Oxidative Stress in Egyptian Hemodialysis Children

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Introduction. Nitric oxide (NO) is one of the endothelium-dependent relaxing factors released by the vascular endothelium. It is decreased in chronic kidney disease. It was found that higher levels of circulating proinflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), IL-6, and IL-13 are associated with mortality. The aim of our study was to evaluate the disturbance in NO in chronic kideny failure and its relationship with hypertension and inflammatory and nutritional parameters, as indirect indexes of uremic oxidative stress.

Materials and Methods. This study included 31 children consisting of 23 children, aged from 4 to 18 years old, with ESRD, on regular hemodialysis, and 8 children admitted to hospital for other diseases (control group). Predialysis blood samples were tested for IL-1β, TNF-α, and NO, and were compared with the control group.

Results. Serum levels of TNF-α and IL-1β were significantly higher in children on hemodialysis as compared to the control group (TNF-α, 104.54 ± 17.31 pg/mL versus 48.19 ± 6.28 pg/mL, $P = .005$; IL-1β, 5.35 ± 0.75 pg/mL versus 2.13 ± 0.61 pg/mL, $P = .02$; respectively). However, the levels of NO, albeit higher in this group had no significant difference with the controls.

Conclusions. The levels of cytokines are high in pediatric patients on hemodialysis, which reflects a state of oxidative stress.

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INTRODUCTION

The uremic syndrome is a micro-inflammatory condition with a significant increase in inflammatory markers. Malnourished uremic patients present elevated levels of circulating cytokines, further aggravating the oxidative and inflammatory characteristics of uremia.[1] Significant uremic oxidative stress increases the inflammatory state and promotes the alterations of tiny molecules such as amino acids, proteins, lipids, and carbohydrates.[2]

Endothelial function is profoundly altered in uremic patients due to cell production of inflammatory mediators and cytokines, biochemical, and enzymatic changes that promote inflammation, as well as inhibitors and compounds that interfere with nitric oxide (NO).[3] Endothelial dysfunction has been consistently linked to atherosclerosis, death, and cardiovascular events in end-stage renal disease (ESRD) patients. This generates the hypothesis that interventions aimed at attenuating or preventing endothelial dysfunction and inflammation may attenuate the exceedingly high cardiovascular risk burden of these patients.[4]

Traditional risk factors cannot explain the high prevalence and incidence of cardiovascular disease in chronic kidney disease; therefore, other nontraditional risk factors such as oxidative stress, the role of NO pathway, adipocytokines, and hemodialysis-induced endothelial dysfunction have increasingly been studied.[5] Hemodialysis is associated with impairment in antioxidant mechanisms. The resulting oxidative stress has been implicated in long-term complications including anemia, amyloidosis, accelerated atherosclerosis,

and malnutrition.[6] Evidence indicates that total NO production is decreased in chronic kidney disease or ESRD contributing to endothelial dysfunction.[7]

The kidneys are responsible for elimination of most cytokines. In ESRD, the half-life of cytokines may be significantly prolonged.[8] Tatiana and coworkers[9] have established that reduced plasma L-arginine and NO production and increased tumor necrosis factor-α (TNF-α), fibrinogen, and C-reactive protein levels in malnourished uremic patients are associated with increased aggregation of platelets. It was found that higher levels of circulating pro-inflammatory cytokines such as interleukin-1β (IL-1β), TNF-α, IL-6, and IL-13 are associated with mortality, whereas IL-2, IL-4, IL-12, and immune parameters reflecting improved T cell function are associated with survival in patients with ESRD on hemodialysis.[10] Our study aimed to assess oxidative stress in children on hemodialysis and also to evaluate the disturbance in NO.

MATERIALS AND METHODS

Patients

This prospective study included 31 children of both sexes and different ages, divided into 2 groups. The first group consisted of 23 children aged 4 to 18 years old, already diagnosed with ESRD (glomerular filtration rate < 15 mL/min/1.73 m^2), on regular hemodialysis. They were recruited from the Hemodialysis Unit of Center of Nephrology and Transplantation, Children Hospital, Cairo University. The second group included 8 children admitted in the hospital for a nonrenal disease (control group). The inclusion criteria for the case group were receiving maintenance hemodialysis as a replacement therapy and age ranged between 4 and 18 years. Children with acute kidney failure on temporary hemodialysis, evidence of acute infection with fever at the time of the study, and recent or current use of other anti-inflammatory agents (eg, ibuprofen and corticosteroids) or lipid-lowering agents, which might affect serum cytokine concentrations, were excluded from the study. Informed consent was obtained from each patient's parent, and assent was obtained from each patient who was older than 14 years before study enrollment. This study was approved by the ethics committee in the Cairo University Hospital and was conducted in accordance with the University bylaws for human research.

