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Epidemiology of chronic kidney disease in the Spanish paediatric population. REPIR II Project

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ABSTRACT

Objective: A national registry of children with Chronic Kidney Disease (CKD) was started in 2007. We analize it to know the incidence, prevalence, demography, etiology, clinical and metabolic state of the children with CKD, in stages 2-5 pre-dialysis, and complying with the K/DOQI guidelines. **Material and methods:** In the REPIR II 46 centers distributed throughout the Spanish geography are involved. To classify and evaluate comorbidity of the disease, the Clinical Practice Guidelines K/DOQI criteria are used. Each center provides an annual developmental data of each patient which is recorded in a On-line database. **Inclusion criteria:** patients with CKD who are between stage 2 and 5 in predialysis and which are 18 years old or less. **Results:** In 2008 there were 605 patients with CKD, the incidence was 8.66 per million of pediatric population (pmpp) and the prevalence was 71.06 pmpp. Structural anomalies was the primary cause of CKD (59% of the cases). The percentage of glomerular diseases was very low (3%). There was a clear predominance of males (66%) and Caucasian race (88%). Mean GFR was 52 ± 2 ml/min/1.73 m^2 with 82% of them in stage 2 and 3. The prevalence of anaemia was 30%. Only 19% of our patients had hypertension and only 17% of them fulfilled the 4 recommendations for calcium-phosphorus metabolism of K/DOQI Guidelines. Mean height Z-Score was —1.03 ± 2. There were 136 patients (25%) who had a mean height Z-

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Score of size ≤—1.88. In a multivariate logistic regression analysis only a meaningful relationship between age and height was identified. All the children under 2 years old had a 40% higher probability of having a short height (OR = 1.40; P <0.01). The percentage of malnutrition (BMI Z-Score ≤1.88) was 7%, mostly in the 0-2 years old group. **Conclusions:** We report the first study that performs a prospective analysis of incidence, prevalence, etiology and comorbidity of CKD in the pediatric population of the Spanish State. Given the short life of this record the data presented is provisional and may suffer meanful changes in coming years.

Key words: Chronic renal disease. Pediatric population. Epidemiology. Incidence. Prevalence. Comorbidity

Epidemiología de la enfermedad renal crónica no terminal en la población pediátrica española. Proyecto REPIR II

RESUMEN

Objetivo: *Describir el funcionamiento del Registro Español Pediátrico de Insuficiencia Renal (REPIR II), dar a conocer la epidemiología de la enfermedad y estudiar aquellos factores que puedan influir en el curso de ésta.* ***Material y métodos:*** *En el REPIR II participan 46 centros distribuidos por toda la geografía española. Para la clasificación y la valoración de la comorbilidad de la enfermedad, hemos utilizado los criterios de las Guías de Práctica Clínica K/DOQI. Cada centro aporta, con una periodicidad anual, los datos evolutivos de cada paciente, que quedan registrados en una base de datos on-line.* ***Criterios de inclusión:*** *Pacientes diagnosticados de enfermedad renal crónica (ERC) que se encuentren entre el estadio 2 y 5 en prediálisis y con una edad igual o inferior a 18 años.* ***Resultados:*** *En el año 2008 se habían incluido 605 pacientes de 37 centros; la incidencia de la ERC no terminal era de 8,66 por millón de población (ppm) menores 18 años y la prevalencia de 71,06. La patología estructural era la primera causa de ERC (59% de casos). El porcentaje de glomerulopatías fue muy reducido (3%). Había un claro predominio de hombres (66%) y de la raza caucásica (88%). El valor medio del GFR era de 52 ± 2 ml/min/1,73 m², con un 82% de pacientes en estadios 2 y 3. La prevalencia de la anemia era del 30%. Solamente el 19% de nuestros pacientes presentaban HTA y únicamente el 17% de ellos cumplían las cuatro recomendaciones de las Guías K/DOQI sobre el metabolismo calcio-fósforo. El valor medio global del Z-Score de la talla era del —1,03 ± 2. Había 136 pacientes (25%) que tenían un Z-Score de la talla ≤1,88. En un análisis de regresión logística multivariante, sólo se detectó una relación significativa entre la edad y la talla baja. Los menores de 2 años tenían una probabilidad un 40% mayor de tener una talla baja (OR = 1,40; p <0,01). El porcentaje de malnutrición (Z-Score de IMC ≤1,88) era del 7%, la mayoría en el grupo de edad de 0-2 años.* ***Conclusiones:*** *Presentamos el primer estudio que realiza un análisis prospectivo sobre la incidencia, prevalencia, etiología y comorbilidad de la ERC en la población pediátrica del estado español. Teniendo en cuenta la corta vida de este registro, los datos presentados son provisionales, y pueden estar sometidos a cambios importantes en los próximos años.*

Palabras clave: *Enfermedad renal crónica. Población pediátrica. Epidemiología. Incidencia. Prevalencia. Comorbilidad*

INTRODUCTION

Chronic kidney disease (CKD) in children is rare. Nevertheless, when it occurs its effects are devastating to the child's development, generating high morbidity.

