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OXIDATIVE STRESS AS A MARKER OF CARDIOVASCULAR RISK IN CHILDREN ON REGULAR HEMODIALYSIS

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Abstract:
Introduction: *Chronic kidney disease (CKD) is associated with a severely increased risk of cardiovascular morbidity and mortality. Numerous structural and functional alterations of the cardiovascular system, e.g. endothelial dysfunction, arterial stiffening, left ventricular hypertrophy (LVH) and remodeling of the vessel wall with hyperplasia and calcification occur early in the course of CKD and contribute to the overt risk of ischemic cardiovascular disease (CVD) and sudden cardiac death.* ***Aims and objectives:*** *The basic aim of the study is to analyze the oxidative stress as a marker of cardiovascular risk in children on regular hemodialysis.* ***Material and methods:*** *This cross sectional study was conducted at Ameer ud din Medical College during 2019. There were 40 children who was selected for this study. At the time of the study, all the patients were on regular three HD sessions per week; each time for 3–4 h for more than 3 months with polysulfone dialyzing membranes, after creatinine clearance had fallen below 8–12 mL/min and/or pharmacological treatment and diet had proved inadequate to control clinical symptoms.* ***Results:*** *We collected all the demographic data of patients. At before-dialysis session, duration of disease positively correlated with HIP-1α ($r = 0.677$, P <0.001) but negatively correlated with VEGF ($r = -0.486$, P < 0.001); VEGF positively correlated with each of pyruvate ($r = 0.316$, P <0.047) and HIF-1α ($r = 0.374$, P <0.018), and, OSI positively correlated with TPX ($r = 0.969$, P <0.001), but, negatively correlated with TAC ($r = -0.469$, P <0.002).*

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INTRODUCTION:

Chronic kidney disease (CKD) is associated with a severely increased risk of cardiovascular morbidity and mortality. Numerous structural and functional alterations of the cardiovascular system, e.g. endothelial dysfunction, arterial stiffening, left ventricular hypertrophy (LVH) and remodeling of the vessel wall with hyperplasia and calcification occur early in the course of CKD (stage 2-4 CKD) and contribute to the overt risk of ischemic cardiovascular disease (CVD) and sudden cardiac death. While an impaired renal function has the potential to aggravate "traditional" risk factors like hypertension, dyslipidaemia, inflammation, and oxidative stress, the concomitant deterioration of mineral homeostasis and thus also bone metabolism is probably the key player leading to accelerated CVD [1]. To highlight the central role of mineral metabolism for both, cardiovascular and skeletal integrity, the term chronic kidney disease-mineral bone disorder (CKD-MBD) was coined recently [2].

Cardiovascular disease (CVD) is the major cause of morbidity and mortality in patients with end-stage renal disease (ESRD) on haemodialysis (HD). Since ESRD frequently results from hypertension and diabetes mellitus, the increased CVD risk in these patients has been assumed to be the result of these underlying diseases. Nevertheless, it has been elucidated how ESRD represents *per se* a CVD risk factor independently by both hypertension and diabetes mellitus [3].

Hypoxia is a state of reduced oxygen pressure below a critical threshold, which restricts the function of organs, tissues and cells. A decrease in oxygen tensions of the kidney was demonstrated in a number of experimental models of CKD [4]. This led to the broad recognition that chronic cellular hypoxia of the kidney is the final common pathway in the progression of CKD leading to eventual kidney failure. A group of transcription factors, designated hypoxia inducible transcription factors, are specifically induced by low tissue oxygen tension and are likely to have a role in the oxygen-sensing mechanism and reparative reaction. Hypoxia induced factor-1 (HIF-1) is a heterodimeric protein consisting of an alpha subunit (with 3 isoforms -1α, -2α and -3α), and a beta subunit (also known as the aryl hydrocarbon receptor nuclear translocator, ARNT), which is constitutively expressed. In normoxia, the regulatory HIF-1α subunit is hydroxylated on two prolines by iron dependent prolyl-hydroxylases to be degraded through the ubiquitin-proteasome pathway - via its interaction with the von Hippel-Lindau tumor suppressor protein [5]. Under cellular hypoxia, inhibition of such hydroxylases spares HIF-1α that translocates into nucleus. There, it heterodimerizes with HIF-1β and binds to the hypoxic response elements of target gene regulatory sequences. This induces the transcription of genes implicated in the control of metabolism and angiogenesis, as well as apoptosis and cellular stress response [6].

Objectives

The basic aim of the study is to analyze the oxidative stress as a marker of cardiovascular risk in children on regular hemodialysis.

MATERIAL AND METHODS:

This cross sectional study was conducted at Ameer ud din Medical College during 2019. There were 40 children who was selected for this study. At the time of the study, all the patients were on regular three HD sessions per week; each time for 3–4 h (total 12 h weekly) for more than 3 months with polysulfone dialyzing membranes, after creatinine clearance had fallen below 8–12 mL/min and/or pharmacological treatment and diet had proved inadequate to control clinical symptoms. The mean dialysis duration was 2.18±1.36 years (range: 1–7 years). All patients were on dietary protein restriction, 1 g/kg body weight per day.

Biochemical analysis

Blood samples (5 mL) with and without EDTA/sodium fluoride as anticoagulant were obtained via venipuncture after the participants had fasted overnight, and serum and plasma were separated and aliquot frozen at −80°C till used. In HD patients, venous blood samples were drawn immediately before and after hemodialysis session. Baseline laboratory investigations were carried out for all patients and controls including complete blood count, serum urea and creatinine, arterial pH, arterial blood gases and infection screening, which included blood and urinary cultures by standard methods.

