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Serum albumin and von Willebrand factor: possible markers for early detection of vascular damage in children undergoing peritoneal dialysis

Abstract

Purpose: Cardiovascular diseases are the main causes of morbidity and mortality in children with end-stage renal disease and the relationships among several relevant potential biomarkers were investigated in pediatric peritoneal dialysis patients.

Methods: Serum homocysteine, von Willebrand factor (vWF), apolipoproteins A and B, lipoprotein-a, high sensitive-CRP, hemoglobin, phosphorus and parathyroid hormone (PTH) levels, systolic (SBP) and diastolic (DBP) blood pressure, carotid intima-media thickness (cIMT) and left ventricular mass index (LVMI) were measured in 21 pediatric peritoneal dialysis patients and control subjects.

Results: All risk factors were higher in patients than controls. LVMI values were negatively correlated with hemoglobin and positively correlated with PTH and phosphorus levels ($p=0.007$, $r = -0.573$; $p=0.013$, $r = 0.532$ and $p=0.035$, $r = 0.461$, respectively). cIMT was negatively associated with serum albumin and positively correlated with vWF levels and with SBP and DBP ($p=0.006$, $r = -0.578$; $p=0.039$, $r = 0.453$; $p=0.02$, $r = 0.503$; $p=0.024$, $r = 0.491$, respectively). Robust regression analyses showed that hemoglobin was an independent predictor of LVMI and serum albumin was an independent predictor of cIMT.

Conclusion: Only uremia-related factors were independent risk factors for predicting LVMI and cIMT. Hemoglobin level may be a critical factor in the development of left ventricular hypertrophy; therefore, effective treatment of anemia is crucial. Low serum albumin and high hsCRP and vWF levels, and their correlations with cIMT, indicate these patients could be at risk of developing malnutrition–inflammation–atherosclerosis syndrome and suggest that serum albumin and vWF levels may be useful markers for early detection of vascular damage.

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Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in patients with end-stage renal disease in dialysis and transplant patients [1]. Vascular complications, including endothelial dysfunction, vascular calcification and atherosclerosis, and cardiac events, including valvular disease and left ventricular hypertrophy (LVH), are the most commonly encountered clinical challenges and the most prevalent reasons for morbidity and mortality. Current United States Renal Data System (USRDS) data show that the mortality rate due to CVD in children undergoing peritoneal dialysis is 28% [2]. The factors predisposing the development of CVD in adult patients with chronic renal failure might be classified as traditional risk factors, such as diabetes mellitus, hypertension, dyslipidemia and obesity, and new risk factors, such as anemia, hyperparathyroidism, hyperhomocysteinemia, inflammation and oxidative stress. Although specific risk factors for CVD are not yet defined in children, they presumably similar to those seen in adults. Investigation of risk factors for CVD in children undergoing peritoneal dialysis will provide information necessary to better understand the underlying factors. Left ventricular hypertrophy (LVH) and increased carotid intima-media thickness (cIMT), for example, are both considered to be important risk factors for CVD in pediatric dialysis patients [3]. Increased cIMT of the large arteries also is an early marker of atherosclerotic changes and has been reported to be a predictor of cardiovascular events in dialysis patients [4]. LVH can be determined by measurement of the left ventricular mass index (LVMI) using echocardiography and cIMT can be determined from 2D Doppler echo imaging.

This paper describes a pilot study involving 21 children undergoing peritoneal dialysis in our department. The aim of the study was to investigate the potential cardiovascular risk factors, including serum homocysteine, von Willebrand factor (vWF), apolipoprotein A (APO-A) and B (APO-B), lipoprotein-a (Lpa), high sensitive-CRP (hsCRP), hemoglobin, phosphorus, parathyroid hormone, systolic (SBP) and diastolic (DBP) blood pressure, in patients and control subjects. We also investigated the relationship between these markers and IMT and LVMI.

Materials and Methods

Patients

Twenty-one pediatric dialysis patients [10 boys (47.6 %) and 11 girls (52.4%)] who had undergone at least 12 months of maintenance dialysis, and their gender-matched controls, were included in the study. Mean age of the patients were $146.5 \pm$

55.4 months. Of the pediatric dialysis patients, four were on automated peritoneal dialysis (APD) and 17 were on continuous ambulatory peritoneal dialysis (CAPD). CAPD patients were treated with five exchanges daily. Mean dialysis time was 3.8 ± 1.5 years. Mean weakly urea-KtV value was 2.6 ± 0.7 . Underlying diseases included reflux nephropathy in ten patients, glomerulopathies in eight patients, hemolytic uremic syndrome in two patients and metabolic disease in one patient. Patients who had 1) peritonitis, 2) systemic or local infection, 3) congenital, structural or primary myocardial disease or 4) congenital, structural or primary vascular disease were excluded from the study.

