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RESEARCH ARTICLE

Evaluation of Ultrasensitive C-Reactive Protein as a Cardiovascular Risk Marker in Pediatric Patients with End-Stage Renal Disease on Peritoneal Dialysis

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Abstract

Background: Patients with End-Stage Renal Disease (ESRD) on Peritoneal Dialysis (PD) experience high morbidity and mortality due to Cardiovascular (CV) disease. In pediatric patients, CV problems include Left Ventricular (LV) abnormalities, hypertension, and arrhythmias. The classic CV Risk Factors (RF) are not adequate to identify CV risk in these patients, but inflammation markers such as Ultrasensitive C-Reactive Protein (USCRP) may be useful in detecting early CV disease. The objective was to assess CV risk in pediatric patients with ESRD on PD and evaluate the utility of USCRP as a CV risk marker.

Methods: We included 12 patients aged 2 to 17 years. Measurements included blood pressure, biochemical profile, insulin resistance (HOMA index), blood count, lipid panel, parathyroid hormone, USCRP, echocardiogram, and carotid Doppler test.

Results: Average time on PD was 8 years. Two patients were overweight/obese. Eight patients had hypertension, and 4 had anemia. Eleven patients had abnormal lipid panel. Blood glucose levels were normal in all patients, but 5 had abnormal HOMA indices. Only one patient met criteria for metabolic syndrome. Ten patients had LV abnormalities, and 8 had increased carotid intimae-media thickness. USCRP was elevated in 7 patients. USCRP values were correlated with HOMA, dyslipidemia, and obesity. The capacity of USCRP to detect CV damage was good, for LV abnormality and increased carotid intimae-media thickness.

Conclusions: Significant CV damage was detected in this group. The classic RF was not always adequate to identify these CV abnormalities. However, USCRP could be superior to other RF in detecting the damage.

Keywords

Cardiovascular diseases, C-reactive protein, End-stage renal disease, Peritoneal dialysis

Introduction

Patients with End-Stage Renal Disease (ESRD) are at elevated risk for morbidity and mortality due to cardiovascular disease [1,2]. As compared to the general population, adverse cardiac events occur at rates 30 times higher in patients with End-Stage Renal Disease (ESRD) and 700 times higher in patients on renal replacement therapy (Peritoneal Dialysis (PD) or hemodialysis), with a concomitant 10-year decrease in life expectancy 10 years after diagnosis [3-6]. The main cardiovascular complications found in pediatric ESRD patients include left ventricular abnormalities (initially hypertrophic and then dilated cardiomyopathy); arrhythmias; pericardial complications (pericarditis and tamponade); and abnormalities indicative of early atherosclerosis, such as thickening of the carotid intimae, and endothelial dysfunction, as measured by brachial artery flow [7-10]. The literature indicates a high prevalence of traditional cardiovascular risk factors in these patients (diabetes, hypertension, smoking, dyslipidemia, obesity, and sedentarism) [1,2] as well as risk factors attributable to the kidney disease itself such as anemia, secondary hyperparathyroidism, and hypervolemia. Furthermo-

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re, new cardiovascular risk factors have been identified that promote atherosclerosis in uremic patients, such as inflammation and oxidative stress [11].

One remarkable development in recent years is the use of Ultrasensitive C-Reactive Protein (USCRP) [12,13] as a cardiovascular risk marker in adult patients with or without ESRD. To date, however, there has not been an adequate evaluation of this marker in a pediatric Chilean ESRD population. C-reactive protein is an acute-phase protein secreted primarily by hepatocytes [14] as a result of various stimuli, indicating a state of systemic inflammation, infection, or tissue damage [15]. There is evidence that CRP is also produced locally in inflamed cells (as occurs with atherogenesis); contributing, for example, to inhibition of the production of nitric oxide synthetase [12] and thereby altering microvascular vasodilation function. Using standard techniques, levels below 10 mg/L are considered normal, 20 to 40 mg/L indicative of a viral infection and up to 60 mg/L indicative of a bacterial infection [15]. The development of ultrasensitive techniques (ultrasensitive CRP, or USCRP) has allowed researchers to establish USCRP levels in the adult population that correlate with a state of chronic inflammation associated with atherosclerosis and cardiovascular disease, with levels below 1 mg/L considered very low risk for cardiovascular disease and levels greater than 3 mg/L high risk [12,13].

