the CPG of Deal et al.[24] the following considerations are proposed:

- Patients with PWS must have a genetically confirmed diagnosis and a multidisciplinary clinical evaluation before initiating the treatment with somatropin. If it has been started, it should be continued as long as the benefits outweigh the risks.[24]
- Somatropin stimulation testing is not required as part of the therapeutic decision-making process in children with PWS.[24]
- Exclusion criteria for the initiation of somatropin treatment in patients with PWS are morbid obesity, uncontrolled diabetes, untreated severe obstructive sleep apnea, active cancer, and active psychosis.[24]
- Scoliosis is not an absolute contraindication, but is a relative contraindication for the treatment with somatropin in patients with PWS. Therefore, strict follow-up must be carried out because the disease may worsen during treatment.[24]

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- The treatment with somatropin should be carried out in the context of appropriate dietary, environmental, and lifestyle interventions for the care of all patients with PWS.[24]

- Cognitive impairment should not be a barrier to treatment with somatropin in patients with PWS.[24]

- IGF-1 levels in patients with PWS under treatment with somatropin can be kept within the upper limit of the normal range (maximum + 2SD),[24] this taking into account that immunoreactive IGF-1 levels do not represent the bioactive IGF-1 levels in children with PWS treated with the hormone. Therefore, increased levels are not an indication of overdose.[73]

- Patients with PWS who receive somatropin should be closely monitored for possible adverse effects of treatment every 3 to 6 months.[24]

Question 20. What are the considerations related to the use of somatropin in patients with CKD?

- Patients with CKD and treatment with somatropin should be interdisciplinary evaluated by pediatric nephrology and endocrinology, because although the pediatric nephrologist could initiate treatment in appropriately selected patients, the pediatric endocrinologist should be in charge of it, ideally from the beginning, and be the responsible for the follow-up.

On the other hand, in accordance with the consensus of Drube *et al*.[26] and with the recommendations from a group of local experts, based on scientific evidence (data to be published), the following considerations are proposed:

- Age, assessment of the pubertal status according to Tanner's scale, eye fundus, etiology of the renal disease, systemic disorders, stage of the CKD, adequation or the dialysis (for patients on dialysis), time of transplantation and degree of graft function, and glucocorticoid therapy (in post-transplant children), the latter given that high doses of glucocorticoids can almost completely suppress the effect of the hormone, should be taken into account for the initiation of treatment with somatropin.[26]

- The efficacy of treatment in properly selected patients will be greater if the therapy is started before puberty and before the deterioration in height is marked.

- Growth-limiting factors associated with CKD, such as protein-calorie malnutrition, metabolic acidosis, electrolyte disorders (hyponatremia), dehydration, and bone mineral disease, including secondary hyperparathyroidism should be controlled before starting therapy with somatropin.[26]

- Evidence suggests that treatment with somatropin increases height in patients with CKD, being higher if it is started before dialysis, less if it is started during it, and intermediate if it is started post-transplant. The treatment is safe from the point of view of the intervention and the kidney disease itself.

- When starting treatment, is important to carry out an auxological assessment, of pubertal development, bone maturation, bone mineral density, lipid profile, glucose, HbA1c, insulin, IGF-1, serum creatinine, estimated glomerular filtration rate, urea, calcium, phosphorus, total alkaline phosphatase, bicarbonate, parathyroid hormone, 25(OH)-vitamin D and albumin.[26]

- In children post-renal transplant, somatropin therapy should be started one year after transplantation if the growth recovery is not spontaneous and immunosuppression without steroids is not feasible.[26]

- Somatropin therapy should be considered in patients with CKD at any stage, because due to the nephropathic cystinosis they present a persistent growth failure despite adequate treatment for this condition.[26]

- In a patient with advanced CKD and treatment with somatropin, quarterly/six-monthly controls

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should be performed to monitor height, GR, pubertal development, renal function, and levels of TSH, free T3, glycemia, calcium, phosphate, bicarbonate, and parathyroid hormone.[26]

- If the GR in the first year of treatment with somatropin is less than 2 cm per year above the baseline, the adherence of the patient to treatment, including the measurement of serum IGF-1 levels, dose of somatropin adjusted to the weight and assessment of nutritional and metabolic factors should be evaluated.[26]

- Somatropin should be discontinued at the time of kidney transplantation, in case of an unexplained decrease in the estimated glomerular filtration rate,[26] in cases of onset of significant proteinuria not explained by recurrence of the primary disease in the graft,[83] in suspicion of malignancy, when the goal has been reached based on the midparental height or 50th percentile for age and when there is epiphyseal closure, displacement of the femoral epiphysis and intracranial hypertension.