When diagnosed, most patients are in little advanced stages of the disease, in which therapeutic interventions to change its course can still be applied. In a small number of patients the disease progresses every year into established chronic kidney disease (ECKD), where the only possible treatment is replacement therapy (dialysis-transplant). Hence, early diagnosis is of paramount importance.[1]

The information on the characteristics of CKD in children is quite limited and has been preferably extracted from patients who were in terminal stages of the disease.[2,3]

The data available concern small populations in specific geographic areas, which are not always related to the general population. In the existing records, the methodology used to classify and establish a ranking of kidney diseases has not been uniform, which has hampered the comparisons of the disease characteristics in the different geographic areas.[4,6]

The existing registries include the European Dialysis and Transplant Association (EDTA), which currently collects data from 12 European registries of terminal patients and patients on replacement therapy (dialysis-transplant),[7] the Australia-New Zealand Registry,[8] the Lorraine Registry in France and the Chilean Registry, among others. The Japanese Society of Paediatric Nephrology has provided very valuable reports on CKD.

The American Registry, that is, the Registry of the North American Paediatric Renal Trials and Collaborative

Studies (NAPRTCS)[9] began in 1987 with the aim of collecting data from most paediatric renal transplant centres in the USA, Canada, Mexico and Costa Rica. In 1992, data of patients who were on dialysis were also included. Since 1994, all patients under 20 years of age with non-terminal CKD and GFR <75 ml/min/1,73 m^2 have been included in the registry. In this context, on 31st December 2008, 7,037 patients with non-terminal CKD had already been included in the registry. Participation in this registry is voluntary, and its main disadvantage is that it only includes approximately 75% of all American patients with CKD.

In 2003, the data of the Italian registry ITALKID[10] were published. This is a prospective project that includes all Italian paediatric patients with CKD. It is the most comprehensive project on the epidemiology of CKD in children. ITALKID began in 1990, and it includes a total child population of 16.8 million children.

In 2007, the Spanish Association of Paediatric Nephrology (AENP) launched the Spanish Paediatric Registry of Renal Failure (REPIR II), which is designed to include all Spanish paediatric patients with non-terminal CKD. The aims of this registry are to assess the incidence and prevalence of CKD in children, describe the natural history of the disease, explore the factors that may influence the course of the disease and develop a standard protocol for the prevention and treatment of these patients.

This paper describes the characteristics of the nascent REPIR II Project and provides the first data on the incidence and prevalence of non-terminal CKD in Spanish children.

MATERIALS AND METHODS

In 2007, a committee was created within AENP to carry out the REPIR II Project. This committee is composed of a chairperson, two coordinators and ten representatives of all the centres participating in the project. The number of participating centres is 46 and these are distributed across Spain, representing all the autonomous regions that make up the Spanish State. At each centre there is a paediatrician responsible for monitoring all children with kidney disease in the region concerned, who is the researcher responsible for including in the registry all patients with non-terminal CKD who meet the inclusion criteria. Furthermore, this paediatrician has the responsibility to contribute to the registry annually, by including the developmental results of each of his or her registered patients. These data should refer to the last consultation prior to 31st December of the current year.

Classification of chronic kidney disease

In this registry we have adopted the CKD classification described by the Clinical Practice Guidelines (CPG) of the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI guidelines)[11] which classify the severity of the disease into five stages: stage 1, where the GFR is >90 ml/min/1.73 m^2; stage 2 where it is between 89 and 60 ml/min/1.73 m^2; stage 3 where it is between 59 and 30 ml/min/1.73 m^2; stage 4 where it is between 29 and 15 ml/min/1.73 m^2; and stage 5 if it is <15 ml/min/1.73 m^2.

Inclusion criteria

Only children whose age does not exceed 18 years and have been diagnosed with CKD between stage 2 and stage 5 of the KDOQI guidelines classification can be entered in the registry. Following the start of the replacement therapy (dialysis or transplant), and although the data is stored in the database, the patient should be moved to another database, that is, the REPIR I, which records only those cases that are on a dialysis-transplant programme.

Since the KDOQI guidelines do not allow for including patients younger than 2 years of age, to know the stage of kidney disease of these children we extrapolated the percentage of loss of kidney function in each stage of the KDOQI guidelines, taking into account the reference values of GFR in children between 0 and 24 months of age.