The objective of this study was to compare the utility of USCRP with that of other cardiovascular risk factors and markers of early atherosclerosis in children with ESRD on PD. Furthermore, we sought to evaluate cardiovascular risk in these patients, the association with metabolic syndrome, and the magnitude of the cardiovascular damage.

Patients and Methods

A total of 13 patients on PD were seen in the Nephrology Unit of Hospital Exequiel Gonzalez Cortes, Santiago de Chile.

Inclusion criteria were: Confirmed diagnosis of ESRD [16]; age between 1 month to 18 years; PD for renal replacement therapy for at least 1 month prior to study; at least one month since any infectious episode; ability to accept the conditions of the study and sign informed consent, or provide assent with signed informed consent of the legal guardian for patients under the age of 10 years.

Exclusion criteria were: Recurrent infectious episodes; congenital, structural, or primary myocardial or vascular disease; refusal to participate.

Anthropometric measurements

Height and weight were measured using a calibrated scale (Seca 769 digital scale, 50 gram graduation) and stadiometer (inextensible metric tape, 1 millimeter graduation) with the child barefoot and in underwear. Body mass index was calculated [BMI = (weight in kg)/(height in m^2)] and expressed as a percentile, as well as Weight/Age (W/A), Weight/Height (W/H), and Height/Age (H/A), expressed as Z-scores [Z = (average value-median)/1 Standard Deviation (SD)] for both chronological and adjusted biological age (according to median height for age). Patients under the age of 6 years were categorized as underweight if their W/H was more than 2 SD below the mean for healthy individuals; at risk of underweight if - 2 to - 1 SD; eutrophic if - 1 to 1 SD; overweight if 1 to 2 SD; and obese if greater than 2 SD. Patients 6 years and older were evaluated according to BMI. Obesity was defined as BMI ≥ 95th percentile; overweight as 85-94th percentile; optimal weight as 10-84th percentile; and underweight as < 10th percentile, as per norms issued by the National Ministry of Health [17,18]. Waist Circumference (WC) was measured using an inextensible metric tape from the midpoint between the right iliac crest and the last right rib, after exhaling, averaging two measurements. Measurements were taken prior to beginning PD, with an empty abdominal cavity, by a single rater. Values were evaluated with respect to the 90th percentile for international norms [19].

Arterial blood pressure was measured according to international standards [20]. Hypertension (HT) was defined as Systolic Blood Pressure (SBP) or Diastolic Blood Pressure (DBP) ≥ 90th percentile for sex, age, and height according to the recommendations of the Chilean Society of Pediatrics [21]. Patients with normal blood pressure measurements but currently on antihypertensive treatment were considered to have HT as a cardiovascular risk factor for the purposes of this analysis.

Laboratory measurements

USCRP was measured using the nephelometric method with a detection limit of 0.1 mg/L, processed in the laboratory of the Clinic Hospital of the University of Chile. The cut-off values used in the literature to define cardiovascular risk in adults are as follows: below 1 mg/L = low risk; 1 to 3 mg/L = intermediate risk; and greater than 3 mg/L = high risk [12,13]. A cut-off value of > 1 mg/L [22] was used to define patients with cardiovascular risk and inflammation for the purposes of this study.

We also measured the following parameters.

Fasting blood glucose: Values ≥ 100 mg/dL were considered abnormal for the purpose of defining metabolic syndrome. Fasting plasma insulin, to evaluate insulin resistance according to the Homeostatic Model Assessment Index (HOMA) [23], using the formula (uU/mL) × glucose (mg/dL)/405; values ≥ 2.5 were used as the cut-off.