Question 21. What are the considerations related to the use of somatropin in SGA children?

By definition, a newborn is SGA when it is born with weight, length and/or head circumference below -2 SD for the weeks of gestation and sex with respect to the standards published in the INTERGROWTH 21st study.[84,85] In this sense, all patients who are or were SGA require an exhaustive study of the probable etiology that led them to this outcome in the first 2 years of life. In case that a specific cause is found, it should be treated or referred for treatment with the pertinent specialist.[82]

SGA children who do not have a growth recovery or height re-catching at 2 years of age require a new clinical evaluation to determine the cause. In case that it is not found or if a hormonal alteration is suspected, an evaluation by pediatric endocrinology for diagnosis and/or treatment is recommended.[44,82]

SGA children without height re-catching at 2 years of age in whom a specific cause of growth failure is not established and syndromic etiology other than the approved indications listed in this text is ruled out are candidates for treatment with somatropin.[44,82]

Likewise, in SGA patients, therapy should be monitored with the clinical and paraclinical parameters exposed in this document, and although there is no consensus about the safety levels of IGF-1, it is suggested to keep them during somatropin therapy within a limit between 1.5 and 2 SD for age and sex.[86]

Question 22. Which patients with SS require evaluation by a specialist in genetics?

An evaluation by clinical genetics is required when a patient presents SS associated with neurodevelopmental delay or cognitive deficit, alteration in body proportions, facial dysmorphism, multiple congenital malformations (understood as two or more affected organs or systems) and/or characteristics that are consistent with a specific syndromic association such as Noonan syndrome, TS, PWS.) In these patients, the cytogenetic or molecular analysis can help determine the cause of the SS and/or the condition of the patient, and may even establish the need to study the parents or other relatives, all this with adequate genetic counseling that allows to determine the risks of recurrence and a timely prenatal diagnosis in future generations.[38,87,88]

Genetic and/or epigenetic tests are not necessary for all children with SS, but they should be used in the diagnostic evaluation of specific groups of children whose phenotype suggests a high probability of a genetic cause such as isolated GHDs, familial SS, specific syndromes with multiple pituitary deficiencies, severe SS (<-3 SD of the population more than 3 SD below their midparental height), body disproportion and/or skeletal dysplasias; they should also be practiced in SGA children without adequate growth recovery.[54]

Conclusion

Somatropin is a drug frequently used in the practice of the pediatric endocrinologist. There are specific

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criteria and doses for its use, as well as diagnostic tests and follow-up, depending on the indication for which it is prescribed. Answering the questions that generate uncertainty in clinical practice allows establishing a unit of criteria at the national level that will generate an impact on the statistical record, research work, clinical follow-up and rational use of resources in the health system, based on the best available evidence and expert agreement in the context of professional practice in Colombia.

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Conflict of interest

There were no conflicts of any nature for the development of this study. All the authors attached and signed their respective conflict of interest document.

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Ethical responsibilities

Each of the authors, through their academic contributions, responded to the ethical consideration to unify the criteria in clinical practice, with social responsibility, and the aim of improving the hormonal health conditions of Colombian children.

Contribution of the authors

We certify that we have contributed with the scientific and intellectual material, data analysis and writing of the manuscript, taking responsibility for its content. We have not conferred any right or interest in the work to third parties. We also certify that all figures and illustrations that accompany this work have not been digitally altered and faithfully represent the reported facts.

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Annex 1. Technical data sheet of the drug somatropin.