All the patients were treated with calcium-containing oral phosphate binders, calcitriol and erythropoietin. In addition, all the children on dialysis were taking a statin for abnormal lipid patterns.

The systolic and diastolic blood pressure levels were measured, with the proper-sized cuff from the right arm of the patient, using an oscillometric device. To control for differences in age and body size, blood pressures were indexed to the age-, gender- and height-specific 95th percentile for each subject. Hypertension was defined as indexed SBP or DBP ≥ 1.0 . The goal of antihypertensive management was to keep the systolic and diastolic blood pressures less than the 95th percentile for the patient's age, height and gender. Hypertensive children were treated with a calcium antagonist and/or angiotensin-converting enzyme inhibitor.

Laboratory studies

Blood samples were obtained in the morning after an overnight fast of at least 12 h. Serum biochemistry was performed with routine laboratory techniques. Systolic and diastolic blood pressure values, serum creatinine, albumin, hemoglobin, total cholesterol; triglyceride, homocysteine, hsCRP, APO-A, APO-B, Lpa, vWF, parathyroid hormone and phosphorus levels were measured at the time of study. Homocysteine levels were determined by fluorometric high-performance liquid chromatography and hs-CRP levels were measured by the nephelometric method.

cIMT is defined as a double-line pattern visualized by Doppler echo 2D imaging (High-resolution B-mode system) on both walls of the common carotid artery in a longitudinal view with minimal compression. The cIMT measurements were performed at 20 mm from the bifurcation in the right and left common carotid arteries. It was measured three times in both sites, and the mean of these measurements was recorded for analysis.

TABLE 1. Measured and assayed parameters in patients and control subjects

	Patients	Controls	P	Power for t Test	Power for Mann-Whitney U Test
Hemoglobin (g/dL) [†]	9.8 ±1.95	13.1±1.3	0.0001		1.00000
Albumin (g/dL) [†]	3.4±1	4.3±0.3	0.0001		0.99568
Triglyceride (mg/dL) *	196.3±87.5	101.7±33.4	0.0001	0.99117	
Total Cholesterol (mg/dL) [†]	205.1±45.4	140.4±43.2	0.0001		0.99910
HDL (mg/dL) [†]	52±18.1	53.1±15.8	0.678 (NS)	NS	
LDL (mg/dL) [†]	141.5±47.9	66.9±51.1	0.0001		0.99935
Lipoprotein-a (mg/dL) [†]	88.5±7	17.4±11.1	0.001		1.00000
Apolipoprotein A (mg/dL) *	155.5±30.8	111.4±21.3	0.0001	0.99817	
Apolipoprotein B (mg/dL) *	110.6±36.2	58.3±17.5	0.0001	0.99981	
hsCRP (mg/L) [†]	6.9±3.4	0.5±0.5	0.001		1.00000
Phosphorus (mg/dL) *	5.3±1.2	4.3±0.6	0.037	0.99999	
Parathyroid Hormone (pg/mL) [†]	486.9±116.8	37.4±20.3	0.0001		1.00000
Von Willebrand Factor [†]	207.3±46.3	91.9±37.5	0.0001		1.00000
Homocysteine (μmol/L) **	15.8±9.5	7.9±3	0.015		0.98789
LVMI (g/m) *	113±48.5	34.1±6	0.0001	1.00000	
Carotid IMT (mm) *	0.5±0.08	0.34±0.09	0.0001	0.99937	
Diastolic Blood Pressure (mmHg) *	76.6±14.9	66.2±8	0.015	0.73733	
Systolic Blood Pressure (mmHg) *	120.1±18.7	96.4±10.9	0.0001	0.99574	

* t test was performed: $p < 0.05$ was taken as significant[†] Mann Whitney U test was performed: $p < 0.05$ was taken as significant

NS: not significant

TABLE 2. Independent predictors of cIMT and LVMI in children undergoing peritoneal dialysis

Variable	Predictors	β	95% confidence limits	P
cIMT * (Carotid intima media thickness)	Serum albumin level	- 0.0314	-0.0371 / -0.0258	< 0.0001
LVMI * (Left ventricular mass index)	Hemoglobin	-26.3471	-33.3028 / -19.3914	< 0.0001

* Robust regression analysis; $p < 0.05$ was taken as significant

FIGURE 1. LVMI values were negatively correlated with hemoglobin levels (Spearman's rho correlation test) and positively correlated with serum PTH and phosphorus levels (Spearman's rho and Pearson's correlation tests were performed respectively).