Lipid panel: Total Cholesterol (TC), HDL Cholesterol (HDL-C), Triglycerides (TG), LDL Cholesterol (LDL-C). Cut-off values for the purpose of defining metabolic syndrome were TG > 110 mg/dL; HDL-C ≤ 40 mg/dL. The American Academy of Pediatrics uses the following values

to define dyslipidemia in establishing criteria for cardiovascular risk prevention in children: TC ≥ 200 mg/dL; LDL-C ≥ 130 mg/dl; HDL-C ≤ 40 mg/dL; TG ≥ 130 mg/dL in children under the age of 10 years and ≥ 150 mg/dL in those 10 years or older [24-28]. Complete blood count and smear were performed, with anemia defined as hematocrit ≤ 30% or hemoglobin ≤ 10 g/dL. Parathyroid Hormone (PTH) was measured to evaluate for hyperparathyroidism, with a cut-off value of 400 pg/mL.

Metabolic syndrome was defined according to Cook [29], based on ATP III criteria for adults, which defines the syndrome as the presence of at least 3 of the following: WC > 90th percentile [19], HDL-C ≤ 40 mg/dl, TG ≥ 110 mg/dL [30], fasting blood glucose level ≥ 100 mg/dl, and SPB ≥ 90th percentile [20].

Imaging measures

A complete echocardiogram was performed by a single cardiologist. The echocardiograph parameters and patient size were used to obtain the Left Ventricular Mass Index (LVMI) according to international recommendations, with hypertrophy defined as > 38 g/m$^{2.7}$ calculated according to the formula described by de Simone, et al. [31].

A carotid Doppler test was used to measure Carotid Intimae-Media Thickness (CIMT) according to the recommendations of Mannheim 2004 [32] by a single radiologist using a Philips/ATL HDI 5000 ultrasound imaging platform. This value was compared with the mean value for healthy individuals + 2 SD. For children 10 years or older, logistic regression was used to calculate a Z-score as suggested by Jourdan, et al. [33]. For children under the age of 10 years, the formula suggested by Ishizu, et al. was used to calculate the whether the value exceeded the mean for healthy individuals + 2 SD [34]. For patients under the age of 5 years (patients 1, 2, 3, and 4), the mean value + 2 SD for children aged 5 years was used, as there are no valid norms for children of this age, and current evidence suggests that values remain relatively stable between 2 and 5 years of age [33,34].

Cardiovascular risk factors were defined as: meeting 3 or more criteria for metabolic syndrome, abnormal HOMA > 2.5, dyslipidemia, overweight or obesity, arterial hypertension (SPB or DBP ≥ 90th or antihypertensive treatment), hyperparathyroidism (PTH > 400 pg/mL), and anemia (hematocrit < 30% and/or hemoglobin < 10 g/dL). Cardiovascular damage was considered significant for CIMT values greater than + 2 SD above the mean for healthy individuals or LVMI > 38 g/m$^{2.7}$. These values were compared with USCRP findings (considered elevated for values > 1 mg/L).

Informed consent/assent was obtained for all subjects, and the protocol was approved by the Ethics Committee of the South Metropolitan Health Service.

Statistical analysis

Descriptive statistics were performed for the variables previously identified. Data were entered in Excel, and STATA and Fisher's exact test were used for the description, considering a maximum probability of 0.05.

Results

A total of 13 patients were eligible for the study, but one patient was not included due to refusal to participate. Age ranged from 2 to 17 years, median 11 years. The causes of ESRD were: bilateral renal dysplasia (4 patients); unknown (4 patients); and one case each of hemolytic uremic syndrome, Prune Belly syndrome, hepatorenal polycystic disease, and congenital nephrotic syndrome (diffuse mesangial sclerosis). The median age at initiation of PD was 8 years (range 3 months to 15 years), and the mean time on PD was 2 years 9 months (range 8 months to 5 years). All patients were undergoing overnight dialysis at the time of the study.

The most relevant clinical, nutritional, biochemical, and USCRP results of the 12 patients are shown in Table 1. Ten of 12 patients presented with short stature, attributable to the chronically compromised nutritional status characteristic of ESRD. In the nutritional evaluation by chronological age, 2 patients were categorized as overweight and one as obese, but when corrected for

Table 1: Clinical, nutritional, biochemical, US-CRP, LVMI, and CIMT results of the 12 patients.