Data Collection

Data on the following were collected: demographic characteristics (age and sex); original kidney disease; date of the start of hemodialysis; comorbid conditions; current treatment; vascular access, its duration, and its complications; and history of recent blood transfusion. Anthropometrics measurements (dry weight and height) were plotted on Egyptian Growth Charts and vital signs (predialysis, every hour during the dialysis session, and at the end of the session) and signs of renal osteodystrophy (ROD) were evaluated. Dialysis prescription for each patient was recorded, including dry weight, weight gain, ultrafiltration volume and rate per hour, flow, and heparin dose (initial and maintenance). Dialysis adequacy (Kt/V) was calculated.

Investigations

Laboratory investigations included predialysis and postdialysis blood urea nitrogen, serum creatinine, serum total calcium, serum phosphorus, serum alkaline phosphatase, serum albumin, hemoglobin level, and hepatitis markers. In addition, predialysis blood samples were tested for IL-1β, TNF-α, and NO using enzyme-linked immunosorbent assay.

All patient serum samples and reagents were brought to room temperature. First, standards were prepared from a 500-pg/mL stock. The appropriate dilutions were made to establish standard curve. Fifty microliters of enzyme-linked immunosorbent assay diluent was pipetted into each well of 96-well plates. Then 100 µL of standards and samples were pipetted into wells and mixed with diluent. After incubation, standards and samples were aspirated from the wells and washed with buffer. A total of 100 µL of a solution that contained a detection antibody was then added. The wells were washed with buffer, and 100 µL of tetramethylbenzidine was subsequently added. Fifty microliter of a solution that contained 1-M phosphoric acid was added. Absorbance was read at 450 nm. Results were initially calculated and converted to pg/mL by log-log computation with application according to the standard curve.[11]

Abdominopelvic ultrasonography and echocardiography (for detection of left ventricular hypertrophy and its relation to NO level) were performed for all participants.

Statistical Analyses

All patient information was tabulated and processed using the SPSS software (Statistical Package for the Social Sciences, version 14.0, SPSS Inc, Chicago, Ill, USA). For quantitative variables, means, and medians (as a measure of central tendency), standard deviation, range, and minimum and maximum (as measures of variability) were reported. Frequency and percentage were presented for qualitative variables. The chi-square test and Fisher exact test were used to estimate differences in qualitative variables. A *P* value less than .05 was considered significant.

RESULTS

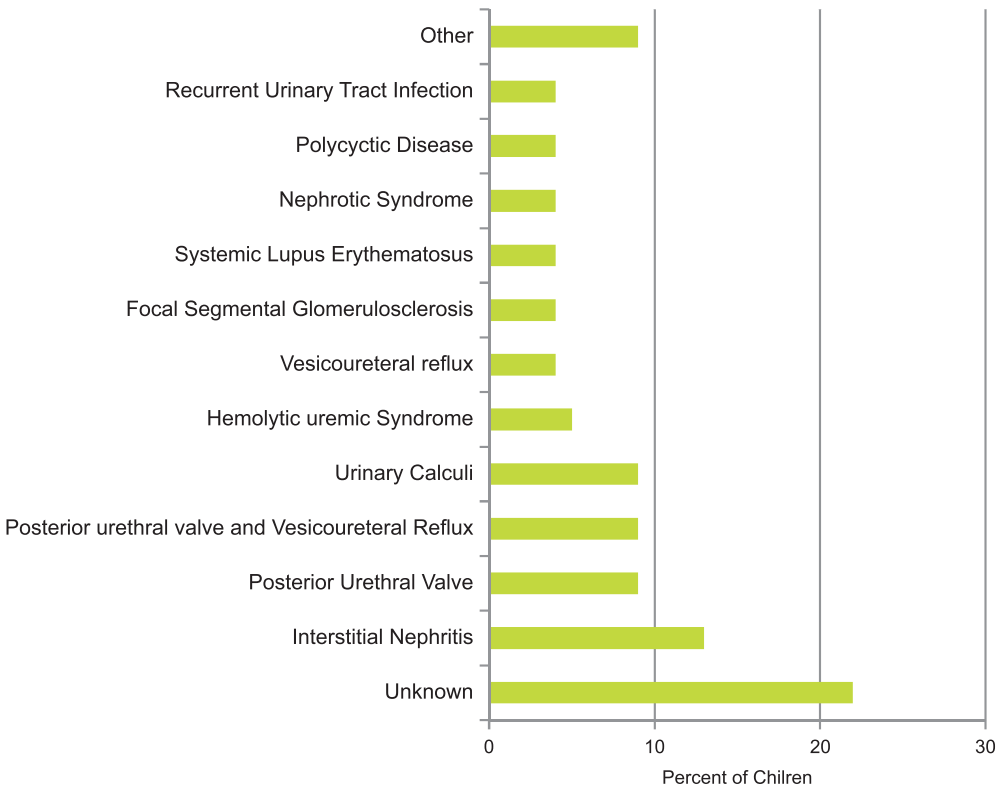
There was no significance between the two groups in terms of sex distribution (12 boys and 11 girls among hemodialysis children and 6 boys and 2 girls among the controls), but the mean age of hemodialysis children was greater (13.25 ± 0.74 years versus 4.56 ± 1.22 years). Fifteen patients were on hemodialysis, while 8 patients were on hemodiafiltration. Twenty-two patients of the hemodialysis group (95.7%) had their weight below the 3rd percentile and only 1 patient was between the 3rd and 5th percentiles. Eighteen patients (78.3%) had their height below 3rd percentile, 1 patient was between the 3rd and 5th percentiles, 2 patients (8.7%) were at the 5th percentile, and 2 patients were between the 10th and 25th percentiles. Other characteristics of the patients are summarized in Table 1.

