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Characterization of thyroid dysfunction in adults with chronic renal disease in dialysis

Caracterización de la disfunción tiroidea en adultos con enfermedad renal crónica en diálisis

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Abstract

Background: There is a clear relationship between thyroid dysfunction and chronic kidney disease (CKD), which is evidenced by the increase in the prevalence of primary hypothyroidism when the glomerular filtration rate decreases
Objectives: Characterize adult patients with thyroid dysfunction and chronic kidney disease on dialysis therapy.
Methods: An observational, descriptive, cross-sectional study was carried out that characterized and collected laboratory reports of patients >18 years of age with CKD in dialysis therapy of a renal unit of the city of Cartagena/Bolívar with TSH control in 2016.
Results: 350 patients with TSH registry were included, with a median age of 59 years and 49.1% were women. The main cause and comorbidity of CKD was hypertension in 36.3% and hyperparathyroidism in 56% respectively. In relation to thyroid dysfunction, 25.4% of the population had TSH levels> 4.5 µIU/mL, of which 5.7% had TSH levels> 10 µIU/mL (hypothyroidism).
Conclusions: The prevalence of thyroid dysfunction was higher than in the general population, however additional studies with measurement of FT4 are necessary to achieve an adequate categorization.
Key words: thyroid gland, kidney, kidney failure, chronic, glomerular filtration rate, dialysis, hypothyroidism, thyrotropin.

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Resumen
Introducción: existe una clara relación entre la disfunción tiroidea y la enfermedad renal crónica (ERC) que se evidencia por el aumento de la prevalencia de hipotiroidismo primario a medida que disminuye la tasa de filtración glomerular.
Objetivo: caracterizar los pacientes adultos con disfunción tiroidea y enfermedad renal crónica en terapia dialítica.
Métodos: se realizó un estudio observacional de tipo descriptivo, transversal, que caracterizó y recolectó datos de laboratorio en pacientes mayores de 18 años con ERC. Estos pacientes se encontraban en terapia dialítica en una unidad renal de la ciudad de Cartagena (Colombia) y se les practicó un control de TSH en el año 2016.
Resultados: se incluyeron 350 pacientes con registro de TSH. La mediana de edad fue de 59 años y el 49.1% eran mujeres. La principal causa de la ERC fue la hipertensión (36.3%) y la principal comorbilidad fue el hiperparatiroidismo (56%). En relación con la disfunción tiroidea, se evidenció que el 25.4% de la población presentó niveles de TSH mayores a 4.5 µIU/mL. Dentro de este segmento, un 5.7% se encontraba en rango de hipotiroidismo (TSH>10 µIU/mL).
Conclusiones: la prevalencia de la disfunción tiroidea fue mayor en la muestra, en comparación con la población general. No obstante, se requieren estudios adicionales con medición de T4L para realizar una adecuada categorización.
Palabras clave: glándula tiroides, riñón, fallo renal crónico, tasa de filtración glomerular, diálisis, hipotiroidismo, tirotropina.

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Introduction

Chronic kidney disease (CKD) has a high prevalence in Colombia. It is associated with multiple complications, among them, thyroid dysfunction.[1,2] The latter is the result of the alteration of the hypothalamic-pituitary-thyroid axis, as well as of the disorder in the synthesis, secretion and peripheral metabolism of thyroid hormones. It produces both structural and functional changes of the thyroid gland: mainly, low levels of T3 and subclinical hypothyroidism.[3,4]

The incidence of hypothyroidism increases proportionally with the deterioration of renal function. It occurs in 10.9 % of patients in stage 2; in 21.0 % of patients in stage 3; and in 23.1 % of those who are in stages 4 and 5.[5] A high prevalence of hypothyroidism has been observed in patients on dialysis: it ranges between 13 % and 25 % in cohort studies.[6] Despite this, hypothyroidism is little recognized in many patients with advanced CKD, probably because the symptoms are indistinguishable from those of uremia (for example, fatigue, cold intolerance and decreased cognition).[6,7]

Recently, hypothyroidism has been associated with an increased mortality risk in patients on hemodialysis and peritoneal dialysis.[8,9] Since patients with end-stage CKD have between 7 and 10-fold higher risk of mortality compared with the general population,[6] it has aroused a growing interest in hypothyroidism as an independent cardiovascular risk factor in this population group.