Patient	1	2	3	4	5	6	7	8	9	10	11	12
Age (years)	2	3	4.5	4.5	6	11	15	15.5	16.5	17	18	18
Sex	M	F	M	F	M	M	M	M	F	F	F	F
Nutritional status	E	E	E	Ob	E	Ob	E	Ow	E	E	Ow	E
Hypertension	-	+	-	-	+	+	+	-	+	+	+	+
Parathyroid hormone	N	↑	N	↑	N	N	↑	N	↑	↑	↑	N
Anemia	+	+	-	-	-	-	+	-	-	-	-	+
Dyslipidemia	+	+	+	+	+	+	+	+	+	-	+	+
Blood glucose	N	N	N	N	N	N	N	N	N	N	N	N
Plasma insulin	N	N	N	N	N	N	N	N	N	N	N	N
Metabolic syndrome	-	+	-	-	-	-	-	-	-	-	-	-
HOMA	N	N	N	↑	N	↑	↑	↑	N	N	↑	N
US-CPR	↑	N	↑	↑	↑	↑	N	↑	N	N	↑	N

CIMT: Carotid Intima-Media Thickness; E: Eutrophic; F: Female; LVMI: Left Ventricular Mass Index; M: Male; N: Normal; Ob: Obese; Ow: Overweight; US-PCR: Ultrasensitive C Reactive Protein; +: Present; ↑: Increased.

Table 2: Criteria for metabolic syndrome and results of the 12 patients.

Patient	1	2	3	4	5	6	7	8	9	10	11	12
Triglycerides ≥ 110 mg/dL	↑	↑	↑	↑	↑	↑	↑	↑	↑	N	N	N
HDL-C ≤ 40 mg/dL	↓	↓	N	N	N	N	N	N	N	N	↓	N
WC > pc90 for age and sex	N	N	N	↑	N	N	N	N	N	N	N	N
Fasting blood glucose level ≥ 100 mg/dL	N	N	N	N	N	N	N	N	N	N	N	N
Blood pressure > pc90 for age, sex and height	N	↑	N	N	↑	↑	↑	N	↑	↑	↑	↑
Criteria = n	2	3	1	2	2	2	2	1	2	1	2	1

HDL-C: HDL-Cholesterol; N: Normal; WC: Waist Circumference; ↑: Increased; ↓: Decreased.

Table 3: Association between US-CRP, and LMVI and CMIT.

Patient	1	2	3	4	5	6	7	8	9	10	11	12
US-CPR	↑	N	↑	↑	↑	↑	N	↑	N	N	↑	N
LMVI	↑	↑	↑	↑	N	↑	↑	↑	↑	N	↑	↑
CMIT	↑	↑	N	↑	↑	↑	N	↑	N	↑	↑	N

CIMT: Carotid Intima-Media Thickness; LVMI: Left Ventricular Mass Index; N: Normal; US-PCR: Ultrasensitive C Reactive Protein; ↑: Increased.

biological age (due to the short stature of the patients), the overweight patients were re-classified as obese, and one of the optimal-weight patients as overweight. Eight of 12 patients had HT, 4 of who were treated with at least one anti hypertensive drug. Six patients had uncontrolled hyperparathyroidism, and 4 patients had anemia. Abnormal values for dyslipidemia were found in 11/12 patients. Blood glucose was normal in all patients despite the use of high-dextrose solution in peritoneal dialysis. HOMA values, however, were abnormal in 5 patients, indicating early insulin resistance.

Table 2 shows the criteria for metabolic syndrome along with the patients' results. It is noteworthy that only one patient met criteria for the syndrome.

The echocardiography results indicated significant cardiovascular damage. Ten of 12 patients had signs of left ventricular hypertrophy, and 8/12 had abnormal CIMT values, indicating early atherosclerotic disease.

Levels of USCPR > 1 mg/L, corresponding to a degree of inflammation associated with atherosclerosis, were found in 7 of the 12 patients. The USCRP results correlated adequately with HOMA, dyslipidemia, and overweight/obesity, but showed no correlation with HT, hyperparathyroidism, anemia, or metabolic syndrome.