1. Available presentations and pharmaceutical forms:

Brand name	Presentation	Concentration	Device	Laboratory	Pharmaceutical form
Genotropin®	5.3 mg	5.3 mg (16 IU)	Pen 0.1 mg per click	Pfizer	Powder
Genotropin®	12 mg	12 mg (36 IU)	Pen 0.2 mg per click	Pfizer	Powder
Saizen®	6 mg/mL	5.83 mg/mL (15 IU)	Easypod	Merck	Liquid
Saizen®	20 mg/2.5 mL	8 mg/mL (26.4 IU)	Easypod	Merck	Liquid
Norditropin®	5 mg/1.5 mL	3.33 mg/mL→10 IU 5 mg → 15 IU	Pre-filled pen	Novo Nordisk	Liquid
Norditropin®	10 mg/1.5 mL	6.7 mg/mL → 20 IU 10 mg → 30 IU	Pre-filled pen	Novo Nordisk	Liquid
Norditropin®	15 mg/1.5 mL	10 mg/mL →30 IU 15 mg →45 IU	Pre-filled pen	Novo Nordisk	Liquid
Omnitrope®	10 mg/1.5 mL	6.7 mg/mL → 20 IU 10 mg → 30 IU	Surepal 10	Sandoz GMBH	Liquid
Omnitrope®	15 mg/1.5 mL	10 mg/mL ◊ 30 IU 15 mg ◊ 45 IU	Surepal 15	Sandoz GMBH	Liquid

Source: Own elaboration.

For other molecules of somatropin available in Colombia consult the INVIMA website.

2. Therapeutic indications:

Somatropin is approved in Colombia for the treatment of the following growth disorders in children and adolescents and its dosage must be adapted to the needs of each child and the type of condition to be treated:

Brand name	Growth hormone deficiency	Turner syndrome	Prader Willi syndrome	Chronic renal failure	Born small for age gestational without catch-up growth after 4-5 years
Genotropin® (Pfizer)	X	X	X	X	X
Saizen® (Merck)	X	X	-	X	X
Norditropin® (Novo nordisk)	X	X	-	X	X
Omnitrope® (Sandoz)	X	X	X	X	X

Source: Own elaboration.

http://dx.doi.org/10.22265/acnef.7.1.375

3. Administration:

The administration of somatropin can be subcutaneous (arm, abdomen, buttocks or thighs with rotation of the injection sites to avoid lipoatrophy) and should be administered between 7 and 8 o'clock at night, 6 to 7 times a week.

4. Contraindications:

Known contraindications for somatropin are:

- Hypersensitivity to excipients.
- Postoperative of major surgery (heart, abdomen, multiple trauma)
- Acute respiratory failure due to increased mortality risk
- Active malignancy
- Pediatric patients with closed epiphyses.
- Active non-proliferative diabetic retinopathy.
- Patients with Prader-Willi syndrome and severe obesity, sleep apnea, airway obstruction, or severe respiratory failure.

5. Adverse reactions:

The adverse reactions of somatropin are classified into:

- *Frequent* (<10%): these reactions include edema, rash, arthralgia, myalgia, headache, rhinitis and paresthesias.
- *Very rare*: these reactions include epiphyseal slippage or avascular necrosis of the femoral head, hypothyroidism, hyperglycemia, nausea, scoliosis, tumor relapse in patients with a history of neoplasia, apnea in patients with Prader-Willi syndrome, hematuria, pancreatitis, infections, hypertension and anaphylaxis.

6. Pharmacological interactions:

The drug interactions of somatropin occur with glucocorticoids, anticonvulsants, cyclosporins, oral estrogens, insulin, and oral hypoglycemic agents.

7. Overdose and toxicological data:

In cases of severe toxicity, somatropin should be discontinued for up to 5 days, then restarted at a 50% dose; If severe toxicity recurs or does not disappear within 5 days, treatment should be stopped, as it causes hypoglycemia and hyperglycemia in the short term and can cause acromegaly in the long term. Similarly, it is likely to cause fluid retention.

8. Pharmacodynamic properties:

Mechanism of action: Somatropin binds to a dimeric receptor on the cell membrane of target cells, resulting in intracellular signal transduction. Some pharmacodynamic effects are mediated by the level of IGF-1 produced in the liver and locally (skeletal growth and protein synthesis), while others are a consequence of the direct effects of the hormone (lipolysis). In this way, somatropin stimulates tissue growth, linear growth (height), and the metabolism of proteins, carbohydrates, lipids, and minerals.

9. Pharmacokinetic properties:

Absorption: somatropin by subcutaneous route has a bioavailability >70%. A subcutaneous dose of 0.035 mg/kg produces plasma Cmax and tmax values in the range of 13-35 ng/mL in 3 and 6 hours, respectively. The absorption velocity is affected by the site of administration, subcutaneous blood flow, muscle activity, the volume and concentration of the drug injected, the depth of injection (onset of action faster intramuscularly than subcutaneously) and body temperature (the increase in temperature produces vasodilation and decreases the viscosity, increasing the solubility of the drug; the opposite effect is achieved by applying cold).

