

Left Ventricular Mass Index and Cardiovascular Compromise in children on dialysis

Evaluación del Compromiso Cardiovascular en niños en diálisis mediante el Índice de Masa Ventricular Izquierdo

Carolina Sugg H.^{a,b}, Francisco Cano Sch.^b

^aPediatric Nephrology Resident, University of Chile, Santiago, Chile

^bPediatrics and Infant Surgery Department, Faculty of Medicine, University of Chile, Luis Calvo Mackenna Hospital, Santiago, Chile.

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What do we know about the subject matter of this study?

The main cause of death in chronic renal disease is cardiovascular pathology secondary to metabolic and hydroelectrolytic disorders, arterial hypertension, and volume overload, typical of this pathology, especially in terminal stages.

What does this study contribute to what is already known?

It emphasizes the importance of the diagnosis and monitoring of cardiovascular involvement in children on dialysis, highlighting the need for a correct diagnosis of left ventricular hypertrophy in those patients with stunting, characteristic of this population.

Abstract

There is a close relationship between chronic kidney disease (CKD) and cardiovascular disease. One of its clinical manifestations is left ventricular hypertrophy (LVH), expressed as Left Ventricular Mass Index (LVMI $\text{gr}/\text{m}^{2.7}$). In CKD patients with growth retardation, the LVMI calculation should be adjusted by correcting age for length/height. **Objective:** To compare the age-corrected LVMI for length/height with the value calculated by chronological age in CKD children on dialysis. **Patients and Method:** Cross-sectional study. We analyzed echocardiographies of CKD children on dialysis aged between 1 and 18, from January 2016 to July 2017. LVMI was evaluated by adjusting the value expressed in $\text{gr}/\text{m}^{2.7}$ to the percentile for the chronological child's age, and then the value was adjusted to the age-corrected length/height. We used descriptive statistics and concordance study for LVMI assessments calculating by chronological age and for age-corrected length/height. **Results:** 26 patients were included and 75 echocardiograms. 56% had left ventricular hypertrophy using chronological age versus 46.6% age-corrected LVMI for length/height. When comparing the percentile groups of LVMI-chronological age vs. age-adjusted LVMI for actual length/height, it was observed that 18.6% of the sample changed percentile groups, 100% of them to a lower percentile group. The agreement evaluated based on the Kappa coefficient was 0.72 (perfect agreement > 0.8), confirming differences when adjusting the LVMI for age-corrected length/height. **Conclusion:** Calculating LVMI by chronological age overestimates the cardiovascular involvement in children with CKD who are characteristically stunted. The results suggest that the age-adjusted, length/height-corrected calculation of LVMI gives greater accuracy to the diagnosis of left ventricular hypertrophy in this group of patients.

Keywords:

Chronic Kidney Disease;
Left Ventricular Mass Index;
Dialysis;
Growth Retardation

Correspondence:
Carolina Sugg H.
carolasugg@yahoo.com

Introduction

Chronic kidney disease (CKD) has a close relationship with cardiovascular disease, which is the main cause of mortality. About 40 to 70% of adults who enter a dialysis program already have cardiovascular signs and the overall mortality due to this cause reaches 40%¹. In children with end-stage renal disease (ESRD), mortality due to cardiovascular disease ranges from 21 to 25%^{2,3}.

The clinical manifestations of cardiovascular disease are secondary to accelerated atherosclerosis and cardiomyopathy. The latter can appear as concentric left ventricular hypertrophy (LVH) in episodes of increased post-load, as left ventricular dilatation (LVD) secondary to volume overload, or as systolic dysfunction due to decreased contractility^{4,5}.

To date, there are different diagnostic tools to evaluate the presence of cardiomyopathies such as electrocardiogram, echocardiography, and MRI, where the most widely used is the echocardiogram due to its accessibility, performance, and cost⁶.

In a Canadian cohort with 432 individuals with ESRD who started dialysis, 45% of them had concentric LVH, 28% LVD, and 16% systolic dysfunction⁷. According to the registry of the International Pediatric Peritoneal Dialysis Network (IPPN), of 471 pediatric patients on peritoneal dialysis evaluated with an echocardiogram, 30% had concentric LVH, 18% eccentric LVH, 26% LV concentric remodeling, and 26% presented normal structure⁸.

To estimate the left ventricular mass (LVM) using echocardiography, M-mode (blinded or 2D- or 3D-guided) can be used. All measurements are made at the end of diastole. The use of M-mode or linear measurements in 2D ultrasound of the LV end-diastolic diameter and wall thickness is based on geometrical formulas to calculate the LV myocardial volume, while the 3D ultrasound can measure it directly⁹.