The Figure demonstrates the original kidney diseases of the patients on hemodialysis. Unknown

Table 1. Characteristics Children on Hemodialysis*

Characteristic	Value
Age, y	13.25 ± 3.53 (4.0 to 17.8)
Weight, kg	24.97 ± 6.11 (12.0 to 39.0)
Height, cm	116.96 ± 13.98 (80.0 to 135.0)
Hemodialysis duration, y	5.32 ± 2.69 (0.5 to 8.8)
Vascular access duration, y	3.41 ± 2.68 (0.1 to 8.0)
Kt/V	1.63 ± 0.40 (1.1 to 2.8)
Predialysis blood urea nitrogen, mg/dL	66.74 ± 15.57 (28.0 to 95.0)
Albumin, mg/dL	3.40 ± 0.62 (2.0 to 4.6)
Calcium, mg/dL	8.54 ± 1.47 (5.3 to 11.3)
Phosphorous, mg/dL	4.09 ± 1.87 (1.4 to 9.6)
Alkaline phosphatase, U/L	583.09 ± 637.17 (80.0 to 2938.0)
Hemoglobin, g/dL	10.12 ± 2.01 (5.0 to 13.0)

*Values are mean ± standard deviation (range).



Original kidney diseases in children on hemodialysis.

cause was found in 22% of the children. Patient with recurrent urinary tract infections had no infection at the time of the study, and in those with systemic lupus erythematosus, the disease was not active at the time of the study. Comorbidities were present in 11 children. Epilepsy was present in 5 patients (21.7%), mental retardation in 2 (8.7%), hypogonadism in 1 (4.3%), myopathy in 1 (4.3%), encephalitis in 1 (4.3%), and hearing impairment in 1 patient (4.3%). One patient had failed kidney transplantation before. One patient had experienced urosurgical operation for vesicoureteral reflux. Eighteen patients (78.3%) had hypertension, 15 of which were controlled. Single anti-hypertensive drug was used in 9 patients (50.0%), 2 drugs in 6 (33.3%), and 3 drugs in 3 patients (16.7%).

Intravenous iron was being used in 21 patients (91.3%). Blood transfusion had been given to 4 patients (17.4%) during the 3 months preceding the study. Renal osteodystrophy was documented in 12 children (52.2%). Seventy percent of the children had an arteriovenous fistula, 22% had a permacath, 4% had an intravenous catheter, and 4% had a saphenous graft. Complications were present in the vascular access of 4 patients (17.4%) in the form of abscess (occurred after taking the study samples) in 1 patient, edema in 1 patient, and thrombosis in 2 patients. Hepatitis C was positive in 8 patients of the hemodialysis group (34.8%), while hepatitis B was negative in all patients. Echocardiography was done for all of the patients. Thirteen patients (56.5%) had left ventricular hypertrophy and the other 10 had no abnormalities.

Table 2 shows a comparison between the children on hemodialysis and the control group with regard to IL-1 β, TNF-α, and NO. Serum levels of IL-1 β and TNF-α were significantly higher in the hemodialysis group, while there was no significant difference between the two groups in NO levels. Table 3 shows the levels of these cytokines in relation to the type of dialysis in the hemodialysis group. There were no significant differences between the patients on hemodialysis and those on hemodiafiltration.