Distribution: the volume of distribution of somatropin can be higher than 1.3 L/kg, being reported values of 12 L in some presentations.

Metabolism: Somatropin works through hepatic metabolism.

Elimination: elimination of somatropin occurs through renal route. After subcutaneous administration,

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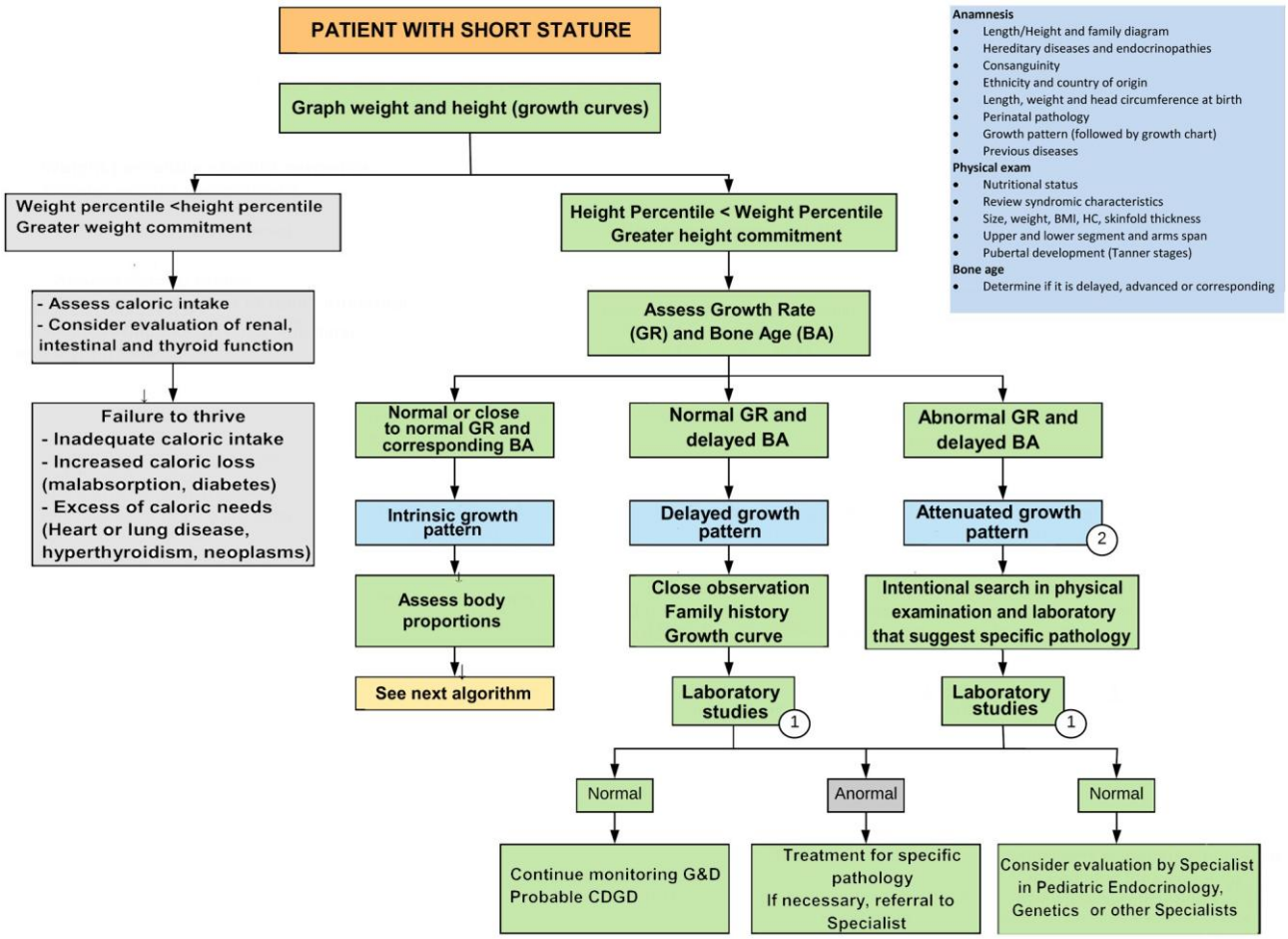
half-lives of 2-3 hours are achieved, although the half-life ($t_{1/2}$) in plasma is short, its biological $t_{1/2}$ is considerably longer, and once-daily administration is sufficient.