Echocardiographic measurements such as left ventricular end diastolic diameters and interventricular and posterior wall thicknesses in diastole were calculated based on the American Society of Echocardiography guidelines via high resolution 2D and full Doppler probe.

Left ventricular mass were calculated using the Devereux formula: $LVM = 0.8[1.04 ([LVEDD + PWT + IVSDT]^3 - [LVEDD]^3)] + 0.6$ g, where LVEDD is left ventricular diameter in end diastole, PWT is posterior wall thickness in diastole, and IVSDT is inter-ventricular septum thickness in end diastole. LVMI was used to evaluate LVH which was calculated as LVM divided by height (meters).

Statistics

Statistical analysis was performed using the Statistical Package for Social Sciences for Windows version 11.0 (SPSS Inc; Chicago, IL, USA). All values were stated as the mean $\pm$ SD. The Shapiro–Wilk test was used to understand which parameters are normally distributed in the patients and control groups. Comparisons of the means were made using Mann–Whitney U for serum albumin, hemoglobin, total cholesterol, LDL, HDL, lp-a, hsCRP, PTH, homocysteine, vWF levels between patients and control subjects. The comparisons of means of the serum triglyceride, APO-A, APO-B, cIMT, LVMI, phosphorus levels and diastolic and systolic blood pressure were also made using t test between the patients and controls. Pearson's and Spearman's rho correlation tests were used for relationship between measured and assayed parameters. Robust regression analysis was performed using all of the parameters to assess the independent predictors of cIMT and LVMI. P values of less than 0.05 were accepted as statistically significant.

Results

Plasma homocysteine, high sensitive-CRP, vWF, APO-A and APO-B and Lpa levels were all higher in patients than in the control subjects (Table 1). LVMI values were negatively correlated with hemoglobin levels in patients ($p=0.007$, $r = -0.573$; Spearman's rho correlation test, Figure 1). In addition, LVMI values were positively correlated with serum PTH and phosphorus levels; $p=0.013$, $r = 0.532$ and $p=0.035$, $r = 0.461$, respectively; Spearman's rho and Pearson's correlation tests, respectively, Figure 1).

Values for cIMT were negatively associated with serum albumin and positively correlated with VWF levels ($p=0.006$, $r = -0.578$; $p=0.039$, $r = 0.453$, respectively, Spearman's rho correlation test, Figure 2). In addition, there were positive

FIGURE 2. Values for cIMT were negatively associated with serum albumin and positively correlated with VWF levels (*Spearman's rho correlation test*). A positive correlation was seen between cIMT and SBP and DBP levels (*Pearson's correlation test*).

correlations between the cIMT and SBP and DBP levels ($p=0.02$, $r=0.503$; $p=0.024$, $r=0.491$, respectively; Pearson's correlation test, Figure 2). Remarkably, there was a significant correlation between serum APO-B and vWF levels ($p=0.003$, $r=0.615$, Spearman's rho correlation test, Figure 3). Contrary to our expectations, the homocysteine levels did not show a correlation with any assayed or measured parameters, including cIMT and LVMI.

Robust regression analyses showed that hemoglobin level was an independent variable for predicting LVMI (Table 2) and serum albumin level was found to be an independent predictor of cIMT (Table 2).

Discussion

We studied traditional and new atherosclerotic/inflammatory cardiovascular risk markers, including apolipoproteins, homocysteine, vWF, LVH, cIMT, hsCRP and blood pressure, and noted significantly elevated levels of all of these markers in the children undergoing peritoneal dialysis. The increase in the above parameters indicated that children on the peritoneal dialysis had CVD; as a result, our patients also had two early indicators of CVD: LVH and increased cIMT.

LVH develops in children with renal insufficiency and progresses as creatinine clearance worsens. Data from the International Pediatric Peritoneal Dialysis Network registry on 507 patients indicated the overall prevalence of LVH to be

FIGURE 3. Positive correlation between apolipoprotein B (APO-B) and von Willebrand factor (vWF). Spearman's rho correlation test was performed.