The LVM is directly related to the lean body mass (LBM), a parameter difficult to estimate in clinical practice, therefore the body surface area (BSA) has been used as an approximation. However, the BSA depends on weight and height, which suggests that overweight or obese individuals will present biased values of LVM. To correct this bias, height has been defined as the best clinical equivalent to LBM. Thus, the LVM values vary according to sex, age, height, and body composition¹⁰, and their evaluation is improved by the LVM index (LVMI) per height to the 2.7 power ($m^{2.7}$), which gives a better correlation with LBM. This last formula is the one recommended by the American Academy of Pediatrics to diagnose LVH establishing a cut-off point in adults values $>51 \text{ gr}/m^{2.7}$ and in children $>38 \text{ gr}/m^{2.7}$ ¹¹⁻¹³.

According to Foster¹⁴, this LVMI would be imprecise for the diagnosis of LVH in children since the body proportions change drastically during childhood and the relationship of LVM and height differs at different developmental ages showing that the LVM adjusted to percentiles for height is better. Khoury¹⁵ manages to determine percentiles of LVM and LVMI by performing echocardiograms on 2,273 healthy children aged from 0 to 18 years and defines LVH with values higher than the 95th percentile. From this study, LVH is considered in boys over 9 years old an $LVMI > 45 \text{ gr}/m^{2.7}$ and for girls over 9 years old an $LVMI > 40 \text{ gr}/m^{2.7}$, but for younger children, this value varies widely with age, so its use is not recommended¹⁵.

Of the children with ESRD, 68% present low height ($< 1.88 \text{ SD}$) and, despite clinical progress and therapeutic management, 35 to 50% remain with height involvement in adult life^{16,17}. Therefore, we propose that in children with ESRD, it might be more accurate to use the percentiles described by Khoury to evaluate LVMI by correcting age for child height.

The objective of this study is to determine whether the calculation of the age-corrected LVMI for height differs from the value calculated by chronological age in children with CKD on chronic dialysis.

Patients and Method

Retrospective, analytical, cross-sectional, observational study in pediatric patients aged between 1 and 18 years, with active ESRD on peritoneal dialysis and chronic hemodialysis program at the Luis Calvo Mackenna Hospital from January 2016 to July 2017. Inclusion criteria were children with ESRD on peritoneal dialysis or hemodialysis aged between 1 and 18 years old. Children with congenital heart disease and chromosomal disorders were excluded from the study.

Data were collected from clinical records since admission to the dialysis program regarding demographic variables (sex and chronological age); clinical variables (weight (kg), height (cm), and systolic and diastolic blood pressure (SBP and DBP, respectively) in mmHg, defining values as higher or lower than 95th percentile according to age, sex, and height as defined in blood pressure tables published by the American Academy of Pediatrics in 2017¹³; CKD etiology (congenital structural anomalies of the urinary tract, glomerulopathies, heritable diseases, vascular nephropathy, others different from the above, and those of unspecified etiology); time of ESRD (months); time of renal replacement therapy (RRT), peritoneal dialysis (PD) and/or hemodialysis (HD). In addition were also registered laboratory parameters (hematocrit (%), hemoglobin (gr/dl), serum ferritin (ng/ml), albumin (gr/dl), serum crea-

tinine (mg/dl), and creatinine clearance estimated by Schwartz (ml/min) $[0.413 \times \text{height (cm)}/\text{serum creatinine (mg/dl)}]^{18}$; and residual renal function (RRF) considering diuresis >100 ml/day, calcemia (mg/dl), phosphatemia (mg/dl), intact PTH (pg/ml), and 25-OH vitamin D levels (ng/ml). We recorded the Kt/V of children on HD and for those on PD, we recorded the peritoneal Kt/V of the month of the echocardiogram.

Growth. We used for height WHO reference standard for children under 5 years old and NCHS growth charts for children over 5 years old. The height was converted into Z-score (standard deviation score) according to the WHO and NCHS height-for-age charts in order to express the data statistically¹⁹⁻²¹.

Height-corrected age was defined as the age at which the child's height matches the 50th percentile for sex according to WHO standard for children under 5 years old and NCHS chart for children over 5 years old.