The capacity of USCRP to correlate with LVMI and CIMT was adequate (Table 3). Six of the 10 patients with altered LMVI had increased USCRP. Also, 6 of 8 patients with altered CMIT had USCRP elevated. All patients with dyslipidemia had LVMI. In terms of association with CIMT, USCRP was superior to other risk factors analyzed; there was also a correlation with overweight and hyperparathyroidism. In terms of association with LVMI, HOMA, HT, and overweight/obesity values were comparable to those for USCRP. The results for metabolic syndrome and dyslipidemia were not significant as only one patient presented with a true positive result. None of the associations reached statistical significance probably due to the small number of cases studied.

Discussion

Cardiovascular disease is prevalent in both adults and children with ESRD, resulting in serious complications that affect quality of life and cause significant morbidity and mortality. Atherosclerosis develops more rapidly in these patients regardless of the presence of the classic cardiovascular risk factors, due mainly to factors related to uremia and inflammation that promote atherosclerosis in these patients. In this group of pediatric patients with ESRD on PD, early cardiovascular damage was identified, as indicated by Left Ventricular Hypertrophy (measured by LVMI) and increased CIMT, which is an index for atherosclerotic disease. These findings are consistent with previous reports in the literature [9,10].

It has been reported that CIMT is greater in patients with hypertension than in healthy controls (among both adults and children) [29]. ESRD patients show elevated CIMT values, and CIMT is a useful predictor of adverse cardiac events [35]. When patients on PD are compared to those who have undergone kidney transplant, values are higher for the PD patients, suggesting that the renal replacement process itself promotes development of early atherosclerosis [36]. It has also been reported that CIMT values tend to normalize after kidney transplant [37], indicating that this damage is reversible upon improving renal function and withdrawing the atherosclerosis-promoting stimulus of the renal replacement therapy.

Left ventricular hypertrophy is also an independent risk factor for mortality in adults [38] and is the most common cardiac abnormality found in pediatric patients with ESRD [39]. Other factors include CIMT, regression of left ventricular hypertrophy after transplant, and high blood pressure [40].

Both the traditional risk factors and those associated with uremia are generally found at increased rates in adult versus pediatric ESRD patients, especially HT, volume overload, dyslipidemia, and diabetes. Therefore, these factors are inadequate to characterize risk of cardiovascular damage in the pediatric population [41]. In our series, the most frequent risk factors were dyslipidemia, elevated HOMA, HT, and hyperparathyroidism, and the association with cardiovascular damage was adequate.

Only one patient in this cohort had metabolic syndrome, which is one of the most-studied cardiovascular risk

factors in children, including in Chilean cohorts, where it has been associated with early heart disease and abnormal values for markers of inflammation [42-44].

The use of USCRP is well-validated in the literature as a cardiovascular risk factor and inflammation marker. Chilean studies [42-44] have validated USCRP as an inflammation marker in obese children with early atherosclerotic changes, but there are no previous reports for the population of patients with ESRD on PD.

For adult patients with chronic kidney disease and on renal replacement therapy, the utility of USCRP as a prognostic tool for the evolution of the kidney disease, cardiovascular risk factors, and mortality has been well established [45,46]. The first studies established the utility of measuring baseline USCRP as a prognostic indicator, but current reports for adult populations indicate that the evolution of USCRP is a better indicator than an isolated measurement [28].

In this group of pediatric ESRD patients on PD, USCRP showed adequate correlation with traditional cardiovascular risk factors as well as those associated with uremia. The increased level of USCRP as an isolated factor to predict cardiovascular damage was greater than that of the other risk factors analyzed. Therefore, the data suggest that USCRP is an adequate tool for detecting cardiovascular damage in pediatric ESRD patients on PD.

Limitations of this study include the lack of a control group of healthy children, the descriptive character of the evaluation, and the small cohort of patients, restricting the ability to extrapolate these results to the population at large.

In conclusion, in this group of patients evaluated, a high cardiovascular risk was found which was considered incipient in most cases. The utility of USCRP in these patients was adequate to detect cardiovascular risk as well as cardiovascular damage, although further study in a larger number of patients will be necessary to generalize these results.