Statistical analysis

A chi-square test was used to examine the difference in the distribution of the fracture modes (SPSS 19.0 for Windows, SPSS Inc., USA).

RESULTS:

We collected all the demographic data of patients. At before-dialysis session, duration of disease positively correlated with HIP-1α ($r = 0.677$, $P < 0.001$) but negatively correlated with VEGF ($r = -0.486$, $P < 0.001$); VEGF positively correlated with each of pyruvate ($r = 0.316$, $P < 0.047$) and HIF-1α (r =

0.374, *P* <0.018), and, OSI positively correlated with TPX (r = 0.969, *P* <0.001), but, negatively correlated with TAC (r = −0.469, *P* <0.002). At after-dialysis session, HIF-1α negatively correlated with each of TPX (r = −0.529, *P* <0.001) and OSI (r = −0.459, *P* <0.003); while, OSI positively correlated with TPX (r = 0.944, *P* <0.001).

Table 01: Correlations among the measured parameters in CKD patients at before- and after-dialysis settings

Parameters	**Duration**	**Lactate**	**Pyruvate**	**Lactate/Pyruvate ratio**	**HIF-1α**	**VEGF**	**TAC**	**Total peroxides**
Lactate								
Before dialysis	−0.208(0.197)							
After dialysis	−0.184(0.256)							
Pyruvate								
Before dialysis	−0.193(0.234)	0.282(0.078)						
After dialysis	−0.095(0.580)	**0.533(0.001)**						
Lactate/pyruvate ratio								
Before dialysis	−0.067(0.640)	**0.513(0.001)**	**−0.457(0.003)**					
After dialysis	−0.037(0.824)	0.212(0.188)	**−0.630(0.001)**					
HIF-1α								
Before dialysis	**0.677 (0.001)**	0.125(0.442)	−0.149(0.359)	0.220(0.173)				
After dialysis	−0.186(0.249)	0.048(0.770)	0.015(0.929)	0.229(0.156)				
TAC								
Before dialysis	0.265 (0.098)	−0.174(0.283)	−0.147(0.366)	−0.142(0.384)	0.068(0.676)	−0.206(0.202)		
After dialysis	0.022 (0.894)	0.048(0.771)	−0.148(0.361)	0.105(0.517)	−0.220(0.173)	−0147(0.366)		
Total peroxides								

Before dialysis	−0.017(0.918)	−0.032(0.843)	−0.194(0.230)	0.128(0.430)	−0.138(0.394)	0.229(0.156)	−0.247(0.124)	
After dialysis	0.283 (0.077)	0.036(0.825)	0.070(0.668)	−0.204(0.207)	**−0.529(0.001)**	−0.006(0.972)	0.168(0.301)	
Oxidative stress index								
Before dialysis	−0.093(0.566)	−0.002(0.989)	0.161(0.322)	0.156(0.337)	−0.172(0.287)	0.245(0.128)	**−0.469(0.002)**	**0.969(0.001)**
After dialysis	0.285 (0.075)	0.015(0.929)	0.113(0.489)	−0.240(0.136)	**−0.459(0.003)**	0.062(0.705)	−0.155(0.340)	**0.944(0.001)**

Data shown are r value (*P*< value). HIF-1α= hypoxia induced factor-1α, VEGF= vascular endothelial growth factor. TAC = total antioxidant capacity.

DISCUSSION:

Relative hypoxia, as the major activator of hypoxia-inducible factor, is detectable in chronic kidney disease tissues irrespective of etiology and is thought to result from a combination of structural and functional changes that include; decreased peritubular blood flow associated with glomerular injury, capillary rarefaction, vasoconstriction, luminal narrowing of atherosclerotic vessels, increased oxygen demand from hyperfiltration and tubular hypertrophy, limited oxygen diffusion as a consequence of extracellular matrix expansion, and renal anemia [7]. Chronically ill patients on HD exist in unique situation because their survival is dependent upon treatments which are operational only 12–18 h per week in six hour sessions. This procedure subjects these patients to innumerable abrupt alterations in the internal environment, especially rapid shifts in pH. In this study, the before-dialysis levels of plasma lactate, HIF-1α and VEGF were significantly higher compared to healthy controls while, lactate/pyruvate ratio was significantly higher compared to after-dialysis level [8]. The lactate level tended to fall with dialysis, at least in part attributable to this procedure. Also, VEGF plasma level was significantly elevated in after-dialysis session compared to healthy controls. Hypoxia is accompanied by a significant increase in blood lactate and severe systemic acidosis as a direct effect of anaerobic metabolism. Beside the direct effects of anaerobic metabolism, catecholamine-induced stimulation of cellular glycolysis and subsequent synthesis of lactate worsens the increased systemic lactate. In such conditions, accumulated pyruvate is metabolized into lactate [9].

Total antioxidant capacity in renal failure group is diminished to a great extent due to antioxidant exhaustion and inhibition. Oxidative stress can also accelerate the apoptosis of leukocytes in HD patients. The activation of neutrophils and the complement pathway during HD session as the result of interactions of the blood with the dialysis membrane and endotoxin contaminated dialysate, iron overload, the presence of advanced glycation end products, high homocysteine levels, intradialytic cytokine activation, among others, could play a role [10].

CONCLUSION:

It is concluded that there is considerable cellular hypoxia in pediatric patients with CKD that leads to oxidative stress. HD leads to decrease hypoxia and increase loss of antioxidants as evidenced by decreased levels of HIF-1α and TAC at before- compared to after-dialysis settings. The resulting oxidative stress could contribute to the long-term complications in uremic patients.

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