10. Considerations for the use of the drug:

- Before administering somatropin it should be verified that the solution for injection should is clear.
- The drug should be kept refrigerated (2-8ºC), but not frozen, and protected from light.
- The stability of the drug molecule varies according to the reference laboratory, for which the specifications of the molecule according to the trading firm must be reviewed.

Anexo 2. Algoritmo propuesto para la clasificación de talla baja.



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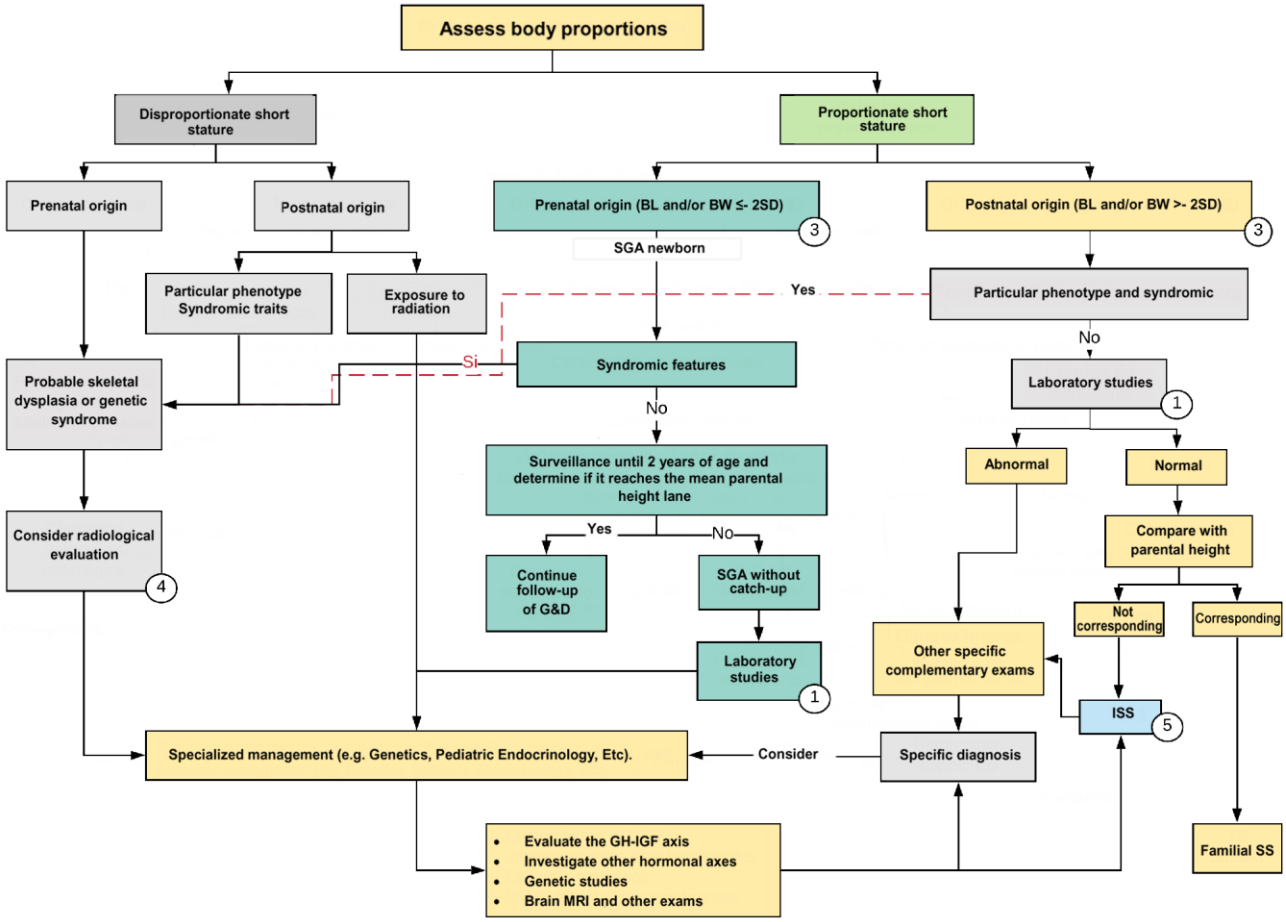

BL: birth length; BW: birth weight; SD: Standard deviation; SGA: small for gestational age; SS: short stature; ISS: idiopathic short stature; GR: growth rate; BA: bone age; GH: growth hormone; G&D: growth and development; CDGD: constitutional delay of growth and development.