48% [5]. Although the exact mechanisms of LVH are still incompletely understood, the presence of pressure overload, volume and sodium retention are considered important factors in the development of LVH. The prevalence of high blood pressure is 50-75% in children with treated dialysis [6]. In that case, hypertension was the strongest independent predictor of LVH in children with chronic kidney disease [7]. In contrast, despite the presence of higher SBP and DBP levels in our patients in comparison with the control subjects, no relationship between SBP and/or DBP levels and LVMI was seen. We found that the major trigger and/or cause of LVH were/low hemoglobin level rather than hypertension: there was a significant negative correlation between LVMI and hemoglobin levels in our patients (Figure 1). In addition, Robust regression analysis showed that hemoglobin level was most important independent predictor of LVMI in children undergoing peritoneal dialysis (Table 2). These results suggest that the relationship between blood pressure and the development of LVH may vary. Consistent with this, Sinha *et al.* reported LVMI was associated with SBP in the absence of overt hypertension [8]. Additionally, a number of studies support the association between hemoglobin levels and LVMI in children [9,10]. Anemia contributes to the pathogenesis of LVH via the increase in cardiac preload and systemic resistance that occurs in response to decreased oxygen capacity [11].

Regression of LVMI with recombinant human erythropoiesis-stimulating agents (ESA) therapy in CKD

patients is still controversial. Most of the several randomized, controlled trials have been reported that the correction of anemia with ESA was not associated with regression of LVH [12-14]. Perhaps the presence of anemia alone may not be sufficient for the development of LVH. We found that there were relationships among LVMI, serum PTH and phosphorus levels. These results suggest that the combination of many risk factors, including anemia and hyperparathyroidism, are necessary for development of LVH. On the other hand, serum PTH and phosphorus levels were not independent risk factors in our patient cohort. The negative impact of PTH on cardiomyocytes, such as chronotropic, inotropic and hypertrophic effects, may play a minor role in the development of LVH in our patients [15]. The increased PTH level observed in 60% of children receiving dialysis therapy is secondary to chronic vitamin D deficiency; thus, it is likely that the observed increase in LVMI is linked to vitamin D deficiency as well. Pantage *et al.* showed that vitamin D deficiency was as independent predictor of increased LVMI in children with chronic kidney disease [16]. According to our results, although high serum PTH level does not appear to be an independent risk factor, treatment of secondary hyperparathyroidism with active vitamin D can contribute to the improvement of LVH in children undergoing peritoneal dialysis. It has been proposed that cIMT be added to the measured cardiovascular risk factors to improve individual risk assessment [17]. Prolonged exposure to the uremic milieu leads to a deterioration in cIMT and an increase in vascular stiffness; therefore, cIMT can be used as a surrogate marker of early atherosclerosis. A relative increase in cIMT has been previously shown in pediatric dialysis patients [18-19]. In the present study, the mean cIMT measurements were significantly elevated in the patients undergoing peritoneal dialysis compared with the controls. This finding is consistent with previous studies and suggests that patients undergoing peritoneal dialysis have vascular damage. Although we did not find any relationship between cIMT and LVMI, both measurements were increased in our patients. These findings suggest that vascular damage develops in parallel with cardiac abnormalities in the children undergoing peritoneal dialysis. According to our results, increased cIMT seems to be associated with serum albumin, vWF and systolic and diastolic blood pressure levels (Figure 2). These results are in contrast with previous studies. Litwin *et al.* stated that hypertension was an important risk factor in pre-dialytic patients, while in children on dialysis, hyperphosphatemia, hyperparathyroidism and treatment with calcium-containing phosphate binders were the major contributing factor of arterial abnormalities

[20]. Our results suggest that 1) the negative effects of hypertension are ongoing in patients on dialysis, as well as pre-dialytic patients and 2) there were no correlations among cIMT, serum PTH and phosphorus levels in our patients. One explanation for this difference might be the effects of vitamin D on calcium-phosphorus homeostasis and/or its proinflammatory properties rather than secondary hyperparathyroidism and hyperphosphatemia. In fact that, Shroff *et al.* showed both low and high levels of active vitamin D are related to high cIMT [18]. Thus, hyperphosphatemia and hyperparathyroidism might be risk markers for arterial abnormalities in children on dialysis, but they were not risk factors for our patients in the present study. Our study also indicates 3) a negative correlation between cIMT and serum albumin levels, increased LVMI, serum hsCRP and decreased albumin levels, which may indicate that patients on dialysis have malnutrition–inflammation–atherosclerosis (MIA) syndrome, which is a strongly predictor of mortality in dialysis patients. Our study also shows 4) that patients on maintenance peritoneal dialysis have endothelial dysfunction as assayed by elevated serum levels of vWF.