To include a patient in the registry it is also necessary that the decrease in GFR is maintained for at least 3 months, thus avoiding to register patients who recover their function and do not, therefore, meet the inclusion criteria.

The assessment of GFR is performed according to the Schwartz formula[12]:

$$\text{GFR in ml/min/1.73 m}^2 = K \times T / PCr$$

where: K is a constant whose value varies with age (in <2 years its value is 0.45; from 2 to 16 years it is 0.55; and from 16 to 21 years it is 0.70 in men and 0.55 in women), T is the length in cm and PCr is the concentration of creatinine in the blood expressed in mg/dl.

In the database it is also possible to assess the GFR using cystatin C according to the Filler formula.[13] However, the criterion for inclusion of a patient is based solely on the GFR estimated with the Schwartz formula.

To define the presence of anaemia we followed the criteria of the KDOQI guidelines, which use the reference values for haemoglobin (Hb) of the NHANES III,[14] considering that a patient has anaemia when his or her Hb falls below the 5th percentile for his or her age and gender.

To define the presence of arterial hypertension (HTN) we used the reference values for blood pressure (BP) of the Task Force, which were obtained from a normal population with an age not exceeding 18 years.[15] We considered that a patient is hypertensive when systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) are above the 90th percentile for his or her gender, age and height.

To assess the state of the calcium-phosphorus metabolism, we used the criteria recommended by the KDOQI guidelines[16] for four parameters (calcium, phosphorus, Ca x P product and PTH), which should be maintained between the reference ranges listed in these guidelines, according to age and the stage of CKD.

Database

The registry has an online database designed specifically for that purpose, which can be accessed using a password. The Registry Commission within AENP manages this database. To register a patient it is necessary to have the informed consent of parents or guardians. This database complies fully with current legislation regarding privacy and data protection.

The database has four main windows. The first includes demographic data: patient's identification code, date of diagnosis, date of data collection, date of birth, place of residence, drop-down list of diagnoses predefined on primary nephropathy (this ensures that there is uniformity in the diagnoses applied to each patient), presence of extra-renal pathology and family history.

The second window includes anthropometric and laboratory parameters: weight, height, body surface area, BMI: body mass index, head circumference (in children under 3 years of age), BUN, urea, creatinine, GFR estimated according to the Schwartz formula, GFR estimated according to the cystatin formula, creatinine clearance in 24-hour urine, BP, haematocrit (Hct), Hb, ferritin, transferrin saturation index (TSI), calcium, phosphorus, PTH and 25-(OH) vitamin D.

The third window registers the treatments received by each patient: statins, preferences of haemodialysis, patients on phosphate binders, vitamin D, 1.25-(OH) vitamin D, iron, erythropoietin, sodium bicarbonate, ion-exchange resins, sodium chloride, growth hormone, folic acid, allopurinol, nasogastric/gastrostomy, nutritional supplements, fluorhydrocortisone, hypotensive and antiproteinuric medicines.

The fourth window shows the reason and/or fate of patients who leave the database: ECKD, loss during follow-up, transfer to another centre, transfer to the adult nephrology department, death, recovery of kidney function and further loss of kidney function after having recovered it.

Finally, it should be noted that, given the short history of the REPIR II Project, this study only reflects the incidence and prevalence data of patients who were registered by the end of 2008.

RESULTS

37 centres with a total of 605 registered patients had been included by 31st December 2008. Of these patients, 74 (12%) were diagnosed with CKD in 2008. The average age of all patients at diagnosis was 3.9 ± 5 years, while at the time of the last consultation it was 9.2 ± 6 years. 59%, 13%, 22% and 6% of the patients had an age at diagnosis of <2, 3-5, 6-12 and 13-18 years, respectively. However, during the last consultation for the same age groups, the percentage was 18%, 18%, 34% and 31%, respectively. The difference between the average age at the last consultation and at diagnosis is high (± 5 years), indicating that a significant number of patients registered have already a prolonged evolution of several years. 66% of the patients (400 cases) were male and the rest were female (205 cases, 34%). The quotient of men and women was 1.95. 88% of the patients were Caucasian, 6% Hispanic, 3% Arabs, 1% Black and 2% were of other races.

At the time of the study, in 2008, on a total Spanish population of 46,157,822 million inhabitants and a population of 11,296,170 million with an age equal to or less than 18 years, the incidence and prevalence of non-terminal CKD was 8.66 ppm and 71.06 ppm under the age of 18 years, respectively.

Primary nephropathy

Structural abnormalities were the most common primary nephropathy (356 patients, 59%). There were 19 cases (3%) with a glomerulopathy, 86 (14%) with a hereditary or cystic disease, 67 (11%) with vascular disease and 75 (12%) with other nephropathies. Table 1 shows the primary nephropathies in relation to the age of the patients. It is evident that in all age groups the

Table 1. Primary nephropathy at diagnosis

	<2 years		3-5 years		6-12 years		13-18 years		Total	
Primary nephropathy	No	(%)	No	(%)	No	(%)	No	(%)	No	(%)
Structural abnormalities	247	(69)	38	(50)	60	(44)	11	(33)	356	(59)
Glomerulonephritis primary and secondary to systemic diseases	2	(1)	4	(5)	8	(6)	5	(15)	19	(3)
Cystic and hereditary diseases	45	(13)	15	(20)	22	(16)	4	(12)	86	(14)
Vascular diseases	46	(13)	6	(8)	12	(9)	3	(9)	67	(11)
Other	19	(5)	13	(17)	33	(24)	10	(30)	75	(13)
Total No of patients	**359**	**(60)**	**76**	**(13)**	**135**	**(22)**	**33**	**(6)**	**603**	**(100)**

prevalence of structural abnormalities remained the same while the number of glomerulopathies was small. 76% of the structural abnormalities occurred in men while glomerulopathies were more common in women (58%). The remaining kidney diseases were distributed equally in both genders.

Renal function

Table 2 shows the renal function in all patients together at the time of the last consultation in 2008 and distributes them according to each age group and stage of the disease. The mean GFR of all patients was 52 ± 2 ml/min/1.73 m^2. 82% of all patients were in stage 2 or 3, that is, the CKD of patients registered up to that point in time was mild-moderate.

Anaemia

The mean values for Hct, Hb, ferritin and TSI when assessed for all patients together was 37.5%, 13 ± 2 g/dl, 91 ± 109 ng/ml and 25 ± 14%, respectively. In addition, 30% of patients had anaemia. As the disease progressed, the percentage of anaemia increased, reaching 14%, 33%, 58% and 54% in stages 2, 3, 4 and 5, respectively. The presence of anaemia in different age groups was irregular and occurred in 31%, 19%, 26% and 39% of children aged <2, 3-5, 6-12 and 13-18 years old, respectively.

Table 3 shows the anaemic and non-anaemic patients according to age and treatment received. 33% (57 patients) of the anaemic patients did not receive any treatment and 67% (117 patients) were inadequately treated with iron and/or erythropoietin. 34% of non-anaemic patients (139 patients) received some type of treatment.

Arterial hypertension

Table 4 shows the prevalence of HTN in registered patients with regard to age groups and the stage of the disease. Notably, the overall percentage of patients with HTN was 19%, and its presence was not related to age or

Table 2. CKD stage at the time of the last consultation in relation to patient age

	0-2 years			3-5 years			6-12 years			13-18 years			Total		
	No	**%**	**GFR**	**No**	**%**	**GFR**	**No**	**%**	**GFR**	**No**	**%**	**GFR**	**No**	**%**	**GFR**
Stage 2	26	25	63 (9)	48	45	72 (8)	91	45	73 (8)	87	52	73 (8)	252	42	72 (9)
Stage 3	48	45	40 (9)	40	38	48 (8)	82	40	47 (9)	70	42	47 (9)	240	40	46 (9)
Stage 4	23	22	19 (6)	15	14	24 (4)	26	13	24 (4)	25	15	22 (5)	089	15	22 (5)
Stage 5	10	09	09 (4)	03	03	12 (1)	04	02	10 (5)	07	04	12 (3)	024	04	10 (4)
Total	**107**	**18**	**38 (20)**	**106**	**18**	**55 (20)**	**203**	**34**	**55 (20)**	**168**	**31**	**57 (21)**	**605**	**100**	**52 (21)**

CKD: chronic kidney disease; No: number of patients in each stage within each age group; %: percentage of patients in each stage within each age group; GFR: mean value and (SD) standard deviation of the glomerular filtration rate, in ml/min/1.73 m^2, in each stage within each age group.

Table 3. Presence of anaemia at the time of the last consultation in relation to age and treatment received

	Patients with anaemia										Patients without anaemia									
	No treatment		Fe		EPO		Fe + EPO		T		No treatment		Fe		EPO		Fe + EPO		T	
Age	No	(%)	No	(%)	No	(%)	No	(%)	No	(%)	No	(%)	No	(%)	No	(%)	No	(%)	No	(%)
0-2 years	3	(9)	9	(28)	4	(13)	16	(50)	32	(100)	29	(42)	25	(36)	1	(2)	14	(20)	69	(100)
3-5 years	7	(37)	6	(32)	1	(5)	5	(26)	19	(100)	47	(57)	26	(32)	0	(0)	9	(11)	82	(100)
6-12 years	16	(30)	21	(40)	3	(6)	13	(25)	53	(100)	109	(73)	28	(19)	3	(2)	10	(7)	150	(100)
13-18 years	31	(44)	18	(26)	2	(3)	19	(27)	70	(100)	84	(79)	10	(9)	1	(1)	12	(11)	107	(100)
Total	**57**	**(33)**	**54**	**(31)**	**10**	**(6)**	**53**	**(30)**	**174**	**(100)**	**269**	**(66)**	**89**	**(22)**	**5**	**(1)**	**45**	**(11)**	**408**	**(100)**

Fe: treatment with iron; EPO: treatment with erythropoietin; Fe + EPO: treatment with iron and erythropoietin..

stage of the disease. 63% of glomerulopathies, 31% of hereditary and cystic diseases, 20% of vascular diseases and 16% of the group of patients with other diseases had HTN. The aetiology group, which had the smallest number of hypertensive patients, was the one with structural abnormalities (14%).

6% of patients with HTN (7/114) were not receiving any hypotensive treatment. ACE inhibitors and/or ARBs were the most used medicines in patients who received treatment (71% of the patients treated). 59% received a single medicine, 33% 2 medicines and 8% 3 or 4 medicines, with an average of 1.52 medicines/patient.

Phosphocalcic metabolism

The average values of calcaemia, phosphataemia, Ca x P product and PTH in all patients evaluated together were 9.8 ± 0.6 mg/dl, 4.7 ± 1.0 mg/dl, 46 ± 10 mg/dl and 104 ± 113 ng/ml, respectively.

Table 5 shows that when the assessment is made based on age, calcaemia does not change significantly. Phosphataemia and the Ca x P product present a slight decrease with age. The PTH remains the same without significant differences in all age groups, except for the group between 0-2 years of age in which it is higher.

The same does not happen when the assessment of these parameters is carried out according to the stage of the disease. Table 5 shows that while calcaemia remains normal and similar in almost all stages, phosphataemia, the Ca x P product and the PTH rise significantly as the severity of the disease increases. 17% of the patients complied with the KDOQI recommendations on phosphocalcic metabolism, keeping these four parameters within the recommended ranges. 35% complied with three of the recommendations, 34% with two, 8% with one and 1% did not comply with any recommendation.

Growth

The overall mean of the size Z-Score in all patients in the last consultation was -1.03 ± 2. The growth deficit was inversely related to the patients' age. Table 6 shows that the age group with the worst growth was 0-2 years. On

Table 4. Frequency of hypertension at the time of the last consultation in relation to age and severity of CKD

	Hypertensive		Normotensive		Total			Hypertensive		Normotensive		Total	
Age	**No**	**(%)**	**No**	**(%)**	**No**	**(%)**	**Estadio**	**No**	**(%)**	**No**	**(%)**	**No**	**(%)**
0- 2 years	19	(18)	86	(82)	105	(100)	2	35	(14)	215	(86)	250	(100)
3-5 years	17	(16)	88	(84)	105	(100)	3	49	(21)	189	(79)	238	(100)
6-12 years	46	(23)	155	(77)	201	(100)	4	25	(25)	63	(72)	88	(100)
13-18 years	37	(17)	157	(83)	189	(100)	5	5	(21)	19	(79)	24	(100)
Total	**114**	**(19)**	**486**	**(81)**	**600**	**(100)**	**Todos**	**114**	**(19)**	**486**	**(81)**	**600**	**(100)**

HTN: arterial hypertension; CKD: chronic kidney disease.

Table 5. Phosphocalcic metabolism: mean and standard deviation values of the various parameters at the time of the last consultation in relation to age and severity of CKD

Age	Calcaemia (mg/dl)	Phosphataemia (mg/dl)	Ca x P (mg/dl)	PTH (pg/ml)	Stage	Calcaemia (mg/dl)	Phosphataemia (mg/dl)	Ca x P (mg/dl)	PTH (pg/ml)
0- 2 years	9.9 (0.7)	5.3 (1.2)	53 (12)	129 (147)	2	9.7 (0.6)	4.4 (0.7)	43 (07)	66 (44)
3-5 years	9.9 (0.6)	4.7 (0.8)	47 (09)	93 (82)	3	9.8 (0.5)	4.7 (0.8)	46 (09)	92 (62)
6-12 years	9.8 (0.5)	4.7 (0.9)	46 (08)	96 (78)	4	9.7 (0.7)	5.3 (1.3)	52 (13)	204 (195)
13-18 years	9.4 (0.6)	4.3 (0.8)	41 (08)	99 (144)	5	10.0 (1.1)	5.8 (1.6)	57 (17)	292 (511)
Total	**9.8 (0.6)**	**4.7 (1.0)**	**46 (10)**	**104 (113)**	**Total**	**9.8 (0.6)**	**4.7 (1.0)**	**46 (10)**	**164 (203)**

CKD: Chronic kidney disease; P x Ca: calcium-phosphorus. The values between brackets correspond to the standard deviation.

the other hand, the more the disease advanced, the worse the growth became, with the patients in stage 5 having the worst growth rate.

However, when performing a multivariate logistic regression analysis, in which various factors were analysed (age, gender, race, primary nephropathy, CKD stage, presence of anaemia, presence of acidaemia, value of PTH and value of the Ca x P product), only age significantly predicted patients with short stature. All the children under 2 years old had a 40% higher probability of having short stature (OR = 1.40; P <0.01).

136 patients (25%) had a size Z-Score of -1.88 or worse. It should be noted that within this group, 82% of the patients were not treated with growth hormone.

7% (42 patients) of the patients were malnourished, with a BMI Z-Score of -1.88 or worse. In addition, most of them were in the 0-2 years age group. That is, the children under two years of age were those with poorer growth and the most malnourished.

DISCUSSION

This is the first registry that makes a prospective analysis of the incidence, prevalence, aetiology and comorbidity of CKD in the Spanish paediatric population.

The natural history of kidney disease is variable and at times unpredictable. However, in children, there is usually a continuing deterioration, which often leads to ECKD. The progression of kidney disease is greater during the two periods of rapid growth, that is, early childhood and puberty, in which the sharp increase in body mass results in an increase in the demand for filtration of the remaining nephrons. Hormonal changes during puberty contribute to the rapid deterioration of glomerular filtration, and may also influence genetic, family, or ethnic factors. Finally, other factors associated with the progression of CKD are also present in adulthood: AHT, proteinuria, obesity, dyslipidaemia, anaemia or alterations in the phosphocalcic metabolism.[17]

In 2008, the incidence of non-terminal CKD in our centres was 8.66 ppm of the population under 18 years of age, while the prevalence was 71.06. These figures are very close to those mentioned in the Italian registry in 2003 (12.1 and 74.07 ppm <18 years of age of incidence and prevalence, respectively).[10] However, given the short history of the REPIR II Project, these data are provisional, and in the coming years, they will likely undergo changes that could become important.

As in all paediatric series, the structural pathology, and therefore the congenital pathology, is the leading cause of

Table 6. Patient growth the at the time of the last consultation in relation to age and severity

Age	*Z-Score* Height	*Z-Score* BMI	Stage	*Z-Score* Height	*Z-Score* BMI
0-2 years	–1.81 (1.73)	–1.18 (1.37)	2	–0.71 (1.44)	–0.08 (1.15)
3-5 years	–1.02 (1.16)	–0.11 (1.08)	3	–1.04 (1.31)	–0.41 (1.06)
6-12 years	–0.81 (1.40)	–0.00 (0.98)	4	–1.48 (1.54)	–0.53 (1.10)
13-18 years	–0.84 (1.41)	–0.24 (0.90)	5	–2.66 (1.58)	–0.65 (1.41)
Total	–1.03 (1.47)	–0.30 (1.13)	**Total**	–1.03 (1.47)	–0.30 (1.13)

BMI: body mass index. The values between brackets correspond to the standard deviation.

CKD, reaching 59% in our series, 56% in the American registry and 67.5% in the Italian one. This results in the age at diagnosis to be under 6 years old in most cases (72% in our registry). The fact that the difference between the average age at the last consultation in 2008 and the age at diagnosis of CKD is high (± 5 years) indicates that a significant number of patients registered in our database now have a prolonged evolution of several years. On the other hand, given the characteristics of the Spanish population, it is comprehensible that we found a clear predominance of Caucasians in our series (88%).

The percentage of glomerulopathies as a cause of non-terminal CKD shown in Table 1 is very small (3%) and contrasts with the one that occurs in ECKD, which may reach 20%. This is because the evolution of glomerulopathies is much faster than that of renal dysplasias, many of which reach ECKD in adulthood.[18]

The mean value of GFR in our patients is 52 ± 2 ml/min/1.73 m^2, with 82% in stages 2 and 3, whereas in the NAPRTCS and the ITALKID it is 39 and 42 ml/min/1.73 m^2, respectively. That is, the patients in our registry have a milder CKD than those of the other two registries (Table 2). This may be related, at least in part, to the fact that paediatric patients with CKD are referred in our centres much earlier (from stage 1) from primary care services to paediatric nephrology departments.

The information available in the medical literature on the comorbidity associated with CKD is very small, while only the NAPRTCS offers annual data on this subject. In this study, we examined the prevalence of anaemia and HTN, as well as the level changes in the calcium-phosphorus metabolism and the growth that occurs in these patients.[9,16,19]

Anaemia is a common complication in advanced CKD and is associated with an increase in morbidity and mortality risk.[18,20,21] The prevalence of anaemia in our patients was 30%. This percentage increased with the severity of CKD, in such manner that in the pre-dialysis stages 4 and 5, it was 58% and 54%, respectively. We found that our anaemic patients were being treated improperly, and that 33% of them received no treatment while the rest received insufficient treatment (Table 3).

Arterial hypertension is a known factor of cardiovascular risk and CKD progression in adults, and although there are no prospective data on children,[22,23] it is logical to think that it is also true in children. In our series, only 19% of our patients had arterial hypertension. This percentage was much lower than that of the American registry, which concerns a 48% prevalence of hypertension.[9] Although this datum has to be confirmed in the coming years, two of the factors that could explain it would be that the most common aetiology among our patients was structural disease, which is not usually associated with HTN, and that most children had mild to moderate kidney disease. On the other hand, at present, we cannot exclude that we have under-diagnosed cases of HTN, since there are indications that there was no unanimity among the various participating centres when defining HTN (Table 4). We only found a relationship between the prevalence of HTN and the aetiology of CKD, in such manner that 63% of the children with glomerulopathy had HTN. We were unable to show an association with age or the stage of CKD. 94% of patients with hypertension received hypotensive treatment and 71% of them were treated with ACE inhibitors and/or ARBs.

Abnormalities in the bone mineral metabolism are a universal finding as they progress to CKD. In children, they also have a deleterious effect on growth.[24,25] Although in our patients the mean values for calcaemia, phosphataemia, the Ca x P product and PTH, which were valued together, were within the limits of the recommendations of the KDOQI guidelines,[26-28] when we analysed the same parameters taking into account the age and the stage of the disease, only 17% met the four recommendations, while most only met three (35%) or two (34%) recommendations. Similar to other authors, we found that the recommendations of the KDOQI guidelines on the management of changes in the Ca-P metabolism are difficult to fulfil (Table 5).

Growth retardation is a common problem in children with CKD and it is associated with a significant morbidity and mortality rate.[18] The final height of children with early-stage CKD is one of the most important factors in their rehabilitation.[18,29-31] The overall mean of the size Z-Score at the last consultation of our patients was -1.03 ± 2. There were 136 patients (25%) who had a size Z-Score of <1.88, a figure that contrasts with those of the American registry, where the number of patients with growth retardation was higher (36%). On the other hand, we found that the growth deficit was inversely related to age and the severity of CKD, presenting a worse growth in younger patients (0-2 years age group) and in those who were in stage 5 pre-dialysis (Table 6). However, when performing a multivariate logistic regression analysis, only age significantly predicted patients with short stature. All the children under 2 years old had a 40% higher probability of having short stature (OR = 1.40; P <0.01).

The percentage of malnutrition (BMI Z-Score <1.88) in our series was 7%, mostly in the 0-2 years age group. That is, the children under two years of age were those with poor growth and the most malnourished.

To conclude, this paper presents the first data from 2008 of the Spanish Registry on non-terminal CKD in children from the REPIR II Project. This is the first study that performed a prospective analysis of the incidence, prevalence, aetiology and comorbidity of CKD in the Spanish paediatric population. Given the short history of this registry, the data presented are provisional and may undergo significant changes in the coming years.

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REFERENCES

1. Warady BA, Chadha V. Chronic kidney disease in children: the global perspective. Pediatric Nephrol 2007;22:1999-2009.
2. Pistor K, Olbing H, Scharer K. Children with chronic renal failure in the Federal Republic Germany: Epidemiology, modes of treatment, survival. Clin Nephrol 1985;23:272-7.[Pubmed]
3. Esbjorner E, Aronson A, Berg U, Jodal U, Linne T. Children with chronic renal failure in Sweden 1978-1985. Pediatr Nephrol 1990;4:249-52.[Pubmed]
4. Lagomarsimo E, Valenzuela A, Cavagnaro F, Solar E. Chronic renal failure in pediatrics Chilean survey. Pediatr Nephrol 1999;13:288-91.[Pubmed]
5. Deleau J, Andre JL, Briancon S, Musse JP. Chronic renal failure in children: an epidemiological survey in Lorraine (France). Pediatr Nephrol 1994;8:472-6.[Pubmed]
6. Esbjorner E, Berg U, Hansson S. Epidemiology of chronic renal failure in children: a report from Sweden 1986-1994. Pediatr Nephrol 1997;11:438-42.[Pubmed]
7. Van der Heijden BJ, Van Dijk PC, Verrier-Jones K, Jager KJ, Briggs JD. Renal replacement therapy in children: data from 12 registries in Europe. Pediatr Nephrol 2004;19:213-21.[Pubmed]
8. Australia and New Zealand Dialysis and Transplant Registry. The 28th annual report. 2005 report-data to 2004. http://www.anzdata.org/
9. North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). 2008 annual report. Rockville, MD: The EMMES Corporation, 2008.
10. Ardissino G, Dacco V, Testa S, Bonaudo R, Claris-Appiani A, Taioli E, et al. Epidemiology of chronic renal failure in children: data from the ItalKid project. Pediatrics 2003;111:e382-e387.[Pubmed]
11. National Kidney Foundation Clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. K/DOQI clinical practice guidelines. Am J Kidney Dis 2002;39:S1-S266.[Pubmed]
12. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 1976;58:259-63.[Pubmed]
13. Filler G, Lepage N. Should the Schwartz formula for estimation of GFR be replaced by cystatin C formula? Pediatr Nephrol 2003;18:981-5.[Pubmed]
14. National Kidney Foundation (2006) KDOQI. II. Clinical practice recommendations for anemia in chronic kidney disease in children. Am J Kidney Dis 2006;47(5 Suppl 3):S86-S108.[Pubmed]
15. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. Pediatrics 2004;114 (2 Suppl 4th Report):555-76.[Pubmed]
16. National Kidney Foundation Clinical practice guidelines for bone metabolism and disease in children with chronic kidney disease. National Kidney Foundation KDOQI Kidney Disease Outcomes quality initiative. Am J Kidney Dis 2005;46(4)Suppl 1:S8-S121.
17. Furth SL, Cole SR, Moxey-Mims M, Kaskel F, Mak R, Schwartz G, et al. Design and methods of the Chronic Kidney Disease in Children (CKiD) prospective cohort study. Clin J Am Soc Nephrol 2006;1(5):1006-15.[Pubmed]
18. Broyer M, Chantler C, Donckerwolke R, Ehrich JHH, Rizzoni G, Scharer K. The pediatric registry of the European Dialysis and Transplantation Association: 20 years'experience. Pediatr Nephrol 1993;7:758-68.[Pubmed]
19. Wong H, Mylrea K, Feber J, Drukker A, Filler GP. Prevalence of complications in children with chronic kidney disease according to K/DOQI. Kidney Int 2006;70(3):585-90.[Pubmed]
20. Warady BA, Ho M. Morbidity and mortality in children with anemia at initiation of dialysis. Pediatr Nephrol 2003;18(10):1055-62.[Pubmed]
21. Gerson A, Hwang W, Fiorenza J, Barth K, Kaskel F, Weiss L, et al. Anemia and health-related quality of life in adolescents with chronic kidney disease. Am J Kidney Dis 2004;44(6):1017-23.[Pubmed]
22. Franscini LM, Von Vigier RO, Pfister R, Casaulta-Aebischer C, Fossali E, Bianchetti MG. Effectiveness and safety of the angiotensin II antagonist irbesartan in children with chronic kidney diseases. Am J Hypertens 2002;15(12):1057-63.[Pubmed]
23. Wuhl E, Schaefer F. Therapeutic strategies to slow chronic kidney disease progression. Pediatr Nephrol 2008;23(5):705-716. Epub 2008 Mar 12.[Pubmed]
24. Seeherunvong W, Abitbol CL, Chandar J, Zilleruelo G, Freundlich M. Vitamin D insufficiency and deficiency in children with early chronic kidney disease. J Pediatr 2009;154(6):906-11. e1.[Pubmed]
25. Salusky IB, Kuizon BG, Juppner H. Special aspects of renal osteodystrophy in children. Semin Nephrol 2004;24(1):69-77.[Pubmed]
26. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in children with chronic kidney disease. Am J Kidney Dis 2005;46(Suppl 1).
27. National Kidney Foundation. K/DOQI clinical practice guidelines for nutrition in children with CKD: 2008 Update. Bone mineral and vitamin D requirements and therapy. Am J Kidney Dis 2009;53:S61.
28. Klaus G, Watson A, Edefonti A, Fischbach M, Ronnholm K,

Schaefer F,l et al. Prevention and treatment of renal osteodystrophy in children on chronic renal failure: European guidelines. Pediatr Nephrol 2006;21(2):151-9.[Pubmed]

29. National Kidney Foundation. K/DOQI clinical practice guidelines for nutrition in chronic renal failure: 2008 Update. Am J Kidney Dis 2009;53(Suppl 2):S1.
30. Andre JL, Bourquard R, Guillemin F, Krier MJ, Briancon S. Final height in children with chronic renal failure who have not received growth hormone. Pediatr Nephrol 2003;18(7):685-91.[Pubmed]
31. Mahan JD, Warady BA. Assessment and treatment of short stature in pediatric patients with chronic kidney disease: a consensus statement. Pediatr Nephrol 2006;21(7):917-30.[Pubmed]

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