Annexes of the numeration contained in the Algorithm:

1. Laboratory studies: Complete blood count, ferritin, CRP, ESR, BUN, creatinine, transaminases, alkaline phosphatase, ionogram, venous gases in <3 years of age, urinalysis, TSH, free T4, IGF-1 and karyotype in all girls. IgA anti-transglutaminase antibodies if celiac disease is suspected.

2. ALERT: It is always a pathological growth pattern and a disease must be ruled out.

3. Using the reference parameters of INTERGROWTH 21.

4. Radiological studies should be performed and, according to semiology, refer to genetics to evaluate the relevance of carrying out specialized studies in the event of suspected congenital skeletal dysplasias (*achondroplasia, hypochondroplasia, multiple epiphyseal dysplasias, RASopathies, among others*). Likewise, identify children with disproportionate acquired TB secondary to malformations, radiotherapy, tumors, and other diseases.

5. Among the causes of short stature of unknown etiology, is idiopathic short stature (ISS). In general, ISS patients have normal weight at birth and GH sufficiency. If there is no specific diagnosis and the short stature is severe or has a familial component, referral to the geneticist should be considered for evaluation of the need for an exome study.

http://dx.doi.org/10.22265/acnef.7.1.375

Annex 3. Informed consent for initiation of treatment with somatropin

INFORMED CONSENT FOR THE USE OF SOMATROPIN IN PEDIATRIC PATIENTS

Mr(s) father (mother) of family and/or guardian:

Taking into account that, according to the medical diagnosis, your child has one of the approved indications for the use of growth hormone in Colombia, below you will find information about the medication offered for this purpose. This information will allow you to clear up any doubts about the treatment and authorize it, which will contribute to its success.

What is growth hormone?

Growth hormone is a substance produced by the pituitary gland that is responsible for regulating the growth of the body, helping to increase height and muscle mass, and decrease body fat. This hormone also helps control the body's metabolism, which is the process by which cells convert food into energy and produce other substances that the body needs. When there is a medical condition that requires the administration of growth hormone, replacement therapy is performed with the synthetic form of the hormone (also called somatropin), which is not covered by the Health Benefits Plan, as it is considered a high-cost medicine and the approval of its administration is done through the MIPRES platform of the Ministry of Health and Social Protection.

What are the indications approved in Colombia for its use?

1. Growth hormone deficiency
2. Turner syndrome
3. Prader-Willi syndrome
4. Chronic kidney disease in children under 18 years of age
5. Children born small for gestational age without catch-up growth

In which cases is the use of growth hormone not approved in Colombia?

1. Family short stature
2. Idiopathic short stature (of unknown cause)
3. Short stature of other syndromic origins (Noonan, Silver Russell, Down, etc.)
4. SHOX gene mutation
5. Cystic fibrosis
6. Congenital adrenal hyperplasia
7. Severe burns
8. Juvenile rheumatoid arthritis
9. Short bowel syndrome
10. Achondroplasia and hypochondroplasia

How is growth hormone administered?

The drug is given as subcutaneous injections (under the skin) once a day, at bedtime and ideally no later than 8:00 p.m., 6 to 7 times a week. It can be applied at home, and even older children can learn how to inject themselves. As it is a biological medicine, it requires refrigeration, and freezing of the product should be avoided (take this into account for transport and storage). This information will be expanded in the respective training for its application.

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The attending physician will decide the dose, frequency and presentation of the medicine to be administered based on the diagnosis, weight or body surface of your child. The application of the drug requires training for which you will be contacted at the time of the first delivery. Follow the indicated instructions for administration exactly.

What are the benefits of treatment with growth hormone?

According to the medical indication for which the drug is prescribed for your child, benefits are expected that will be widely explained by the treating physician and that not only involve the recovery of height but also changes in body composition (normalization of muscle mass and bone) and decreased cardiovascular risk. According to the medical indication for which the drug is prescribed for your child, benefits are expected that will be widely explained by the treating physician and that not only involve the recovery of height but also changes in body composition (normalization of muscle and bone mass) and decreased cardiovascular risk. Regarding the height, the sooner the treatment is carried out, the greater the probability that your child will grow until reaching an adult height close to that expected according to the established therapeutic goals. During the first year of treatment, the highest growth rate is expected, which will slow down a little bit during the next 2 years. After this, the growth rate slowly decreases.