Table 2. Levels of IL-1 β, TNF-α and NO in the 2 groups:

Parameter	Hemodialysis	Control	*P*
Interleukin-1β, pg/mL	5.35 ± 0.75	2.13 ± 0.61	.02
Tumor necrosis factor-α, pg/mL	104.54 ± 17.31	48.19 ± 6.28	.005
Nitric oxide, pg/mL	6.76 ± 0.64	6.34 ± 1.50	.77

Table 3. Levels of cytokines in relation to type of dialysis:

Parameter	Hemodialysis	Hemodiafiltration	*P*
Interleukin-1β, pg/mL	4.67 ± 0.91	6.63 ± 1.25	.22
Tumor necrosis factor-α, pg/mL	86.56 ± 18.09	138.25 ± 35.10	.16
Nitric oxide, pg/mL	6.88 ± 0.85	6.53 ± 1.02	.81

There were no significant differences in the level of NO between hypertensive and nonhypertensive patients (P = .79) or between those with left ventricular hypertrophy and those with normal heart (P = .78). The serum level of TNF-α was significantly higher in the patients with ROD, as compared with those with no ROD (P = .02), while IL-1β level was not significantly higher in the patients with ROD (P = .44).

DISCUSSION

Cytokines are polypeptide or glycopeptide molecules. They are essential mediators of the immune response and inflammatory reactions. They are released by immune cells.[12] Impaired immune response coupled with persistent immune stimulation in ESRD may have a role in the low-grade systemic inflammation and altered cytokine balance that characterizes the uremic state, which may translate into increased risk for vascular disease.[13] During a hemodialysis session, cytokines are released mainly by monocytes activated by endotoxin-type compounds in dialysis fluid, complement factors, and direct contact with dialysis membrane.[12]

While most investigators report low levels of NO in uremic subjects, the levels in hemodialysis patients have not been characterized adequately. This is because hemodialysis patients are exposed to both stimulatory and inhibitory factors of NO synthesis.[14] Nitric oxide derived from endothelial cells is related to the maintenance of physiological vascular tone and renal hemodynamics. Impairment of endothelial NO generation is considered one of the major deterioration factors for progressive renal disease.[15]

Our study aimed to assess oxidative stress in hemodialysis children and to evaluate the disturbance in NO. Fifteen patients of our case group were on hemodialysis while 8 patients were on hemodiafiltration. There was no significant difference between the two groups in terms of sex, but there was the mean age of the patients

was greater than the control group. Shiba and colleagues[16] reported that 60% of pediatric patients on regular hemodialysis were females and that the mean age of them was 9.6 ± 3.9 years.

Twenty-two patients of case group (95.7%) had their weight below the 3rd percentile and only 1 patient was between 3rd and 5th percentiles. Also, 18 patients (78.3%) had their height below the 3rd percentile; only 1 patient was between the 3rd and 5th percentiles and 2 patients (8.7%) at the 5th percentile. It is obvious from these results that both weight and height percentile can be affected by the chronic kidney disease. Pundziene and coworkers[17] found only 43.7% of patients with ESRD had heights below the 3rd percentile.

In our study, an unknown cause of ESRD was found in 22% of the case group. Near to our results, Shiba and colleagues[16] reported that among etiologies of kidney failure, unknown cause was present in 39% of children with ESRD. On the contrary, Gulati and colleagues[18] found an undetermined etiology in 4.2% and in a study done by Al-Eisa and colleagues,[19] no specific etiology could be detected in 1.7% of the patients. Eighteen patients of our case group (78.3%) had hypertension, 15 of them were controlled. In agreement, Shiba and colleagues[16] reported that 73.3 % of their patients on regular hemodialysis were hypertensive, controlled by medications in 63.6% of the hypertensive patients.

In our study, the levels of TNF-α and IL-1β were significantly higher in the case group than the control group, while the levels of NO were higher in the case group but of no statistical significance. Similarly, Rysz and associates[12] reported that TNF-α and IL-1β concentrations were significantly increased in hemodialysis patients when compared with healthy controls. Also, Aygun and coworkers[20] reported that baseline IL-1β, IL-6, IL-8, and TNF-α concentrations were elevated compared with those of age-matched controls. Similarly, Ahmed and colleagues[21] reported the presence of significantly higher levels of TNF-α in these patients compared to the detectable level of TNF-α in healthy controls. Goldstein and colleagues[22] suggest that in pediatric hemodialysis patients, there is an imbalance toward a pro-inflammatory state and that treatment with aspirin results in decreased TNF-α level. This can be explained by what Ward[23] states that contact of blood with dialyzer membrane leads to neutropenia and morphological changes of polymorphonuclear leukocytes and activation of monocytes with subsequent release of cytokines.