The relationship between cIMT and vWF levels has not been studied previously in children undergoing peritoneal dialysis. vWF is a traditional marker of the endothelial dysfunction that is the first phase in the development of atherosclerotic plaques; therefore, atherosclerosis may be a determinant of vWF levels. We suggest that serum vWF levels may provide an important clue to the linking of a systemic marker of inflammation to atherosclerosis. Further studies with larger sample sizes are needed to clarify whether vWF is causative agent or merely a byproduct of the increased cIMT.

On the other hand, we found that serum albumin level was an independent risk factor for predicting cIMT (Table 2). Low serum albumin levels seems to be risk a factor for vascular disease development in children undergoing peritoneal dialysis in our study. The mechanism of vascular disorder and serum albumin association likely involves its oxidant properties: it has been suggested that albumin is a powerful oxidant scavenger in human plasma and can inhibit hydroxyl radicals, peroxyl radicals and hypochlorous acid [21]. Albumin, therefore, is a vasculoprotective factor. Impaired vasculoprotective effects of serum albumin, due to its oxidative modification in a uremic setting, may significantly contribute to the increased oxidative stress and, perhaps, development of vasculopathies in our patients undergoing peritoneal dialysis. Hypoalbuminemia due to renal failure, as was seen in our patients, may be a consequence of activation of the acute phase response and may represent a MIA syndrome. As a consequence, our results

including low serum albumin and elevated hsCRP and vWF levels may support the recommendation that the measures targeting higher albumin levels and treatment of inflammation might alleviate vasculopathies in children undergoing peritoneal dialysis.

Arterial IMT is a measure of preclinical vascular disease such as atherosclerosis. The complex interaction between hyperhomocysteinemia, oxidative stress and microinflammation may result in accelerated atherosclerosis in chronic kidney patients [22]. No solid biochemical mechanisms have emerged linking homocysteine and vascular damage. Moreover, the relationship between homocysteine levels and cardiovascular risk is controversial. While several cross sectional studies have reported weak positive relationships between serum homocysteine levels and cIMT, other studies claim robust relationships between them [23–24]. In spite of increased serum homocysteine levels in our patients, their levels were not found to be related to cIMT and LVMI. These findings indicate that circulating homocysteine may be a surrogate marker of another, yet-to-be-identified, risk factor(s) for CVD. A recent study showed that high-dose folic acid, vitamin B6 and vitamin B12 supplementation did not reduce CV complications or mortality [25]. Moreover, our present observations regarding the relationship among hyperhomocysteinemia, early nephrosclerosis, and increased homocysteine levels without the risk of CVD due to C677T transition of the methylenetetrahydrofolate reductase gene are consistent with previous studies [26].

Chronic systemic inflammatory processes are commonly seen in children with end-stage renal disease [27] and hsCRP is a perfect indicator of chronic systemic inflammation [28]. In the present study, serum hsCRP levels were higher in the patients than in control subjects and hs-CRP level was not found to be related to either LVMI or cIMT. Furthermore, serum hs-CRP level was not an independent risk factor for predicting LVMI and cIMT. These results suggest that elevated serum hsCRP level is a secondary phenomenon rather than a causal relation in these children undergoing peritoneal dialysis. One possible explanation for the lack of correlation among hsCRP levels, LVMI and cIMT might be the dialysis patients' relatively low inflammatory cytokines levels [29].

We are aware that the present study has several limitations, including the observations restricted to a single center, being a cross-sectional study with a small number of subjects and having only one baseline measured or assayed value and no follow-up values.

In conclusion, the present findings indicate that traditional and non-traditional risk factors can mutually

predispose development of either vascular damage or heart muscle damage; however, hemoglobin and albumin levels are known to be uremia-related risk factors and were found to be independent risk factors for predicting LVMI and cIMT, respectively, in the current study. Uremia-related risk factors seemed to be more effective than traditional risk factors for estimating the development or progression of the vascular damage and/or heart muscle damage in the present study. Maintenance of normal hemoglobin, phosphorus and PTH levels might be the key point in reducing LVH during peritoneal dialysis. On the other hand, adequate peritoneal dialysis and stringent control of hypertension may be necessary to prevent the development of MIA syndrome in children undergoing peritoneal dialysis. Since serum vWF levels reflect endothelial dysfunction, assaying of serum vWF levels might be a useful approach for predicting early vascular damage. Prospective and longitudinal multicenter studies are needed to clarify their interrelationship.

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