Cardiovascular

Echocardiograms performed at Luis Calvo Mackenna Hospital by 2 pediatric cardiologists with Vivid E9 GE Healthcare® equipment were analyzed. Echocardiograms performed at least 6 months apart were included in the study group. Data were obtained from echocardiographies performed using M-Mode (2D-guided) the LV posterior wall (LVPW) thickness, interventricular septal thickness (IVST), and LV end-diastolic diameter (LVEDD) in cm.

The LVM was calculated using the software <http://lvmass.parameterz.com> based on formulas recommended by the American Society of Echocardiography²². LVMI was estimated according to $\text{LVM}/\text{height}^{2.7}$. The percentile range of LVM and LVMI was established according to curves and charts by Khoury et al. by age and then by age corrected for height¹⁵. Since this chart does not present the LVM and LVMI as a continuous variable but shows cut-off values in percentiles 10, 25, 50, 75, 90, and 95, the inter-percentile range was used in each corresponding case. Thus, patients were grouped into percentile ranges as follows: group 1 ($<p10$), group 2 ($p10-25$), group 3 ($p25-50$), group 4 ($p50-75$), group 5 ($p75-90$), group 6 ($p90-95$), and group 7 ($>p95$). LVH was defined as those values above the 95th percentile of LVM and LVMI according to Khoury et al¹⁵.

This work was evaluated by the Ethics and Research Committee on Human Beings of the Faculty of Medicine of the University of Chile. Informed consent was requested from legal guardians and informed assent for children over 12 years of age.

Statistical analysis. Data tabulation was carried out in an Excel spreadsheet, and data analysis with a two-tailed test. STATA 11.0 software was used for statistical

analysis. Categorical variables were expressed as absolute value and percentage, the continuous ones with normal distribution as arithmetic mean $\pm$ standard deviation, and for those non-parametric ones as median and interquartile interval (25th percentile - 75th percentile). A concordance study with the calculation of kappa and Cronbach's alpha coefficient was used for the evaluation of LVM and LVMI by chronological age versus age corrected for height. We considered concordance for both coefficients with a > 0.8 value²³. This study used an opportunity sampling method since all the echocardiographies of subjects on chronic dialysis were selected and in which an estimation error cannot be measured. Echocardiographic studies of the same patient at least 6 months apart were included since the variable of interest was the LVMI.

Results

Initially, 30 active ESRD carrier patients were selected for the peritoneal dialysis and chronic hemodialysis program at the Luis Calvo Mackenna Hospital, from January 2016 to July 2017. Two children with diagnosis of congenital heart disease and chromosomal disorder were excluded, and two due to they did not have a pediatric cardiologist's echocardiogram at the Luis Calvo Mackenna Hospital. Regarding CKD etiology, 53.9% presented congenital structural anomalies of the urinary tract, 26.9% glomerulopathies, 3.9% heritable diseases, 7.7% vascular nephropathy, 3.9% others different from the above, and 3.9% of unspecified etiology. The average age was 8.2 ± 4.1 years. The average age corrected for height was 7.01 ± 3.8 years. 33% of the sample presented short height (< 1.88 SD). Table 1 shows demographic and laboratory characteristics.

During the analysis period, 75 echocardiograms were obtained, an average of 2.88 echocardiograms per patient (range 1-10), with an average time interval between echocardiograms of 30.7 months (7-143 months). When evaluating LVM and LVMI by chronological age, 37.3% and 56% of the studies were for LVM and LVMI, respectively. When adjusting by age corrected for height, 50.7% were LVM $> p95$ and 46.7% were LVMI $> p95$ (tables 2 and 3).

Cronbach's alpha correlation coefficient was used to evaluate the internal consistency of the measuring instruments used, with and without age corrected for height adjustment. We obtained a coefficient of 0.92 for LVM and 0.97 for LVMI, later, deducting the agreement obtained randomly, we analyzed the concordance between both measurement instruments using Cohen's kappa correlation coefficient, resulting in a coefficient of 0.42 for the measures related to LVM and 0.72 for those of LVMI.

Table 1. General characteristics of the patients at the time of the echocardiogram

n (%)	75
Gender	
Female	39 (52)
Male	36 (48)
Chronological age in years	
Range	(1.08-14.9)
$\bar{x}$	8.23 $\pm$ 4.14
Age in years corrected for height	
Range	(0.5-13.25)
$\bar{x}$	7.01 $\pm$ 3.81
Height (cm)	(66-158)
Range	119.18 $\pm$ 24.96
$\bar{x}$	
Z score height < 0,0 n (%)	88(66)
Z score height $\leq$ -1,88 n (%)	33.3 (25)
Blood pressure n (%)	
< p95	33 (44)
> p95	42 (56)
Hematocrit (%)	
Range	(19-41.5)
$\bar{x}$	32.41 $\pm$ 5.77
Hemoglobin (gr/dl)	
Range	(5.8-18.6)
$\bar{x}$	10.76 $\pm$ 2.15
Ferritin (ng/ml)	
Range	(38.9-2368)
Mediana	224
Albumin (gr/dl)	
Range	(2.1-5.1)
$\bar{x}$	3.76 $\pm$ 0.48
Calcium (mg/dl)	
Range	(7.9-12.8)
$\bar{x}$	9.7 $\pm$ 0.84
Phosphoro (mg/dl)	
Range	(2.4-9.5)
$\bar{x}$	5.55 $\pm$ 1.47
Creatinine depuration ml/min/1,73 (Schwartz)	
Range	(4.24-26.9)
$\bar{x}$	8.26 $\pm$ 4.74
25 OH vitamin D (pg/ml)	
Range	(10-55.2)
$\bar{x}$	31.26 $\pm$ 9.77
Dialysis (%)	
Hemodiálisis	27 (36)
Peritoneodiálisis	48 (64)
Time of ESRD (months)	
Range	(1-172)
$\bar{x}$	57.01 $\pm$ 44.68
Time RRT (months)	
Range	(1-81)
$\bar{x}$	23.82 $\pm$ 21.86
RRF	
> 100 ml/day. n (%)	32 (42.67%)
Peritoneal dialysis	27 (84.38)
Hemodialysis	5 (15.63)
Adequacy parameters in Dialysis	
Kt/v (n: 27)	
Range	(1.31-2.88)
$\bar{x}$	1.96 $\pm$ 0.42
URR (n: 27)	
Range	(39-90)
$\bar{x}$	77.78 $\pm$ 10.21
Peritoneal Kt/V (n: 44)	
Range	(0.78-2.9)
$\bar{x}$	1.82 $\pm$ 0.57

Data are presented as number (%), mean ($\bar{x}$), $\pm$ standard deviation, range, and median. CKD: Chronic kidney disease; RRF: Residual kidney function; Kt/V: Dialysis dose; URR: Urea reduction ratio.

When comparing the LVMI percentile groups with age-adjusted LVMI for height, it was observed that 18.6% of the sample changed percentile groups, 100% of them to a lower percentile. Of the cases that changed groups, 50% no longer belonged to the 7th percentile group that establishes the diagnosis of LVH.

Discussion

Left ventricular hypertrophy is one of the complications that must be evaluated periodically in patients with ESRD, which is associated with a worse cardiovascular prognosis. The method widely used in clinical practice to diagnose this complication is the echocardiogram, both due to its accessibility and its cost.

In the clinical practice of pediatric nephrology, it is usual to calculate the LVMI in grams/m (height) to the 2.7 power^{10,11,13}, which allows setting a cut-off value for diagnosing ventricular hypertrophy. Height is used as a better clinical parameter related to LBM; however, since LVM varies according to changes in LBM/height for age, which is higher at a younger age, Foster et al¹⁴ have suggested that a single cut-off value is not applicable in pediatrics, especially in children under 9 years of age, so they proved that the LVMI value gr/height^{2.7} should be adjusted using the height percentiles of the population studied in order to fit the height/chronological age and thus effectively represent the 95th percentile in each patient. Therefore, authors such as Khoury et al¹⁵ have proposed charts that correct the LVM and LVMI according to age and sex but adjusting to the height/ chronological age percentile. This allows us to consider that an "x" value of height in a patient who is chronologically 7 years old should be read according to the age corrected for the real height of the CKD patient, which could correspond to a "5"-years-old child.

In our study, we found that 56% of the cases meet the LVH criteria, similar to those described by Lehman²⁴, but when adjusted for age corrected for height, the LVH decreases to 46.6%. When analyzing the degree of agreement of this result using the kappa assessment scale, we found that the coefficient for both LVM and LVMI is lower than our cohort point (0.8), and it is possible to conclude that there are differences in the percentile ranges of LVM and LVMI obtained when adjusting the age corrected for height.

This study involved the analysis of 75 echocardiograms of 26 patients, resulting in an average of 2.9 echocardiograms per patient with at least 6 months between each test. This could be considered a potential source of bias if the variables analyzed were static over time. However, the detailed analysis of each case allows us to observe a characteristic fact of pediatric

Table 2. Groups of LVM and LVMI percentile ranges by chronological age

Group (Percentile ranges*)	LVM (n, %) n: 75	LVMI (n, %) n: 75
Group 1 (< p 10)	10 (13.33)	4 (5.33)
Group 2 (p 10-25)	4 (5.33)	3 (4)
Group 3 (p 25-50)	13 (17.33)	8 (10.67)
Group 4 (p 50-75)	8 (10.67)	4 (5.33)
Group 5 (p 75-90)	5 (6.67)	10 (13.33)
Group 6 (p 90-95)	7 (9.33)	4 (5.33)
Group 7 (> p 95)	28 (37.33)	42 (56)

*Percentil ranges from Khory et al.¹⁵. LVM: Left ventricular mass. LVMI: Left ventricular mass index.

Table 3. Groups of percentile ranges of LVM and LVMI for age corrected for height

Group (Percentiles ranges*)	Ajusted MVI (n, %)	Ajusted IMVI (n, %)
Group 1 (< p 10)	6 (8)	5 (6.67)
Group 2 (p 10-25)	1 (1.33)	6 (8)
Group 3 (p 25-50)	7 (9.33)	5 (6.67)
Group 4 (p 50-75)	10 (13.33)	6 (8)
Group 5 (p 75-90)	9 (12)	12 (16)
Group 6 (p 90-95)	4 (5.33)	6 (8)
Group 7 (> p 95)	38 (50.67)	35 (46.67)

*Percentil ranges from Khory et al.¹⁵. LVM: Left ventricular mass. LVMI: Left ventricular mass index.

patients on dialysis, that is, that the same subject presents significant changes in growth (H/A), as well as in cardiovascular status, especially in pre-adolescent age, which allows us to use this test on the same patient in different periods to obtain the information that the objective seeks.

When analyzing in detail how these groups of percentile ranges change when age is corrected for the child's height, we observe that 100% of the cases that change from one group to another do so to a lower percentile group, which reflects an overdiagnosis of LVH in 10% of the echocardiograms and 30% of the subjects included in this study.

In pediatric patients on dialysis, volume overload is frequent and one of the main causes of hypertension and ventricular hypertrophy, which makes an accurate diagnosis of LVMI especially important as an objective parameter of this cardiovascular involvement.

Overdiagnosis of LVH may mean making unnecessary adjustments in therapy based on overestimated ventricular hypertrophy by not adjusting LVMI according to the patient's age corrected for height.

Excessive ultrafiltration (UF) in both PD and HD can lead to unwanted effects such as hypotension. It has been observed in pediatric patients that intradialytic hypotension in conventional HD pro-

duces myocardial toxicity with a decrease in the LV fractional shortening²⁵. In addition, an excessive UF leads to an early loss of residual renal function that hinders maintaining euolemia, creating the need for hypertonic solutions in PD to optimize UF knowing their deleterious effect on the peritoneal membrane, secondary to decreased angiogenesis and peritoneal fibrosis, and also a worse metabolic control due to hyperglycemia produced by such solutions^{26, 27}. The loss of residual renal function prevents the clearance of heavy molecules, increases the inflammatory state, and is associated, at least in adults, with a higher risk of mortality²⁸⁻³².

This study has the limitations of a retrospective design. Although the echocardiogram is very useful for evaluating cardiovascular complications in this group of patients, it would have been more useful to estimate whether the LVH is due to volume overload and/or an increase in post-load based not only on the echocardiographic report but also on the use of complementary tools such as bioimpedance analysis and inferior vena cava collapsibility index and to determine the presence of arterial hypertension with outpatient blood pressure monitoring^{33,34}.

As with all laboratory tests, we should consider a potential bias derived from the echocardiographic report performed by a single observer, without intra- or

inter-observer analysis of concordance, which in daily clinical practice is not possible, therefore, we used the reports of two pediatric cardiology experts from the Hospital Center.

Based on the results of this study, we suggest considering the height of the patients when evaluating the LVMI, since the charts by Khoury et al. were created from a population of healthy children with a normal height/age distribution curve, and the height of children with ESRD means that in this group the distribution of height belongs to lower percentiles, which prevents them from being included in a normal distribution group and therefore favors the over-diagnosis of cardiovascular involvement, as observed in this study.

In conclusion, cardiovascular involvement in chronic dialysis must be accurately diagnosed in order to adopt measures focused on optimizing treatments. In the studied group, the traditional calculation of LVMI by chronological age overestimates the cardiovascular involvement so the adjustment of LVMI by age corrected for the patient's height should be evaluated. This method of evaluating LVH may be important in a group of patients who characteristically have a delay in height due to CKD.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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