Owen and Lowrie[24] suggest that the possible cause of inflammation in uremic patients includes bioincompatible materials, membranes, contaminated dialysate fluids, lipopolysaccharides, tubing, infections, hypovolemia, and hypervolemia, as well as surgical trauma including vascular access. Sebekova and colleagues[25] showed that variation in the cytokine levels in patients on hemodialysis could be related to transient nature of the dialysis-induced secretion, poor nutritional status, administration of antihypertensive drugs as angiotensin-converting enzyme inhibitors and calcium channel blockers that suppress cytokine production, individual variation and type of assay and technical factors.

In our cohort of hemodialysis children, there were no statistical significant differences between patients on hemodialysis and hemodiafiltration as regard levels of IL-1β, TNF-α, and NO. Odamaki and associates[26] stated that the type of the dialysis membrane is another determinant for level of cytokines.

In our study, there was no statistical significant difference in the level of NO between hypertensive and nonhypertensive patients. Sarkar and colleagues[14] showed that lack of NO could result in disruption of the balance between NO and vasoconstrictor agents, with resultant vasoconstriction and disease progression, hypertension, and accelerated atherosclerosis.

Hepatitis C was positive in 8 patients of the case group (34.8%), while hepatitis B was negative in all patients of the case group. The level of IL-1β in the 8 patient with hepatitis C infection was 4.9 ± 3.9 pg/mL, which was lower compared to the level in the patients negative for hepatitis C (5.6 ± 3.5 pg/mL). Also, the level of NO in the 8 patient with hepatitis C infection was 5.2 ± 2.7 pg/mL, which is lower compared to the level in patients negative for hepatitis C (7.6 ± 3.0 pg/mL). The level of TNF-α in the 8 patient with hepatitis C infection was 129.3 ± 81.2 pg/mL and was higher than the level in patients negative for hepatitis C (91.4 ± 83.7 pg/mL). Thus, hepatitis C infection seems to affect only the level of TNF-α. Hepatitis C infection still remains a major problem among patients on maintenance hemodialysis.[27]

Ghonemy and colleagues[28] reported that chronic viral hepatitis increases inflammatory mediators as IL-1 and TNF-α.

In our study, serum albumin was somewhat low (3.4 ± 0.6) indicating malnutrition. There was no correlation between albumin and levels of NO, IL-1β, and TNF-α. Similarly, Kuhlmann and Levin[29] found no correlation between pro-inflammatory or anti-inflammatory cytokine concentrations and serum albumin. A plausible explanation is that albumin may not be the optimal indicator of nutrition in pediatric dialysis patients. Schaefer and colleagues[30] stated that studies in children reveal that serum albumin may be affected by hydration and therefore may not be a consistently reliable indicator of nutritional status. On the contrary, Ohshima and coworkers[31] suggested that malnutrition might contribute to the pro-inflammatory state. Another study[32] demonstrated that the effect of hemodialysis on the different nutritional parameters was of no significant correlation.

In our study, serum alkaline phosphatase was high (583.09 ± 637.17 U/L) indicating ROD and hemoglobin was low indicating anemia (10.12 ± 2.01 U/L). More than half of the patients had ROD. The TNF-α level was significantly higher in patients with ROD, compared with those with no ROD, while IL-1β level was not significantly higher in patients with ROD, as compared with those with no ROD. Sebekova and colleagues[25] found that dialysis patients show high plasma TNF-α that may play a significant role in the pathogenesis of ROD. Also, Pertosa and coworkers[33] stated that IL-6 and TNF-α may induce an inflammatory state and are believed to play a significant role in dialysis-related morbidity, among of them is bone disease.

We had 13 patients (56.5%) who had left ventricular hypertrophy. Levey and Eknoyan[34] stated that left ventricular hypertrophy is an independent risk factor of cardiovascular-specific mortality in patients with kideny failure. In our study, there was no significant difference in the level of NO between those with left ventricular hypertrophy and those with normal heart. Similarly, Mottaleb and associates[32] reported that end diastolic dimensions and ejection fraction did not show significant correlations between their levels and the levels of pro-inflammatory cytokines.

The low number of patients was the main limitation of the study and its reason was that kidney transplantation started in our center 3 years before the time of our study, and therefore, the number of patients still on regular hemodialysis subsequently decreased.

CONCLUSIONS

Our study demonstrated that TNF-α and IL-1β were significantly higher in children on hemodialysis as compared to the control group of children with no kidney disease, reflecting a state of oxidative state. However, the levels of NO, albeit higher in this group had no significant difference with the controls.

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CONFLICT OF INTEREST

None declared.

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