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Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The protocol was approved by the Ethics Committee of the South Metropolitan Health Service.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Longenecker JC, Coresh J, Powe NR, Levey AS, Fink NE, et al. (2002) Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE study. J Am Soc Nephrol 13: 1918-1927.
2. Goicoechea M, de Vinuesa SG, Gómez-Campderá F, Luño J (2005) Predictive cardiovascular risk factors in patients with chronic kidney disease (CKD). Kidney Int Suppl S35-S38.
3. Shik J, Parfrey PS (2005) The clinical epidemiology of cardiovascular disease in chronic kidney disease. Curr Opin Nephrol Hypertens 14: 550-557.
4. Jara A, Mezzano S (2008) Vascular damage in chronic kidney disease. Rev Med Chil 136: 1476-1484.
5. Mitsnefes MM (2005) Cardiovascular morbidity and mortality in children with chronic kidney disease in North America: lessons from the USRDS and NAPRTCS databases. Perit Dial Int 25: S120-S122.
6. Schiffrin EL, Lipman ML, Mann JF (2007) Chronic kidney diseases: effects on the cardiovascular system. Circulation 116: 85-97.
7. Mitsnefes MM (2008) Cardiovascular complications of pediatric chronic kidney disease. Pediatr Nephrol 23: 27-39.
8. Matteucci MC, Wühl E, Picca S, Mastrostefano A, Rinelli G, et al. (2006) Left ventricular geometry in children with mild to moderate chronic renal insufficiency. J Am Soc Nephrol 17: 218-226.
9. Briese S, Wiesner S, Will JC, Lembcke A, Opgen-Rhein B, et al. (2006) Arterial and cardiac disease in young adults with childhood-onset end-stage renal disease-impact of calcium and vitamin D therapy. Nephrol Dial Transplant 21: 1906-1914.
10. Jun Oh, Rainer Wunsch, Martin Turzer, Malte Bahner, Paolo Raggi, et al. (2002) Advanced coronary and carotid arteriopathy in young adults with childhood-onset chronic renal failure. Circulation 106: 100-105.
11. Ross R (1999) Atherosclerosis--An Inflammatory Disease. N Engl J Med 340: 115-126.
12. Lagrand WK, Visser CA, Hermens WT, Niessen HW, Verheugt FW, et al. (1999) C-reactive protein as a cardiovascular risk factor: more than an epiphenomenon? Circulation 100: 96-102.
13. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, et al. (2003) Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 107: 499-511.
14. Ballou SP, Kushner I (1992) C-reactive protein and the acute phase response. Adv Intern Med 37: 313-336.
15. Albrecht C, Kaeppel N, Gauglitz G (2008) Two immunoassay formats for fully automated CRP detection in human serum. Analytical and Bioanalytical Chemistry 391: 1845-1852.
16. Kidney Disease: Improving Global Outcomes (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 3: 1-150.

17. Barlow SE, Expert Committee (2007) Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. Pediatrics 120: S164-S192.

18. Ministry of Health Nutrition Unit (2004) Advisory council on nutrition. Technical norm of nutritional evaluation of the child of 6 to 18 years. Rev Chil Nutr 31: 128-137.

19. Fernández JR, Redden DT, Pietrobelli A, Allison DB (2004) Waist circumference percentiles in nationally representative samples of African-American, European-American and Mexican-American children and adolescents. J Pediatr 145: 439-444.

20. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (2004) The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 114: 555-576.

21. Lagomarsino F, Saieh A, Aglony I (2008) Recommendation of branches: Updates in the diagnosis and treatment of arterial hypertension in pediatrics. branch of nephrology, chilean society of pediatrics. Rev Chil Pediatr 79: 63-81.

22. Civilibal M, Caliskan S, Oflaz H, Sever L, Candan C, et al. (2007) Traditional and "new" cardiovascular risk markers and factors in pediatric dialysis patients. Pediatr Nephrol 22: 1021-1029.

23. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, et al. (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28: 412-419.

24. Kavey RE, Allada V, Daniels SR, Hayman LL, McCrindle BW, et al. (2006) Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes research: endorsed by the American Academy of Pediatrics. Circulation 114: 2710-2738.

25. Schrott HG, Bucher KA, Clarke WR, Lauer RM (1979) The Muscatine hyperlipidemia family study program. Prog Clin Biol Res 32: 619-646.

26. (1992) National Cholesterol Education Program (NCEP): Highlights of the report of the expert panel on blood cholesterol levels in children and adolescents. Pediatrics 89: 495-501.