It must be borne in mind that the action and application of growth hormone therapy is daily and therefore strict adherence is required, not only to the application of the drug but also to the adjustments required in the determining factors of growth such as sleep hygiene, physical activity and healthy eating (free of processed food). Failure to follow these recommendations can lead to non-response to the action of the drug; therefore, the commitment of the entire family nucleus is required for the success of the treatment.

A small percentage of patients do not respond to treatment, so the impact should be evaluated in periodic controls, eventually requiring dose adjustment or drug withdrawal when it is considered that there has been no response to it.

What are the risks of treatment with growth hormone?

Adverse events are classified medically as common (affecting 1 to 10 out of 100 patients), uncommon (affecting 1 to 10 out of 1,000 patients), rare (affecting between 1 and 10 out of 10,000 patients), very rare (affecting 1 out of 100,000 patients), and of unknown frequency (frequency cannot be estimated from the available data). According to this classification, the adverse effects described with the use of somatropin are the following:

1. *Common adverse effects*: redness and itching at the injection site. If this is especially disturbing, you should discuss it with the attending physician.

2. *Uncommon adverse effects:* carpal tunnel syndrome, characterized by a persistent sensation of "electric shock", with a burning sensation, pain and/or numbness in the hand; headache (isolated): edema (swelling); muscle pain; and joint pain and disorders. These adverse effects usually appear at the beginning of treatment and are transitory (similar to "growing pains").

3. *Very rare adverse effects:* epiphyseal slipping of the femoral head (a problem in the hip that occurs if the growth cartilage of the femoral head shifts) and avascular necrosis of the femoral head (a pathological process in which cells that make up the head of the femur die when they do not receive enough blood

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supply). If your child has an unexplained lameness and hip or knee pain, you should discuss it with the attending physician. Reduction in thyroid hormone levels may also occur and, if necessary, appropriate treatment will be prescribed, which is generally transient during the use of growth hormone therapy.

4. *Unknown frequency:* headache, vision problems, malaise (nausea) and the urge to vomit, manifestations that may be symptoms of increased intracranial pressure. Hyperglycemia (high blood glucose levels), skin rash, breathing difficulty, swollen eyelids, face or lips, and syncope may also occur. Any of these symptoms may indicate an allergic reaction, so if they occur, the drug should be discontinued and you should consult the attending physician. If symptoms are severe take your child to the emergency department.

Although there is no evidence of an increased incidence of leukemia in patients treated with growth hormone and who do not have predisposing factors, some cases of leukemia have been reported in patients treated with somatropin for growth hormone deficiency. Inflammation of the pancreas has been described rarely.

Likewise, cases of sleep apnea and sudden death have been described in patients with Prader-Willi syndrome treated with growth hormone, as well as sudden appearance or accentuation of spine alignment disorders (scoliosis).

In cases where growth hormone deficiency is secondary to cancer treatments, there is a risk of reactivation and relapse of the tumor; this risk depends on the characteristics of the underlying disease or of the treatment used, as is the case with intracranial tumors and the previous requirement for radiotherapy. Patients with chronic overdosage can acquire acromegaloid features (excessive growth of certain parts of the body).

Finally, on rare occasions, the appearance of gynecomastia (development of breast tissue) has been described in prepubertal males treated with growth hormone.

If you consider that any of the adverse effects suffered by your child is serious or if you notice any adverse effect not mentioned in this document, you should inform the treating physician, as the dose may need to be reduced or the medication should be discontinued.

Are there long-term risks of using growth hormone?

The results of long-term follow-up studies of patients who have used growth hormone do not show a carcinogenic effect generated by the use of recombinant growth hormone in patients without previous cancer. The study of possible effects on bone cancer, bladder cancer and Hodgkin lymphoma is currently under investigation.

Is it possible to change the brand of the drug?

Somatropin is a biological medicine whose molecular structure is the same as that of the hormone naturally produced by the human body, so the risk of any adverse reaction is very low. When changing the brand of the drug, a response of the immune system (antibodies) that can affect the effectiveness of the drug in a low proportion is expected; however, the available evidence on possible effects on the results of treatment is scarce, so this consideration should be taken into account before starting the change to another brand of medicine and analyze the risks and benefits with the attending physician on an individual basis.