Its impact could be modified with hormone replacement therapy.[9,10,11,12] However, there is no clear recommendation currently in this regard, especially when the TSH levels are below 20 IU/mL since it has been demonstrated that it produces a negative balance of nitrogen products due to the increased muscle catabolism.[4]

Due to the high prevalence of hypothyroidism in patients with CKD, it is necessary to conduct local studies that expand knowledge on this topic, and also allow us to know the behavior of this association in our population, reason for which a study was carried out in order to characterize the thyroid dysfunction in adults with CKD on dialysis.

Materials and methods

An observational, descriptive cross-sectional study was designed. The information was obtained from the clinical records of patients over 18 years with stage 5 chronic kidney disease (CKD-5), who were on dialysis therapy (hemodialysis or peritoneal dialysis) and attended a renal unit in the city of Cartagena (Colombia) and had a control of TSH in the last year.

The data were tabulated in an Excel matrix. The quantitative variables were summarized with medians and interquartile ranges, due to their nonparametric nature (estimated with the Shapiro-Wilk normality test). On the other hand, the qualitative variables were described by means of absolute and relative frequencies. To compare the general, clinical and paraclinical characteristics of the subjects of study with suspected thyroid dysfunction, the Chi^2 test or the Fisher's exact test were used in the qualitative variables, as necessary. The Mann-Whitney test was used in the quantitative variables. A p value<0.05 was considered statistically significant.

Results

In the renal unit evaluated, 538 patients with CKD-5 were assigned at the time of the study. Among them, 350 who had registered in their clinical record the report of ultrasensitive TSH were identified. In this population group, the primary cause of CKD was hypertension (36.3 %), followed by diabetes mellitus (34.9 %) (Figure 1). The median age was 59 years (IQR=47- 70), 50.9 % were male, 52.3 % belonged to the contributory regime; and 46.6 %, to the subsidized.

The most frequent comorbidities were hyperparathyroidism (56 %) and hypertension (55.4 %). The drugs most frequently used were the erythropoiesis stimulants (84%), followed by medications used for the management of hyperparathyroidism (60.6%). Among the

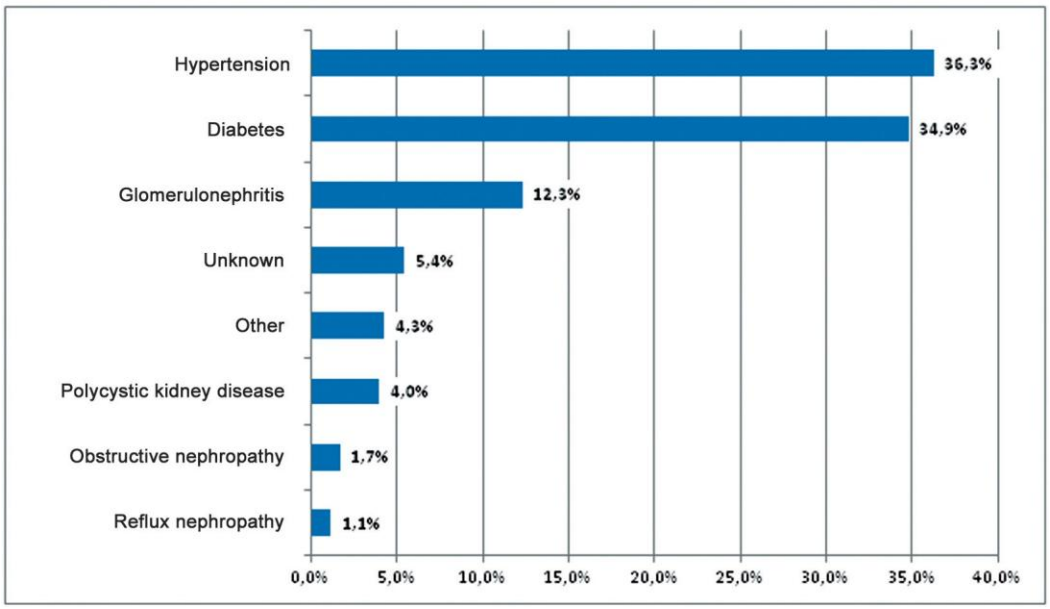

Figure 1. Primary cause of CKD.

antihypertensive agents, the most commonly used were the ARA-II and the calcium antagonists (49.7 % and 43.1 %, respectively). Meanwhile, the analysis of the nutritional status showed that 48 % of patients were in some state of malnutrition: overweight and obesity predominated (27.7 % and 13.4 %, respectively) (Table 1).

Regarding the modality of dialysis therapy, the most frequent was hemodialysis (65.4 %). In addition, it was observed a median time of initiation of renal replacement therapy of 3 years (IQR=2-6). In relation to the thyroid dysfunction defined by alteration of the TSH level, it was evidenced that 25.4% of the population had TSH levels higher than 4.5 µIU/mL. Of this segment, 5.7 % was within the range of hypothyroidism (TSH>10 µIU/mL) (Table 2).

When the distribution of the frequency of thyroid dysfunction stratified by the type of dialysis was compared, it was found that in the peritoneal modality, the prevalence was 31.4%; and in hemodialysis, 22.3% (with no statistically significant differences) (Figure 2). The behavior of the laboratory tests performed shows that the median of hemoglobin was 11.1 g/dL (IQR =10.1-12.0) with a frequency of anemia of 21.7%; for potassium, 4.8 meq/L (IQR =4,2-5,4); for calcium, 8.7 mg/dL (IQR =8.3-9.3); for phosphorus, 4.5 mg/dL (IQR =3.6-5.6); for PTH, 368.5 pg/mL (IQR =191.0-609.0); and for Kt/V, 1.5 (IQR =1,3- 1,7). When comparing the results with the goals of follow-up, it was identified an adequate control of the parameters of hemoglobin (54.3 % of cases), potassium (75.4 %), calcium (64 %), phosphorus (52 %), PTH (22.6 %) and Kt/V (29.4 %) (Table 2).

Comparing the socio-demographic and clinical characteristics, stratified by thyroid dysfunction, it was found that the median age for hypothyroidism was 70 years (IQR =57-80). There was a statistically significant difference when this group was compared with the one that did not have thyroid dysfunction (p=0.0054) and with the group with subclinical hypothyroidism (p=0.0180).

When making the comparison in function of the comorbidities, nutritional status, type of dialysis, time on dialysis and paraclinical tests in adequate control of hemoglobin, potassium, PTH and Kt/V, no statistical differences was found in the different groups analyzed. On the other hand, when comparing the calcium levels of the group of subclinical hypothyroidism with those of the group

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Table 1. General characteristics and antecedents of the patients with CKD-5.

"Age Me (IQR)" 59 (47-70 years)	N	%
Gender		
F	172	49.1
M	178	50.9
RSSS		
Contributory	183	52.3
Subsidized	163	46.6
Special	4	1.1
Comorbidities		
Hyperparathyroidism	212	60.6
HBP	194	55.4
Rheumatologic pathology	21	6.0
Heart failure	15	4.3
Ischemic heart disease	12	3.4
DM	10	2.9
Neoplasms	5	1.4
CVD	2	0.6
Other	35	10.0
Treatment		
Erythropoiesis stimulants	294	84.0
Hyperparathyroidism management	212	60.6
ARAII	174	49.7
Calcium antagonist	151	43.1
Alpha 2 adrenergic	132	37.7
Diuretic	124	35.4
Beta blocker	111	31.7
Insulin	85	24.3
Alpha 1 antagonist	66	18.9
Vasodilator	50	14.3
ACEI	17	4.9
BMI		
Underweight	24	6.9
Normal weight	182	52.0
Overweight	97	27.7
Obesity	47	13.4

without thyroid dysfunction, it was found a statistically significant difference (p=0.0022). Likewise, a statistically significant difference was found when comparing the levels of phosphorus of the group with hypothyroidism with those of the group without thyroid dysfunction (p = 0.0004) and the group with subclinical hypothyroidism (p = 0.0053). (Table 3).

Table 2. Characteristics of the dialysis and control paraclinical tests in patients with CKD-5.

Years on dialysis Me (IQR) 3 (2- 6)	N	%
Type of dialysis		
Automated peritoneal	48	13.7
Manual peritoneal	73	20.9
Hemodialysis	229	65.4
Paraclinical tests		
TSH	2.62 (1.72-4.56)	
Hypothyroidism	20	5.7
Subclinical hypothyroidism	69	19.7
Normal	261	74.6
Hemoglobin	11.1 (10.1-12.0)	
Potassium	4.8 (4.2-5.4)	
Calcium	.8.7 (8.3-9.3)	
Phosphorus	4.5 (3.6-5.6)	
PTH	368.5 (191.0-609.0)	
Kt/V	1.5 (1.3-1.7)	
Paracinical tests in goals		
Kt/V	284	81.1
Potassium	264	75.4
Calcium	224	64.0
Hemoglobin	190	54.3
Phosphorus	183	52.3
PTH	79	22.6

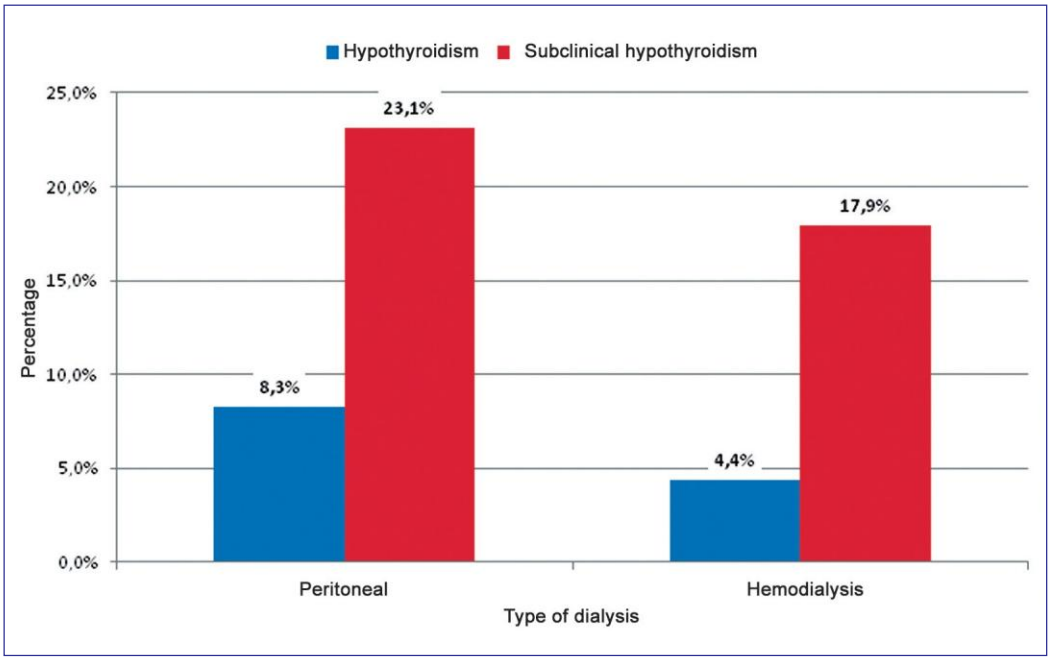

Figure 2. Distribution of thyroid dysfunction stratified by type of dialysis.

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Table 3. Comparison of socio-demographic and clinical characteristics, stratified by thyroid dysfunction by TSH

	Hypothyroidism (N=20)	Subclinical hypothyroidism (N=69)	Normal (N=261)	p-Value*	p-Value†	p-Value‡
Age	70 (57-80)	62 (51-69)	58 (76-69)	0.0054	0.3289	0.0180
F Gender	10 (50.0)	37 (53.6)	125 (47.9)	0.9593	0.4796	0.9764
Comorbidities						
Hyperparathyroidism	11 (55.0)	42 (60.9)	159 (60.9)	0.7773	0.8897	0.8396
HBP	11 (55.0)	39 (56.5)	144 (55.2)	0.8290	0.9545	0.8911
Rheumatologic pathology	2 (10.0)	5 (7.3)	14 (5.4)	0.7233	0.7558	0.9390
Heart failure	0 (0.0)	2 (2.9)	13 (5.0)	0.6364	0.6751	0.9313
Ischemic heart disease	1 (5.0)	7 (10.1)	4 (1.5)	0.7904	0.0015	0.7959
DM	1 (5.0)	2 (2.9)	7 (2.7)	0.9194	0.7459	0.8062
Neoplasms	0 (0.0)	1 (1.5)	4 (1.5)	0.1045	0.5776	0.5264
CVD	0 (0.0)	1 (1.5)	1 (0.4)	0.1045	0.8638	0.5264
Other	1 (5.0)	4 (5.8)	30 (11.5)	0.6004	0.2451	0.6785
Nutritional status						
Underweight	3 (15.0)	7 (10.1)	14 (5.4)	0.2129	0.2528	0.8343
Normal weight	13 (65.0)	29 (42.0)	140 (53.6)	0.4511	0.1144	0.1188
Overweight	3 (15.0)	23 (33.3)	71 (27.2)	0.3521		0.3961 0.1916
Obesity	1 (5.0)	10 (14.5)	36 (13.8)	0.4363		0.1393 0.4529
Years on dialysis Me (IQR)	3 (2-6.5)	4 (2-7)	3 (2-6)	0.9278		0.9632 0.8781
Type of dialysis						
Automated peritoneal	3 (15.0)	10 (14.5)	35 (13.4)	0.8905		0.9684 0.7613
Manual peritoneal	7 (35.0)	18 (26.1)	48 (18.4)	0.1309		0.2103 0.6191
Hemodialysis	10 (50.0)	41 (59.4)	178 (68.2)	0.1555		0.2177 0.6230
Paraclínical tests in goals						
Kt/V	16 (80.0)	56 (81.2)	212 (81.2)	0.8695		0.8625 0.8392
Potassium	14 (70.0)	49 (71.0)	201 (77.0)	0.6614		0.3809 0.8473
Calcium	12 (60.0)	33 (47.8)	179 (68.6)	0.5852		0.0022 0.4796
Hemoglobin	8 (40.0)	36 (52.2)	146 (55.9)	0.2527		0.6793 0.4796
Phosphorus	10 (10.0)	33 (47.8)	140 (53.6)	0.0004		0.4701 0.0053
PTH	5 (25.0)	17 (24.6)	57 (21.8)	0.9578		0.7385 0.7965

* p-Value in the comparison between the group of hypothyroidism and the normal group
† p-Value in the comparison between the group of subclinical hypothyroidism and the normal group;
‡ p-Value in the comparison between the group of hypothyroidism and the group of subclinical hypothyroidism

Discussion

Hypertension, diabetes mellitus and obesity stand out among the causes or risk factors for CKD.[12] It is estimated that the prevalence of hypertension worldwide is 26 %; and of diabetes 6.4%, and they are the two main entities associated with the development of CKD.[12]

In Colombia, it has been observed that 28% of diabetic patients and between 21% and 36% of hypertensive patients develop CKD.[13] Similarly, it was observed in this study that arterial hypertension and diabetes mellitus were the main causes of CKD in more than 60 % of the patients. Meanwhile, the antecedent of overweight or obesity was found in 41 % of cases.

Regarding hypertension as comorbidity, a low percentage was observed in our patients, compared with what was reported by other international studies that show a prevalence of hypertension between 80 % and 85 % in patients with CKD.[14] However, these data are consistent with national reports that estimate a prevalence between 54 % and 67 %.[15]

CKD has been associated with other alterations in metabolism, such as hyperparathyroidism. This alteration was the main comorbidity observed in this study, since it was present in more than half of patients, which is greater than what is described by the international multicenter study DOPPS II, which reported a frequency of 26.7 %.[16] However, is similar to that reported by Douth et al. in Argentina, who found levels of PTH higher than 300 pg/mL in 54.5 % of patients with CKD.[17]

Anemia represents another of the main conditions associated with CKD. It has been estimated that approximately 90 % of patients with GFR less than 30 mL/min/1.73 m^2 have anemia;[18] and although a proportion lower than 30 % with this diagnosis was found in this study, the difference can be attributed to the use of erythropoiesis stimulants in more than 80 % of patients.

Primary hypothyroidism is the main cause of thyroid dysfunction in adults.[19] A higher prevalence is observed in patients with CKD, according to several studies.[7,20,21,22] In the Third National Health and Nutrition Survey of the United States,[23] is estimated that the prevalence of hypothyroidism is 23 % when the GFR is lower than 30 mL/min/ 1.73m^2; and according to the results observed in other studies, it varies according to the modality of dialysis therapy used.

According to Rhee et al., the prevalence of hypothyroidism in patients on hemodialysis is 22 %.[10] Meanwhile, Yung et al. found that it is 15.6 % in patients on peritoneal dialysis.[24] In the present study, it was observed a prevalence similar to that reported at the international level on thyroid dysfunction, especially in a subclinical form and independent of the type of dialysis. It tended to be higher in the group of peritoneal dialysis, in contrast to that of hemodialysis. In addition, it stands out the fact that the majority of patients included in the study were receiving hemodialysis, which represents a situation different to that found by other authors.

When comparing the variables between the groups with thyroid dysfunction, a higher median age was found in the patients with hypothyroidism, with respect to those with subclinical hypothyroidism or normal TSH. The foregoing is consistent with the current evidence, which points out that the risk of thyroid dysfunction increases with age. It increases, usually, by the seventh decade of life.[25,26]

Although it is described in the literature that the serum calcium levels are significantly lower and the serum phosphorus levels are higher in patients with hypothyroidism (compared with the general population);[27,28,29] and despite that, when analyzing the data, a statistically significant alteration thereof was evidenced, this information must be interpreted with caution, due to the alteration of the bone mineral metabolism in CKD, in addition to the presence of secondary hyperparathyroidism.[30]

In this study, a higher prevalence of thyroid dysfunction was observed in patients on dialysis therapy (compared with the general population).[19] However, there was a limitation regarding the precise diagnosis of clinical and subclinical

hypothyroidism, since not enough levels of thyroid hormones were available (and, as demonstrated in some studies, low levels are associated with increased mortality).[31,32] This condition occurred, although it is clearly described that, in CKD, the TSH is the clinical gold standard to evaluate the thyroid function (since the thyroid hormones are affected by the lower conversion of T4 into FT3, the increased conversion into RT3, the displacement from their protein binding site and the decrease in the albumin level). Therefore, the interpretation is subject to confusion.[4,8] Even so, the recognition of this entity is important because, as demonstrated in several studies, it is related to the increase in mortality, mainly of cardiovascular origin.[8,10,33]

Considering the foregoing, it is important to conduct studies of analytical design, with the measurement of the profile of thyroid hormones, for a correct diagnostic approach. According to this diagnosis, a therapeutic management should be established, since, as shown in previous studies, treatment can reduce the mortality of these patients[8] and can improve renal function.[21,34]

Currently, experimental studies to determine the impact of hormone replacement on cardiovascular disease and mortality are needed, since levothyroxine has a narrow therapeutic range and, in patients with advanced CKD, it can lead to complications such as increased protein catabolism, alterations in bone density and arrhythmias.[35]

Conclusions

- The prevalence of thyroid dysfunction was higher in patients on dialysis therapy, compared with the general population. For this reason, it is recommended to carry out additional studies that include a thyroid profile, in order to perform an adequate categorization of the alteration.
- It is recommended to conduct a long-term experimental analytical study to determine the impact of the levothyroxine substitution in this group of patients, since there is currently little information on the impact of this therapy.
- The main comorbidity in these patients was hyperparathyroidism, which is why it is indispensable to conduct a study on the prevalence of this condition and the factors associated with the failure in its treatment.

Conflict of interest

The authors declare that they do not have any current or potential 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 to privacy and informed consent

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

Contribution of the authors

All authors participated in the process corresponding to the elaboration of the article.

1. Idea; 2. Pilot test 3. Collection of the information; 4. Writing; 5. Analysis.

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