27. American Academy of Pediatrics. Committee on Nutrition (1998) American academy of pediatrics. Committee on nutrition. cholesterol in childhood. Pediatrics 101: 141-147.

28. Berenson GS, Srinivasan SR, Cresanta JL, Foster TA, Webber LS (1981) Dynamic changes of serum lipoproteins in children during adolescence and sexual maturation. Am J Epidemiol 113: 157-170.

29. Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH (2003) Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988-1994. Arch Pediatr Adolesc Med 157: 821-827.

30. National Cholesterol Education Program (1991) Report of the expert panel on blood cholesterol levels in children and adolescents. National Heart, Lung, and Blood Institute Information Center.

31. de Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, et al. (1992) Left ventricular mass and body size in normotensive children and adults: Assessment of allometric relations and impact of overweight. Journal of the American College of Cardiology 20: 1251-1260.

32. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, et al. (2004) Mannheim intima-media thickness consensus. Cerebrovasc Dis 18: 346-349.

33. Jourdan C, Wuhl E, Litwin M, Fahr K, Trelewicz J, et al. (2005) Normative values for intima-media thickness and distensibility of large arteries in healthy adolescents. Journal of Hypertension 23: 1707-1715.

34. Ishizu T, Ishimitsu T, Yanagi H, Seo Y, Obara K, et al. (2004) Effect of age on carotid arterial intima-media thickness in childhood. Heart Vessels 19: 189-195.

35. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M (2007) Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation 115: 459-467.

36. Litwin M, Wühl E, Jourdan C, Trelewicz J, Niemirska A, et al. (2005) Altered morphologic properties of large arteries in children with chronic renal failure and after renal transplantation. J Am Soc Nephrol 16: 1494-1500.

37. Litwin M, Wühl E, Jourdan C, Niemirska A, Schenk JP, et al. (2008) Evolution of large-vessel arteriopathy in paediatric patients with chronic kidney disease. Nephrol Dial Transplant 23: 2552-2557.

38. Bakiler AR, Yavascan O, Harputluoglu N, Kara OD, Aksu N (2007) Evaluation of aortic stiffness in children with chronic renal failure. Pediatr Nephrol 22: 1911-1919.

39. Mitsnefes MM, Schwartz SM, Daniels SR, Kimball TR, Khoury P, et al. (2001) Changes in left ventricular mass index in children and adolescents after renal transplantation. Pediatr Transplant 5: 279-284.

40. Becker-Cohen R, Nir A, Ben-Shalom E, Rinat C, Feinstein S, et al. (2008) Improved left ventricular mass index in children after renal transplantation. Pediatr Nephrol 23: 1545-1550.

41. Groothoff JW, Lilien MR, van der Kar NC, Wolff ED, Davin JC (2005) Cardiovascular disease as a late complication of end-stage renal disease in children. Pediatr Nephrol 20: 374-379.

42. Arnaiz P, Acevedo M, Barja S, Berrios X, Guzman B, et al. (2007) Subclinical arteriosclerosis, classic and emerging cardiovascular risk factors in obese Chilean children. Rev Chil Pediatr 78: 135-142.

43. Acevedo M, Arnaíz P, Barja S, Berríos X, Bambs C, et al. (2007) Proteína C-Reactiva y su relación con adiposidad, factores de riesgo cardiovascular y aterosclerosis subclínica en niños sanos de la Región Metropolitana. Rev Chil Cardiol 26: 43-54.

44. Barja S, Acevedo M, Arnaiz P, Berríos X, Bambs C, et al. (2009) Early markers for atherosclerosis and metabolic syndrome in children. Rev Med Chil 137: 522-530.

45. Panichi V, Rizza GM, Paoletti S, Bigazzi R, Aloisi M, et al. (2008) Chronic inflammation and mortality in haemodialysis: effect of different renal replacement therapies. Results from the RISCAVID study. Nephrol Dial Transplant 23: 2337-2343.

46. Tekin IO, Pocan B, Borazan A, Ucar E, Kuvandik G, et al. (2008) Positive correlation of CRP and fibrinogen levels as cardiovascular risk factors in early stage of continuous ambulatory peritoneal dialysis patients. Ren Fail 30: 219-225.