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What happens if I do not accept that my child receives the hormone?

Timely initiation of growth hormone treatment increases the likelihood of proper growth. Girls with Turner syndrome who do not receive treatment will express a much shorter stature than what is genetically expected, in addition to less accretion of bone mass. In general, if you decide not to start therapy, your child may have a delayed growth and short stature for age, which could have implications for his/her emotional and social health. Furthermore, up to now there are studies that suggest the possibility that this treatment reduces cardiovascular risk.

First and last name of the patient: _____
Type of document: _____ Document number: _____
Date of birth: _____
Age: _____ years _____ months _____

Through the legal representative (father or mother)
First name and last names: _____ Type of document: _____
Document number: _____
Indicate relationship (father, mother, legal guardian): _____

I declare that I have been informed by the physician
First name and last names: _____
Type of document: _____ Document number: _____
M.D. License: _____ Specialist in: _____

That, according to the diagnosis: _____, I have been told that my child should start drug treatment with growth hormone (somatropin), with the following characteristics:
Brand name: _____
Dosage (indicate route, dose, (mcg/kg/day) and frequency):_____
Expected duration of treatment: _____

Similarly, I have been informed about the effectiveness of the treatment:
An increase in final height is foreseeable in the accepted indications, ***but there is the possibility of non-response to treatment.*** There are no data available on final height in Turner syndrome for the Colombian population.

Description of personalized risks and probable discomforts (Information from the doctor regarding the particular circumstances of the patient _____
_____

Declaration of the patient and/or the caregiver:
After receiving this information, as the parent and/or his legal representative, **I declare that:**

- I have received the information from the doctor about the personalized risks of the treatment and have read the package leaflet of the pharmaceutical specialty.

- I am satisfied with the information received and have obtained clarification from the doctor about the doubts raised.

http://dx.doi.org/10.22265/acnef.7.1.375

- I know the possibility of revoking the consent given at any time, without expression of cause and without consequences for future care.

- I accept to be included and attend the medical appointments of the growth hormone program within the established for the control and follow-up of the patients with use of it as a requirement to continue the provision of the supplies and the drug.

Data collection:
I _____identified with _____ number _____ from _____ authorize the medical staff of the institution **to prescribe GROWTH HORMONE (SOMATROPIN) to my child.**

Likewise, I declare, having the legal capacity to do so, that:
• I have been informed about the nature and purpose of the procedures described in this document, as well as on what is related to the most frequent complications derived from them; furthermore, I have been given the opportunity to ask questions and all of them have been answered to my satisfaction.
• I have been informed of the alternative treatment methods, in case there was any, as well as of the advantages and disadvantages of each of them.
• I informed the doctor of the current condition and general diseases of my child for the assessment of possible contraindications.
• I am aware that I can withdraw or revoke the authorization for the use of the medicine if I deem it appropriate, without this having an impact on medical care.
• I am aware of the risks of the indicated treatment.
• I have been informed that there are no absolute guarantees that the result of the treatment will be satisfactory.

I, Dr. _____, as treating physician, after explaining to the legal representative of the patient the procedure and the content of this document, I have asked him/her if he/she wants additional information or if he/she has any concerns about the treatment, to which he/she stated_____
_____
In the same way, the legal representative of the patient is consulted if he authorizes taking photographs and recording the intervention for academic or scientific purposes without his name or that of his relatives being disclosed, to which he replied: YES____ NO____
In witness thereof, it is signed in _____, on the _____ day of the month of _____ 20_____
Name of the legal representative of the patient: _____
ID card: _____
Signature: _____**Fingerprint:**
Physician (Signature and Stamp):_____
M.D. License: _____**Fingerprint:**

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Annex 4. Informed dissent for the initiation of treatment with somatropin

INFORMED DISSENT

I _____identified with _____ number _____ from _____, after being informed of the nature and risks of the administration of growth hormone (somatropin), the consequences of non-application and the absence of alternatives for the treatment of my illness or that of my child, in the light of current scientific knowledge present, I freely and consciously manifest the DENIAL OF CONSENT for its realization, making myself responsible for the consequences that may arise from this decision, for the following reason(s):_____ _____

In witness thereof, it is signed in _____, on the _____ day of the month of _____ 20_____

Name of the legal representative of the patient: _____
ID card: _____

Signature: _____Fingerprint:
Physician (Signature and Stamp):_____
M.D. License: _____ Fingerprint: