

How to Cite:

Fadel, F. I., Madani, H. A., Kamel, S. M., Othman, S. A., & Salah, D. M. (2022). Plasma Netrin-1 & cardiovascular risk in children with end stage renal disease. *International Journal of Health Sciences*, 6(S4), 1747–1772. <https://doi.org/10.53730/ijhs.v6nS4.6105>

Plasma Netrin-1 & cardiovascular risk in children with end stage renal disease

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Abstract--Background: Cardiovascular disease (CVD) is the most common cause of mortality and morbidity in children with end stage kidney disease (ESKD) which arises from the interaction of several risk factors. The aim of the study is to assess CV risk of ESKD children and outline the impact of KTX on this CV risk. Also valuate the relation between plasma Netrin-1, chronic inflammatory markers and CV risk. Methods: Sixty ESKD (30 on regular hemodialysis (HD),

30 recipients of kidney transplant (KTX) were assessed using 24 hour AMBP assessment, laboratory (including lipid profile and markers of chronic inflammation namely N/L and HsCRP) and echocardiographic data. Plasma netrin-1 was assessed by ELISA technique for all patients. Results: showed significant higher prevalence of hypertension, higher number of patients with 24hrs BP > 95th percentile by ABPM, more prevalence of nocturnal non-dipping BP, higher percentage of obese and overweight patients, worse biochemical analysis, higher chance of medical calcification by higher Po₄ and Ca X Po₄, higher triglyceride level and lower HDL level and higher N/L in HD than KTX group. Significant inverse relation was detected between plasma netrin 1 and Hs CRP and between netrin 1 and N/L (p<0.001) in HD group which meaning that netrin1 has lower level with increasing severity of chronic inflammatory condition. Netrin1 was significantly lower (p=0.007) and N/L is significantly higher (p=0.48) in the presence of LVH among HD group. Conclusions: Hypertension, LVH, dyslipidemia, CKD-MBD and a state of chronic inflammation are considered common CV risk factors in ESKD patients. The lower level of plasma Netrin-1 level could predict the CV risk in ESKD children. KTX has positive impact of decreasing CV risk encountered by ESKD children.

Keywords---Cardiovascular risk, Hemodialysis, kidney transplantation, Netrin-1, HsCRP, neutrophil lymphocytes ratio, ABPM.

Introduction

End stage Kidney disease (ESKD) is the stage 5 of Chronic kidney disease (CKD) in which renal replacement therapy (RRT) becomes necessary for sustaining of life (Vogt and Avner, 2007). ESKD is considered the “tip of the iceberg” of CKD (Coresh et al., 2003). It is a major health problem with multiple medical, social, and financial problems (Jha, 2009). Although kidney transplant (KTX) remains the treatment of choice to maximize survival, growth, and development, 75% of children with ESKD require treatment with dialysis prior to receiving a kidney transplant (Foster et al., 2011). Dialysis is therefore a lifesaving therapy for children with ESKD while they await transplant (McDonald et al., 2004).

The 2 most common causes of death in children with ESKD are cardiovascular disease (CVD) and infection (Chavers et al., 2002). After KTX, cardiovascular (CV) events and infections remain the leading causes of death but CVD is the second most common cause of death after infections (Borchert et al., 2017). Transplantation improves but does not eliminate the pathophysiologic features of ESKD that contribute to CVD (Dharnidharka et al., 2014).

The development of CVD in children with ESKD arises from the interaction of several risk factors that can be categorized into 3 groups: (1) traditional risk factors (diabetes mellitus, obesity, hypertension, and impaired lipid profile), (2) factors related to loss of kidney function (secondary hyperparathyroidism,

anemia, hypoalbuminemia, and thrombotic factors), and (3) emerging risk factors (chronic inflammation, oxidative stress, and endothelial dysfunction) (Lilien and Groothoff, 2009). Combinations of these risk factors could cause accelerated manifestations of cardiac and vascular changes in children (Wilson and Mitsnifes, 2009).

Hypertension is one of the most common traditional modifiable CV risk factors in patients on regular HD for ESKD in childhood (Staples et al., 2010). Ambulatory blood pressure monitoring (ABPM) has been shown to have stronger association with cardiovascular morbidity than office BP (Banegas et al., 2018). It is superior to casual office BP obtained at time of dialysis in delineating cardiovascular morbidity in ESKD patients (Shah et al., 2019)

ESKD has been considered a state of chronic inflammation, which is the cornerstone of pathogenesis of atherosclerosis; it is increased in ESKD patients compared to normal population. Also it is thought that early detection of inflammation might improve the quality of the life of those patients and decrease rate of morbidity and mortality (Dai et al., 2017). The measurement of inflammatory markers such as high sensitivity C-reactive protein (Hs-CRP) which promotes atherosclerosis is helpful in predicting CVD in ESKD patients (Elshafie et al., 2016). Also ESKD patients have higher values for neutrophil-to-lymphocyte ratio (N/L) with a significant positive correlation with hs-CRP levels (Ahbap et al., 2016).

Netrin-1 is a soluble protein, expressed by both the endothelium and macrophages and can directly regulate leukocyte chemotaxis through the UNC5B (unc-5 netrin receptor B) receptor (Lin et al., 2018). For CVD, Netrin-1 has been shown to play an important role in atherosclerosis and considered a cardioprotective agent (Passacquale et al., 2015).

Aim of the work

The aim of the study is to assess CV risk of ESKD children (on regular HD and after KTX) using ambulatory blood pressure monitoring (ABPM) with Electrocardiographic study (Echo) and outline the impact of KTX on this CV risk by comparing both groups of patients. Evaluate the relation between plasma Netrin-1 and CV risk in children with ESKD by comparing its level to ABPM, Echo and markers of chronic inflammation. Also to study the markers of chronic inflammation (neutrophil-to-lymphocyte ratio & HsCRP) as simple predictors of CV risk in ESKD children.

Patients and Methods

Patients

This study included 60 ESKD children (thirty patients on regular hemodialysis (HD group) and thirty kidney transplant recipients (KTX group)). HD and KTX patients were recruited while receiving their dialysis therapy at Hemodialysis section and during their follow up at KTX Clinic of Cairo University Children Hospital (CUCH) respectively.

Patients were included into the study according to the following criteria: a) children with ESKD according to KDIGO 2012 clinical practice guidelines (KDIGO, 2013) of both sexes aged between 4-15 years, b) On trice weekly regular HD therapy (HD group) for at least 1 year duration, c) Recipients of living renal transplant for at least 1 year duration (KTX group) with stable graft function ($GFR \geq 60$ ml/min/1.73 m²). Patients with evidence of primary CVD; such as congenital heart disease, rheumatic heart disease or active vacuities and patients with recent/active infection were excluded from the study.

Methods

This is a cross sectional study that was conducted between 2019 and 2021. The study protocol was approved by Research Ethical Committee of Pediatric Department, Faculty of Medicine, Cairo University. Demographic characteristics (ie, sex, age, age of diagnosis and original renal diseases), duration of follow up, onset of renal replacement therapy (RRT) and clinical data (weight, height, and body mass index (BMI) calculation) were assessed.

ABPM was performed to all patients, monitoring was initiated at the end of midweek dialysis treatment and for 24 h thereafter, readings were taken every 20 min during 24hrs. Patients kept a log of activity which defined sleep and awake readings. ABPM data were considered to be acceptable if at least 65% successful readings were obtained in less than a 24-h period with minimum duration of the monitor worn for 18 h or 40 readings in a 24-h period. 24 hours pulse pressure (PP) was calculated as the difference between the systolic (SBP) and diastolic (DBP), while 24 hours mean arterial pressure (MAP) was calculated as the sum of DBP and a third of PP. Values of >95th percentile were considered to indicate hypertension according to published references. Masked hypertension was defined as a normal casual BP of <95th percentile and ABPM values of >95th percentile. Non-dippers were defined as patients without a nocturnal decrease of between 10 to 20% of the mean night-time SBP compared to the mean day-time SBP. The value of variability is the value of the standard deviation of BP for day and night time period. The aim of antihypertensive treatment was to maintain the BP below the 95th percentile for age, gender, and height. Published normative values in children was used to calculate age and gender related SD scores for 24h BP values (*Wuhl et al., 2002; Litwin et al., 2005*). The diagnosis of hypertension was made when ABPM BP values exceeded the 95th percentile. Age-Based Percentiles of Measured 24hours MAP in Pediatric Patients was used according to Roberts et al. (2020). Normal ranges of heart rate in children from birth to 18 years of age as in centile charts of Fleming et al. (2011).

Review of Echocardiographic presence of left ventricular hypertrophy (LVH) within last 3 months of HD group and within one year of KTX group. Laboratory investigations: Samples were withdrawn before dialysis session in HD patients & during routine laboratory follow up withdrawal in KTX patients. Blood sample: Eight ml venous blood were withdrawn, 4ml were divided into 2 EDTA vacutainers, one for CBC analysis and the other for plasma netrin1 and 4ml were evacuated into serum vacutainer, kept to clot for 15 min then centrifugated for 10 min. Serum is separated to two eppendorf tubes, one for routine chemistry

analysis and one for HsCRP. Serum for HsCRP and plasma for netrin1 were kept at -20°C till the time of assay.

The following blood tests were done on beckman coulter blood chemistry analyzer according to the manufacturer's instructions (Beckman coulter , Inc. Diagnostics head quarters 250 south Kraemer Boulevard Brea, California): Kidney function tests: Including blood urea nitrogen (BUN) & serum creatinine level. Serum electrolytes: Including potassium and sodium levels. Calcium and phosphorus & alkaline phosphatase (ALP) levels. Hyperphosphatemia, elevated calcium phosphate product (Ca X Po₄) and elevated ALP were defined based on age according to the Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines for bone metabolism and disease in children with chronic kidney disease (KDOQI, 2005).

Serum albumin, iron & ferritin. Fasting blood glucose (FBG) and lipid profile including cholesterol level, HDL, LDL and triglycerides, plasma cholesterol levels were defined as acceptable, borderline or high according to the National Cholesterol Education Program (NCEP) Expert Panel on cholesterol levels in children (NCEP, 1992), hypercholesterolemia: total cholesterol >200 mg/dL (Saland et al., 2010).

Complete blood count (CBC): It was done on Sysmex- Xs 800i. Anemia was defined as a hemoglobin value of <11g/dl (KDOQI, 2000). N/L was calculated as the ratio of neutrophils to lymphocytes from the differential white blood cells count.

Measurement of HsCRP: By enzyme linked immunosorbent assay (ELISA). Enzyme immunoassay test technique principle: The HsCRP ELISA is based on the principle of a solid phase ELISA. The assay system utilizes a unique monoclonal antibody directed against antigenic determinant on the CRP molecules. This mouse monoclonal anti CRP antibody is used for solid phase immobilization. A goat anti CRP antibody is in the antibody enzyme conjugate solution. The test sample is allowed to react simultaneously with the two antibodies, resulting in the CRP molecules being sandwiched the solid phase and the enzyme linked antibodies. After a 45 min incubation at room temperature, the wells are washed to remove unbound labeled antibodies. A tetramethylbenzidine reagent is added and incubated for 20 min, resulting in the development of the blue color. The color development is stopped with addition of stop solution and the color is changed to yellow. The concentration of CRP is directly proportional the color intensity of the test sample. Absorbance is measured spectrophotometrically at 450 nm (Roberts et al., 2000).

Sensitivity: The minimum detectable concentration of the HsCRP ELISA assay as measured by 2SD from the mean of a zero standard is estimated to be 1 ng/ml. Specificity: Serum Bilirubin, Hemoglobin, Triglyceride and human IgG were tested for cross reactivity and found with zero reaction.

Markers of chronic inflammation including complete blood picture with calculation of neutrophil to lymphocyte ratio and quantitative Hs-C reactive protein (HsCRP).

Assessment of plasma Netrin-1 level: Plasma Netrin-1 levels was quantified by ELISA technique. **Principle:** By using the Sandwich-ELISA principle. The micro ELISA plate provided in this kit has been pre-coated with an antibody specific to Human Ntn1. Standards or samples are added to the micro ELISA plate wells and combined with the specific antibody. Then a biotinylated detection antibody specific for Human Ntn1 and Avidin-Horseradish Peroxidase (HRP) conjugate are added successively to each micro plate well and incubated. Free components are washed away. The substrate solution is added to each well. Only those wells that contain Human Ntn1, biotinylated detection antibody and Avidin-HRP conjugate will appear blue in color. The enzyme-substrate reaction is terminated by the addition of stop solution and the color turns yellow. The optical density (OD) is measured spectrophotometrically at a wavelength of $450 \text{ nm} \pm 2 \text{ nm}$. The OD value is proportional to the concentration of Human Ntn1. You can calculate the concentration of Human Ntn1 in the samples by comparing the OD of the samples to the standard curve. Sensitivity: 18.75pg/ml, Specificity: No significant cross reactivity or interference between human netrin1 and analogues was observed, Detection range: 31.25- 2000pg/ml.

Statistical analysis

Data is tabulated and subjected to computer-assisted statistical analysis using Statistical Package for the Social Sciences (SPSS) version 21. Nominal data is described as frequency and percentage and compared using the chi-squared test. Numerical data is described as mean and standard deviation and compared using t tests. Non parametric data is described as median and interquartile range and is compared using Mann-Whitney test. One way Anova test for comparison of quantitative variable between more than two groups which will be normally distributed while Kruskal-Wallis test for not normally distributed variables. Numerical associations are tested using Pearson correlations. A p-value less than 0.05 is considered significant.

Results

Table 1 shows that there is significant differences regarding age, age of diagnosis and duration of dialysis between both groups, HD group showed larger number of patients who developed hypertension than KTX group ($P < 0.001$). KTX group has significantly higher weight and height if compared to HD group ($p < 0.001$). HD group has significantly elevated serum creatinine, BUN, Na, K, Po_4 , Ca X Po_4 , iron, and lower FBS than KTX group. Ca X Po_4 was above solubility product (> 55) in 63.33% ($n=19$) of HD group and 6.66% ($n=2$) of KTX group. Five patients (16.7%) of HD group compared to 14 patients (46.6%) of KTX group have low serum iron level. 90% of HD patients has serum ferritin more than 140ng/ml which is parallel to the state of chronic inflammation in this group. Plasma netrin1 levels were insignificantly lower in HD the KTX group (median = 562.5 pg/ml in HD group versus 586.1pg/ml in KTX group, $p=0.5$). Twenty four transplanted patients (80%) have HsCRP $> 3 \text{ mg/L}$ while only 18 patients (60%) of HD group have HsCRP $> 3 \text{ mg/L}$ (high risk of CVD). Only 1 patient (3.3%) in HD group and 2 patients (6.6%) in KTX group have HsCRP $< 1 \text{ mg/L}$ (Low risk of CVD). HD group has insignificantly lower Hs CRP than KTX group ($p=0.25$). The atheroprotective HDL cholesterol was significantly lower in HD than KTX group

($p < 0.001$). TAG level was significantly elevated in HD than KTX group ($p = 0.001$) but no significant difference between both groups as regard total cholesterol ($p = 0.369$) or LDL cholesterol ($p = 0.106$) (Table 1). Serum triglycerides (TG) were > 129 mg/dl in 24 patients of HD group and 18 patients (60%) of KTX group considering high pediatric risk. Regarding HDL cholesterol; 50% of HD group had HDL < 40 mg/dl which is too low to be atheroprotective (Table 2). HD group showed significantly lower platelet count and elevated N/L than KTX group ($p < 0.001$). The latter is considered as independent predictor of CV risk (Table 1).

Table (1)
Basic and Laboratory data findings of HD and KTX groups

	HD group (n=30) (Mean± SD)	KTX group (n=30) (Mean± SD)	P value
Basic Data			
Age (years)	9±2.4	12.4±3	<0.001
Weight (Kg)	23.4±8.5	40.3±14.7	<0.001
Height (cm)	107.4±18.2	139.2±21.8	<0.001
Age at diagnosis (years)	3.5±2.1	5.4±3.1	0.006
Dialysis duration(months)	40.8±18	14.4±7.2	<0.001
Blood pressure	N (%)	N (%)	
Not hypertensive	11(36.7)	18(60)	<0.001
Hypertensive	19(63.3)	12(40)	
Laboratory data	Median (IQR)	Median (IQR)	
Creatinine (mg/dl)	7.2(6.3:9.1)	1.1(0.8:1.5)	<0.001
BUN (mg/dl)	167(148:208)	28.3(19:34)	<0.001
Na (mmol/L)	141(137:145)	139(137:141)	0.023
K (mmol/L)	6.4(5.8:7.1)	4.6(4:4.9)	<0.001
Albumin (g/dl)	4(3.7:4.3)	4.1(3.9:4.6)	0.057
Ca(mg/dl)	9.6(9.1:10.8)	9.6(9.1:10.2)	0.613
Po4 (mg/dl)	6(4.7:7.4)	4.4(3.7:4.9)	<0.001
CaXPo4 (mg ² /dl ²)	59.4(45.1:73.2)	43.1(36.4:47)	<0.001
ALP (IU/L)	228(134:354)	216(156:279)	0.807
PTH (pg/ml)	285.5(197:459)	200(48.5:166)	0.51
Iron (mcg/dl)	95.5(54:123)	50(39:76)	0.002
Ferritin (ng/ml)	1356(1090:1800)	1237(282:130)	0.114
FBS (mg/dl)	88.5(80:97)	99.5(93:105)	0.007
HsCRP(mg/L)	5.5(2.4:13)	10(3.9:13)	0.255
Netrin1 (pg/ml)	562.5(354.4:942)	586.1(459.9:741)	0.515
Cholesterol (mg/dl)	182.5(157:218)	192.5(165:216)	0.369
HDL (mg/dl)	39.5(30:52)	52(47:66)	<0.001
LDL (mg/dl)	92(61:131)	111(98:133)	0.106
TG (mg/dl)	224(135:303)	151(96:184)	0.001
Hemoglobin (g/dl)	11.6(9.7:12.7)	10.7(9.9:12)	0.23
Platelets(cells/mm ³)	216.5(184:245)	271.5(242:349)	<0.001

TLC (cells/mm ³)	7.1(5.6:11.4)	6.2(5.3:7.9)	0.053
N/L	6.1(3.5:7.8)	2.1(1.4:3.2)	<0.001

Table (2)
Lipid profile categories in HD & KTX groups

	HD group (n=30) N (%)	KTX group (n=30) N (%)	p value
Cholesterol categories			
Acceptable	11(36.7)	9(30)	0.892
Borderline	6(20)	7(23.3)	
High	13(43.3)	14(46.7)	
LDL categories			
Acceptable	19(63.3)	15(50)	0.62
Borderline	3(10)	5(16.7)	
High	8(26.7)	10(33.3)	

Data are represented as frequency and percentage. P-value less than or equal 0, 05 is considered significant. Acceptable cholesterol <170 mg/dl, borderline cholesterol >170mg/dl, High cholesterol >200mg/dl. Acceptable LDL <110mg/dl, borderline LDL =110-129mg/dl, High LDL ≥ 130 mg/dl

By plotting body measurements (weight, height and BMI) on Egyptian growth curves for age and sex; we found that most of HD & KTX groups were <25th percentile for weight & heights with no significant difference between both groups as regard BMI percentiles but significant regard height percentiles (p=0.04) (Table 3).

Table (3)
Anthropometric measurement of HD & KTX group

Anthropometric measures	HD group (n=30)		KTX group (n=30)		P value
	N	%	N	%	
Weight percentiles					0.531
< 25 th	23	76.7%	18	60%	
25 th -50 th	3	10%	3	10%	
50 th -75 th	2	6.7%	4	13.3%	
>75 th	2	6.7%	5	16.7%	
Height percentiles					0.040
< 25 th	29	96.7%	22	73.3%	
25 th -50 th	1	3.3%	5	16.7%	
50 th -75 th	0	0%	0	0%	
>75 th	0	0%	3	10%	
BMI percentiles					0.366
<5 th (underweight)	4	13.3%	5	16.7%	
5-85 th (Normal)	8	26.7%	14	46.7%	
85-95 th (overweight)	6	20%	3	10%	
>95 th (obese)	12	40%	8	26.7%	

Data are represented as frequency and percentage. P-value less than or equal 0, 05 is considered significant.

BMI (Body mass index)

Table 4 showed that 56.7% of HD group and 50% of KTX group have LVH without significant difference between them ($p=0.6$).

Table (4)
Echocardiographic findings of HD & KTX groups

Echo	HD group (n=30) N (%)	KTX group (n=30) N (%)	P value
LVH	17 (56.7%)	15 (50%)	0.605
Intracardiac thrombus	2 (6.7%)	0 (0%)	0.492
FS (%)	37.1±6.9%	38.5±2.8%	0.322

Data are represented as frequency and percentage. P-value less than or equal 0, 05 is considered significant.

*LVH (left ventricular hypertrophy), FS (fractional shortening).

Table 5 illustrates 24 hour's analysis of ABPM for patients on HD & KTX groups. Average 24hrs PP was significantly more in KTX group than HD group ($p=0.001$) (Table 25). 24 hours diastolic BP > 95th percentiles ($p=0.05$) and 24 hours MAP > 95th percentile ($p=0.038$) were more prevalent in HD group (Table 5). The value of variability in systolic and diastolic BP in day time monitoring was more than that of night time (as normal variability) in both HD & KTX groups (Table 6). Percentage of patients with high values of systolic and diastolic variability was more in day time readings than in night time in both groups (Table 7). Night time HR in HD group was significantly more than that of KTX group ($p=0.015$), while average night MAP, diastolic BP were insignificantly more in HD than KTX group (Table 6). No significant difference in % nocturnal fall of either systolic or diastolic BP between HD & KTX groups (Table 8). Four patients (13.3%) and 6 patients (20%) of HD group while 5 patients (16.7%) and 4 patients (13.3%) of KTX group respectively showed normal nocturnal falling in BP (Dipper). Twenty patients (66.7%) and 17 patients (56.7%) of both groups showed non dipping pattern at night time which worsen the CV risks. 20% of patients of HD group and 16.7% (for systolic), 13.3% (for diastolic) of KTX group showed reverse dipping (night peaker) which characterized by higher night time compared with day time blood pressure values. Only 1 patient (3.3%) of HD group and 2 patients (6.7%) of KTX group showed hyperdipping in nocturnal fall in diastolic BP. There is no significant difference between both groups regarding nocturnal dipping in ABPM (Table 9). 24 hours systolic BP, nocturnal average systole and night variability in systole were higher in the presence of LVH of KTX group (Table 10).

Table (5)
24hrs ABPM readings of both groups

	HD group (n=30)	KTX group (n=30)	P value
24hr ABPM	Median(IQR)	Median(IQR)	
Average SYS (mmHg)	115(100:125)	119(114:127)	0.315

Average DIA (mmHg)	83.5(67:90)	74.5(68:83)	0.371
Average MAP (mmHg)	96.5(82:105)	90.5(83:99)	0.487
Average Pulse Pressure (mmHg)	38(33:40)	44(37:50)	0.001
Average HR (b/m)	90.5(84:100)	87.5(82:90)	0.256
24hrs ABPM percentiles	N (%)	N (%)	
SYS Percentiles			
<90 th controlled pressure (Normal)	9(30)	17(56.7)	0.061
90-95 th Prehypertention	3(10)	4(13.3)	
>95 th Hypertention	18(60)	9(30)	
DIA Percentiles			
<90 th controlled pressure (Normal)	10(33.3)	16(53.3)	0.050
90-95 th Prehypertention	1(3.3)	4(13.3)	
>95 th Hypertention	19(63.3)	10(33.3)	
MAP Percentiles			
<95 th controlled pressure	10(33.3)	19(63.3)	0.038
>95 th uncontrolled pressure	20(66.7)	11(36.7)	
Pulse pressure			
Normal	19(63.3)	12(40)	0.069
Wide	10(33.3)	18(60)	
Narrow	1(3.3)	0(0)	
HR Percentiles			
Normal range (10-90 th)	26(86.7)	27(90)	1
Upper limit (90-99 th)	4(13.3)	3(10)	

SYS (Systolic blood pressure), DIA (Diastolic blood pressure), MAP (Mean arterial pressure), HR (Heart rate)

Table (6)
Day and night time ABPM analysis of HD and KTX groups

	HD group (n=30)	KTX group (n=30)	P value
	Median(IQR)	Median(IQR)	
Day time			
Average SYS (mmHg)	115.5(105:123)	119.5(116:126)	0.144
Average DIA(mmHg)	76.5(64:89)	75(70:83)	0.814
Variability in SYS(mmHg)	10(9:13)	10.5(9:13)	0.927
Variability in DIA(mmHg)	10(9:11)	10(8:12)	0.856
Average MAP (mmHg)	96.5(81:103)	91(83:101)	0.822
Average HR (b/m)	92.5(89:103)	91(88:102)	0.977
Night time			
Average SYS (mmHg)	113.5(101:122)	112(106:123)	0.908
Average DIA(mmHg)	82(68:90)	71(65:81)	0.077
Variability in SYS(mmHg)	7.5(7:10)	8(7:10)	0.719

Variability in DIA(mmHg)	8(6:10)	8(6:9)	0.692
Average MAP(mmHg)	99(76:108)	88(79:94)	0.095
Average HR (b/m)	88(77:95)	78(73:84)	0.015

Data are represented as Median (IQR). P-value less than or equal 0, 05 is considered significant.

Table (7)

Level of day and night time variability in ABPM analysis of HD and KTX groups

Blood pressure variability	HD group (n=30)		KTX group (n=30)		P value
	N (%)		N (%)		
Day time variability in SYS					
High (>15mmHg)	3(10)		3(10)		1
Normal	27(90)		27(90)		
Day time variability in DIA					
High (>14mmHg)	4(13.3)		3(10)		1
Normal	26(86.7)		27(90)		
Night time variability in SYS					
High (>15mmHg)	1(3.3)		1(3.3)		1
Normal	29(96.7)		29(96.7)		
Night time variability in DIA					
High (>12mmHg)	3(10)		3(10)		1
Normal	27(90)		27(90)		

Data are represented as frequency and percentage. P-value less than or equal 0, 05 is considered significant.

Table (8):

Degrees of pressure falling in night time ABPM

	HD group (n=30)		KTX group (n=30)		P value
	Median(IQR)		Median(IQR)		
Night time	Median(IQR)		Median(IQR)		
Degree of nocturnal fall SYS%	3.5(1:7)		6.5(2:9)		0.105
Degree of nocturnal fall DIA %	4.5(2:8)		4(2:9)		0.982

Data are represented as Median (IQR). P-value less than or equal 0, 05 is considered significant.

Table (9)

Dipping in night time ABPM

Degree of nocturnal fall SYS %	HD group (n=30)		KTX group (n=30)		P value
	N	%	N	%	
Dipper (10-20%)	4	13.3%	5	16.7%	1
Non dipper (0-10%)	20	66.7%	20	66.7%	
Reverse Dipper (Night peaker) (<0%)	6	20%	5	16.7%	

Degree of nocturnal fall DIA %	N	%	N	%	
Dipper (10-20%)	6	20%	4	13.3%	0.684
Non dipper (0-10%)	17	56.7%	20	66.7%	
Reverse Dipper (Night peaker) (<0%)	6	20%	4	13.3%	
Hyper dipper (>20%)	1	3.3%	2	6.7%	

Data are represented as frequency and percentage. P-value less than or equal 0, 05 is considered significant.

Table (10): Relation between LVH and 24 hours ABPM readings

LVH	HD group (n=30)		p value	KTX group (n=30)		p value
	No (n=13)	Yes (n=17)		No (n=15)	Yes (n=15)	
	Median(IQR)	Median(IQR)		Median(IQR)	Median(IQR)	
Average SYS	111(98:128)	118(110:125)	0.742	115(102:120)	121(115:131)	0.011
Average DIA	81(63:90)	85(72:88)	0.65	72(68:77)	81(66:87)	0.126
Average Pulse pressure	38(35:40)	37(32:40)	0.3	43(34:44)	46(37:53)	0.089
Nocturnal Average SYS	112(94:126)	114(107:121)	0.711	108(98:117)	123(107:129)	0.037
Nocturnal Average DIA	79(61:88)	85(70:95)	0.281	69(65:73)	77(63:86)	0.098
Night Variability in SYS	7(6:8)	8(7:11)	0.183	7(6:9)	8(8:12)	0.05
Night Variability in DIA	8(6:9)	8(6:11)	0.563	7(5:9)	8(7:9)	0.412

Data are represented as Median (IQR). P-value less than or equal 0, 05 is considered significant.

Table 11 illustrates a strong significant inverse relation between plasma netrin1 and Hs CRP and between netrin1 and N/L ($p < 0.001$) in HD group patients which meaning that netrin1 has lower level with increasing severity of chronic inflammatory condition. There is direct strong significant relation between N/L ratio in CBC and serum HsCRP level ($p < 0.001$). There are significant inverse correlations between netrin1 level and serum total cholesterol ($p < 0.001$), LDL cholesterol ($p = 0.003$) and TG ($p = 0.009$) in KTX group patients. There is no significant relation between lipid profile of KTX group with HsCRP and N/L.

Table (11)

Correlation between Netrin1, HsCRP, N/L with each other's and with lipid profile in both groups

HD group (n=30)	Netrin1 pg/ml		Hs CRP mg/L		N/L	
	r	p value	R	P value	r	P value
Cholesterol mg/dl	-0.312	0.093	0.343	0.064	.384*	0.036
HDL mg/dl	-0.014	0.941	-0.029	0.881	-0.182	0.335
LDL mg/dl	-0.305	0.101	0.158	0.405	0.306	0.1
TG mg/dl	-0.215	0.254	0.168	0.374	0.324	0.081
Netrin pg/ml			-.714**	<0.001	-.664**	<0.001
Hs CRP mg/L	-.714**	<0.001			.900**	<0.001
N/L	-.664**	<0.001	.900**	<0.001		
KTX group						

(n=30)						
Cholesterol mg/dl	-.785**	<0.001	0.144	0.449	-0.079	0.68
HDL mg/dl	-0.033	0.863	-0.171	0.366	-0.184	0.33
LDL mg/dl	-.523**	0.003	0.271	0.147	-0.127	0.505
TG mg/dl	-.471**	0.009	0.01	0.956	-0.275	0.141
Netrin1			0.012	0.949	0.115	0.545
Hs CRP mg/L	0.012	0.949			-0.223	0.235
N/L	0.115	0.545	-0.223	0.235		

Netrin1 is significantly lower (p=0.007) and N/L is significantly higher (p=0.48) in the presence of LVH among HD group only, but no significant association was detected between HsCRP and presence or absence of LVH in both group despite higher median values in case of presence of LVH(Table 12).

Table (12)
Netrin1, HsCRP levels and N/L in relation with LVH in both groups

LVH	Netrin1pg/ml	P value	HsCRP mg/L	P value	N/L	P value
	Median(IQR)		Median(IQR)		Median(IQR)	
HD group (n=30)						
No (n=13)	941.8(604.6:1283)	0.007	2.7(1.6:6.2)	0.059	4.2(3.3:6)	0.048
Yes (n=17)	408.4(354:568.6)		11.5(2.7:13)		7.2(5:8.1)	
KTX group (n=30)						
No (n=15)	717.2(640.2:763.6)	0.518	2.7(1.6:6.2)	0.711	4.2(3.3:6)	1
Yes (n=15)	539.3(374.7:704)		11.5(2.7:13)		7.2(5:8.1)	

Data are represented as Median (IQR). P-value less than or equal 0, 05 is considered significant.

Inverse correlation was detected between netrin1 level and degree of nocturnal fall in diastolic BP (p=0.032). Also a direct relation between degree of nocturnal fall in diastolic BP and each of HsCRP (p=0.002) and N/L (p=0.025) in HD group (Table 13). Inverse correlation was detected between netrin1 level and variability of diastolic BP during day time in KTX patients. Also a direct significant relations between serum Hs CRP and each of average 24hrs systolic BP (p=0.047), average 24hrs diastolic BP (p=0.037), average 24hrs MAP (p=0.032) and average night time MAP (p=0.036) in KTX group (Table 14). No significant difference in comparison between levels of different parameters and percentile of ABPM readings and netrin1 or HsCRP level or N/L in HD group. Patient with uncontrolled 24hrs MAP showed lower netrin1 and higher HsCRP median levels if compared to controlled MAP patients but with no statistical significance (Table 15).No significant differences in values ofnetrin1 levels with different parameters of ABPM readings in KTX group except in day time diastolic pressure variability which has significantly higher netrin1 level which higher than normal variability. The median (IQR) of HsCRP is significantly high in case of uncontrolled 24hrs systolic hypertension and 24hrs MAP above 95th percentile (p=0.018 and p=0.009 respectively).Also a significant higher value of N/L was noticed in uncontrolled diastolic pressure (less than 90th percentile for age and sex) (p=0.023) (Table 16).

Table (13)
Correlation between Netrin1, HsCRP levels and N/L with ABPM readings in HD group

HD group (n=30)	Netrin1pg/ml		HsCRP mg/L		N/L	
	R	p	R	p	r	p
24 hours						
Average MAP	0.136	0.474	-0.197	0.298	-0.074	0.696
Average SYS	0.162	0.392	-0.233	0.215	-0.114	0.548
Average DIA	0.207	0.272	-0.208	0.27	-0.108	0.57
Average Pulse Pressure	0.223	0.237	-0.181	0.339	-0.175	0.355
Average HR	- 0.071	0.711	-0.008	0.966	0.138	0.466
Day time						
Average SYS	0.118	0.534	-0.181	0.339	-0.069	0.719
Average DIA	- 0.076	0.691	0.045	0.813	0.187	0.321
Variability in SYS	- 0.106	0.577	0.128	0.499	0.249	0.185
Variability in DIA	0.271	0.148	-0.151	0.427	-0.052	0.785
Average MAP	0.045	0.812	-0.118	0.535	-0.006	0.976
Average HR	0.069	0.716	-0.1	0.6	0.052	0.786
Night time						
Average SYS	0.266	0.155	-0.339	0.067	-0.214	0.256
Average DIA	0.176	0.351	-0.288	0.123	-0.203	0.283
Variability in SYS	- 0.067	0.725	0.151	0.425	0.174	0.357
Variability in DIA	0.168	0.376	-0.106	0.577	-0.117	0.536
Degree of nocturnal fall in SYS	-0.31	0.096	0.359	0.052	0.261	0.163
Degree of nocturnal fall in DIA	- .392*	0.032	.535**	0.002	.409*	0.025
Average MAP	0.29	0.12	-0.353	0.056	-0.256	0.172
Average HR	- 0.012	0.948	-0.036	0.851	0.163	0.388

P-value less than or equal 0, 05 is considered significant.

Table (14)
Correlation between Netrin 1, HsCRP, N/L and ABPM readings in KTX group

KTX group (n=30)	Netrin1pg/ml		HsCRP mg/L		N/L	
	r	p	R	p	r	p
24 hours						
Average MAP	0.002	0.991	.393*	0.032	-0.197	0.296
Average SYS	0.107	0.575	.366*	0.047	-0.165	0.382
Average DIA	-0.032	0.867	.383*	0.037	-0.17	0.369

Average Pulse Pressure	0.069	0.718	0.06	0.752	-0.129	0.496
Average HR	0.012	0.949	0.123	0.519	0.039	0.838
Day time						
Average SYS	0.015	0.936	0.318	0.086	-0.061	0.747
Average DIA	-0.104	0.585	0.327	0.077	-0.131	0.491
Variability in SYS	-0.219	0.244	0.023	0.902	0.062	0.745
Variability in DIA	-.382*	0.037	0.096	0.615	-0.094	0.622
Average MAP	-0.059	0.758	0.279	0.136	-0.107	0.574
Average HR	0.004	0.981	0.043	0.822	0.233	0.215
Night time						
Average SYS	0.076	0.688	0.335	0.07	-0.255	0.174
Average DIA	-0.05	0.792	0.288	0.123	-0.232	0.216
Variability in SYS	0.297	0.11	0.145	0.444	0.059	0.757
Variability in DIA	0.086	0.652	0.067	0.725	0.167	0.377
Degree of nocturnal fall in SYS	-0.132	0.486	-0.254	0.175	0.297	0.111
Degree of nocturnal fall in DIA	-0.179	0.345	-0.184	0.331	0.146	0.44
Average MAP	0.005	0.978	.384*	0.036	-0.245	0.192
Average HR	-0.152	0.421	0.107	0.573	0.001	0.995

P-value less than or equal 0, 05 is considered significant.

Table (15)
Comparison Detailed data of ABPM regarding netrin1, HsCRP and N/L levels in HD group

HD group (n=30)	Netrin1pg/ml		HsCRP mg/L		N/L	
	Median (IQR)	P	Median(IQR)	P	Median(IQR)	P
24 hours ABPM						
24 hours SYS Percentiles						
<90 th controlled pressure (Normal)	556.5(383.8:796)	0.75	6.3(2.7:13)	0.82	4.9(3.5:7.6)	0.95
90-95 th Prehypertention	899.9(354:1413)		2.7(2.6:13)		5(3.3:8.6)	
>95 th Hypertention	548.4(354.4:941.8)		5.5(2.2:12.1)		6.3(4.2:7.8)	
24 hours DIA Percentiles						
<90 th controlled pressure (Normal)	472.8(354:796)	0.47	9.3(2.7:13)	0.25	6.2(3.5:8.1)	0.268
90-95 th Prehypertention	354.4(354.4:354.4)		13.1(13.1:13)		8.7(8.7:8.7)	
>95 th Hypertention	570.6(408.4:991.7)		3.8(2.2:11.5)		6(3.4:7.5)	
24 hours MAP Percentiles						
>95 th uncontrolled pressure	472.8(354:796)	0.75	9.3(2.7:13)	0.33	6.2(3.5:8.1)	0.812
<95 th controlled pressure	569.6(381.4:966.7)		4.3(2.3:12)		6.1(3.8:7.7)	
Pulse pressure						
Normal	477.4(329:941.8)	0.36	8.3(2.4:13)	0.65	7.2(3.5:7.9)	0.815
Wide	615.7(389.2:1200)		4.3(1.6:12)		5.6(3.1:7)	
Narrow	899.9(899.9:899.9)		2.6(2.6:2.6)		5(5:5)	
HR Percentiles						
Normal range (10-90th)	542.4(354:899.9)	0.22	6.3(2.6:13)	0.14	6.3(3.5:7.8)	0.746
Upper limit (90-99th)	915.3(623.6:1096)		2.5(1.8:5.4)		4.7(3.8:6.7)	
Day time variability in SYS						
High	626.8(389.2:941.8)	0.74	6.2(1.6:13.)	0.74	7.8(3.1:8.4)	0.6
Normal	556.5(354:979.8)		4.8(2.4:13)		6(3.5:7.6)	
Day time variability in DIA						
High	615.7(520.9:913.4)	0.46	2.1(1.6:6.7)	0.89	4.1(3.1:5.7)	0.177
Normal	542.4(354:941.8)		6.3(2.6:13)		6.7(4.2:7.9)	
Night time variability in SYS						
High	626.8(626.8:626.8)	0.8	1.6(1.6:1.6)	0.18	3.1(3.1:3.1)	0.333
Normal	556.5(354.4:941.8)		6.2(2.6:13)		6.2(4.2:7.8)	

Night time variability in DIA						
High	899.9(626.8:1200)	0.18	2.6(1.6:2.6)	0.33	5(3.1:5.1)	0.35
Normal	528.2(354:941.8)		6.3(2.4:13)		6.3(3.5:7.9)	
Degree of nocturnal fall in SYS (Dipping)						
Dipper (10-20%)	413.2(359.1:1042.6)	0.74	12(8.6:13.2)	0.14	7.1(5.6:8.2)	0.474
Non dipper(0-10%)	587.6(381.4:960.8)		2.9(2.3:12)		5.1(3.5:7.7)	
Night peaker (<0%)	456(354:626.8)		8.4(1.6:13)		6.8(3.1:7.6)	
Degree of nocturnal fall in DIA (Dipping)						
Dipper (10-20%)	395.8(308.1:1200)	0.71	11.9(6.3:13)	0.16	6.9(5.1:8.7)	0.197
Non dipper(0-10%)	570.6(383.8:899.9)		3.2(2.2:12)		5(3.4:7.5)	
Night peaker (<0%)	577.5(408.4:979.8)		3.2(1.6:8.3)		5.4(3.1:8.3)	
Hyper dipper (>20%)	389.2(389.2:389.2)		13.1(13.1:13)		8.4(8.4:8.4)	

Data are represented as Median (IQR). P-value less than or equal 0, 05 is considered significant.

Table (16)
Comparison Detailed data of ABPM regarding netrin1, HsCRP and N/L in KTX group

KTX group (n=30)	Netrin1 pg/ml		HsCRP mg/L		N/L	
ABPM	Median (IQR)	P	Median(IQR)	P	Median(IQR)	P
24 HR SYS Percentiles						
<90 th controlled pressure (Normal)	586.2(484.7:704)	0.87	7.4(2.9:11.6)	0.018	2.2(1.7:3.4)	0.39
90-95 th Prehypertention	539.7(473.1:639)		8.1(2.9:13)		2.6(1.4:3.3)	
>95 th Hypertention	597.1(428.4:858)		13(12.2:13.2)		1.5(1.2:2.4)	
24 HR DIA Percentiles						
<90 th controlled BP (Normal)	586.5(492.1:699)	0.27	7.2(3.1:12.3)	0.127	1.9(1.4:3)	0.023
90-95 th Prehypertention	467.4(445.1:535)		6.8(0.4:13.1)		1(0.7:1.5)	
>95 th Hypertention	668.9(417.3:884)		12.6(7.4:13.1)		2.4(2:3.4)	
24 HR MAP Percentiles						
>95 th uncontrolled pressure	586(484.7:693.7)	0.83	13(7.4:13.2)	0.009	2.1(1.6:3.4)	0.445
<95 th controlled pressure	597.1(417.3:884)		5.3 (2.8:13)		1.5(1.2:3)	
Pulse pressure						
Normal	535.3(434.3:775)	0.42	8.9(4.7:13)	0.632	2.3(1.6:3.5)	0.391
Wide	586.5(490.7:741)		10.6(3.9:13)		2(1.2:3.2)	
Narrow						
HR Percentiles						
Normal range (10-90th)	586.2(452.7:786)	0.55	9.2(3.3:13)	0.253	2(1.2:3.2)	0.35
Upper limit (90-99th)	462.5(459.9:666)		13(11.7:13)		2.1(2:5.4)	
Day time variability in SYS						
High	597.1(450.1:109)	0.74	2.1(1.6:6.7)	0.897	4.1(3.1:5.7)	0.177
Normal	586(459.9:740.8)		6.3(2.6:13)		6.7(4.2:7.9)	
Day time variability in DIA						
High	586.2(490.7:704)	0.02	7.4(5.3:13.2)	0.744	3(0.8:3.6)	0.795
Normal	455(428.4:493.5)		10.4(3.3:13)		2(1.4:3.2)	
Night time variability in SYS						
High	586(428.4:597.1)	0.55	12.2(7.4:13.1)	0.426	1.2(1.2:1.2)	0.4
Normal	586.2(459.9:786)		9.7(3.3:13)		2.1(1.5:3.2)	
Night time variability in DIA						
High	2134(2134:2134)	0.07	13.2(13.2:13)	0.2	3(1.2:3.2)	0.845
Normal	586(459.9:704)		9.7(3.9:13)		2(1.4:3.4)	
Degree of nocturnal fall in SYS (Dipping)						
Dipper (10-20%)	493.5(428.4:213)	1	12.2(2.4:13.2)	0.795	3.4(2.2:3.6)	0.221
Non dipper(0-10%)	586.2(459.9:741)		9.7(3.9:13)		2(1.2:3.2)	
Night peaker(<0%)			5.3(2.9:9.7)		2(1.5:2.1)	
Degree of nocturnal fall in DIA (Dipping)						
Dipper (10-20%)	704(490.7:1090)	0.418	10.4(3.6:13)	0.431	1.8(1.2:2.6)	

Non dipper(0-10%)	583(451.4:666)		11.7(10.4:13)		2.2(1.5:3.3)	0.757
Night peaker (<0%)	740.8(462.5:884)		3.9(2.6:9)		1.9(1.1:3)	
Hyper dipper (>20%)	538.1(494.8:583)		11(5.9:13)		2.7(1.4:4)	

Data are represented as Median (IQR). P-value less than or equal 0, 05 is considered significant.

Discussion

The identification of ESKD patients on regular HD or after KTX who are at increased CV risk is critically important effective preventive measures. Among the well-established risk factors for atherosclerosis are hypercholesterolemia, hypertension, diabetes mellitus, and obesity however, despite their value for CV risk assessment at large scale, these parameters lack specificity for prediction of individual CV event risk (Ridker et al., 2003). Much preclinical research has been done to investigate a function for Netrin-1 and chronic inflammatory markers in CVD.

LVH is used as a surrogate outcome for CV risk in children (Lurbe et al., 2016). In the present study, 56.7% of HD group had LVH at assessment. Prevalence of LVH among HD children was reported to be as low as 17% (Chavers et al., 2011) or as high as 69% (Civilibal et al., 2007). Data of LVH after KTX in children is lacking, however, incidence of LVH has been well documented in this high-risk population (Hamdaniet al., 2017). In our study; 50% of KTRs had LVH at assessment, which is more than previous reports of 7.6% (Cameron et al., 2014) and 43% (Borchert-Mörlinset al., 2017). Differences in hemoglobin level and of mean BP readings of different studies cause this wide range of LVH prevalence variation. In hypertension, LVH is the heart's response to the presence of increased left ventricular load and neurohumoral stimuli, which results in an augmentation of oxygen consumption (Diez and Frohlich, 2010). In this study, we found significant higher average 24hrs systolic blood pressure, night time systolic pressure and night time median systolic variability by ABPM in patients with LVH than in patients without LVH in KTX group. The prevalence of LVH might underlay the benefit from the systematic application of ABPM at yearly intervals for the evaluation and management of hypertension after KTX (Cameron et al., 2014).

Hypertension is highly prevalent in children receiving dialysis and considered one of the major contributors to morbidity associated with ESKD (Agarwal et al., 2010). In addition to the traditional etiologies of hypertension like volume overload and rennin angiotensin activation pathway, there are some newly discovered etiologies including endothelial dysfunction (ED), hyperparathyroidism, and sympathetic activation (Hadtstein and Schaefer, 2008). In our study, significant correlations were found between early markers of endothelial dysfunction (HsCRP, N/L) and ABPM readings which indicated the role of endothelial dysfunction in the development of hypertension in these patients. ABPM may be a more sensitive and specific method of substantiating diagnosis of hypertension (Chaudhuri et al., 2011). In HD patients the prevalence of hypertension ranged widely across studies from 21% to 79% (Galiyeva, 2017). In this study; 60% of patients have 24hrs systolic hypertension, 63.3% have 24hrs diastolic hypertension and 66.7% have MAP above 95th percentile. Our reported percentage of hypertension is more than that of Chaudhuri and his colleagues

(2011) (42%, 46% and 25% of their studied dialysis patients had 24hrs systolic, diastolic and MAP hypertension respectively) and less than that of Skrzypczyk et al. (2019)(in regard of 24hrs systolic and pulse pressures).The identification of increased BP variability by ABPM may be one way of detecting the high-risk subject among hypertensive patients; however, the exact mechanisms underlying the link between BP variability and CV risk remain unclear(Kim et al., 2016).Skrzypczyk et al. (2019)reported similar day time systolic and diastolic BP variability as ours but night time variability and degree of nocturnal fall (dipping) were more than the present study. Nondipping in nocturnal BP in HD patients is reported to be an independent predictor of poor clinical CV outcomes and is associated with a worsened CV survival rate compared with dipping (Thompson and Pickering, 2006). In the present study; we found that 66.7% of HD group have nondipping systolic BP and 56.7% have nondipping diastolic BP. Our results are worse than Chaudhuri et al., 2011(48% with systolic and 25% with diastolic BP nondipper) denoting increased CV risk among our HD patients. Data available on the routine use of ABPM following KTX are lacking (Peterson and Miyashita, 2017).Pooled data from four pediatric studies, showed that the point estimate prevalence of recipients with normotension in the clinical setting, who in fact were diagnosed as having true or sustained hypertension by ABPM criteria was 30%(Bulum et al., 2015, Hamdani et al., 2016,Hamdani et al., 2017).In the present study; we found lower percentage (6.7%) of KTX patients had their hypertension uncovered by ABPM rather than routine BP assessment (masked hypertension).The opposite condition, i.e., hypertension the clinical setting while normotensive by ABPM (white coat hypertension) has been observed in transplant recipients in 9%ofHamdanistudies (2016, 2017). In the present study;6.7% of KTX patients were hypertensive in the clinical setting despite one of them not hypertensive or controlled by ABPM and the other one was prehypertensive. Uncontrolled hypertension defined upon ABPM in 457 treated hypertensive recipient's was54% (Bulum et al., 2015; Hamdani et al., 2017). In the present study; the use of ABPM in KTX group has resulted in increased diagnosis of controlled BP and decreased diagnosis of uncontrolled hypertension (23%). Nocturnal BP and circadian rhythm are often abnormal in adult and pediatric patients after KTX (Kimura, 2008). This should carry the implication that ABPM would offer a unique perspective for chronotherapy, i.e., bedtime dosing of antihypertensive medication in patients displaying an abnormal nondipping profile (Zhao et al., 2011). Salles et al., 2016 study found that in untreated hypertensive transplanted adults, both blunted nocturnal BP decline and extreme dipping are associated with worse CV prognosis as compared to normal dippers. In the present study; systolic and diastolic pressure in twenty patients (66.7%) of KTX group showed non dipping pattern at night time which worsen the CV risks and only two patients (6.7%) showed hyperdipping (extreme) in nocturnal fall in diastolic BP. InBorchert-Mörlinset al., (2017)study, a missing nocturnal decrease (non-dipper) was apparent in 42% of patients.

The use of BMI alone in determining the nutritional status of ESRD patients on HD group may not be appropriate because of inter-dialytic weight gain and variable dry weight status (Foster and Leonard, 2004). Despite these concerns, 13.3% of our studied HD patients were under weight (under nutrition), 20% were overweight and 40% were obese. Our increased prevalence of overweight/ obesity among HD patients than previous studies (Mudi et al., 2017; Borchert-Mörlinset

al., 2017) which may be due to that patients undergoing dialysis, those who are short for their age are more likely to become overweight (height standard deviation score for chronological age and increased BMI were inversely correlated), underscoring the potential role of the complex maladaptive metabolic response described in children with ESKD which same as Krmar and Barany, 2013 study too. In the present study; prevalence of obesity was more in HD than KTX group making them has more cardiovascular risk. (46.7% and 26.7% of KTX group had normal BMI and obese respectively). Our finding in this regard does not go with previous report stating increased prevalence of obesity after KTX than with HD children (Bonthuis et al., 2013), but with Chavers et al., 2009 study that reported the prevalence of obesity is more in a dialysis population as ours.

Regarding lipid profile; our KTX and HD groups had similar prevalence of hypercholesterolemia $> 200\text{mg/dl}$ (43.3%). Similar prevalence was reported by Galiyeva (2017) (prevalence of hypercholesterolemia among multiple transplanted studied groups ranged from 15 to 58%). Our prevalence of hypertriglyceridemia (60 %), however, was more than that of Galiyeva study. Low HDL cholesterol concentration (in 50% and 15%) and hypertriglyceridemia (in 80% and 30% of HD & KTX groups respectively) were reported by our study denoting increased CV risk among HD than KTX population as Bonthuis et al., 2012 study too.

CKD-MBD is a systemic disorder and a trinity of bone/laboratory abnormalities, and vascular calcification that are linked to hard outcomes as CV morbidity and mortality (Moe et al., 2006). In the present study; 63.33% of our HD patients had increased Ca X Po₄ ($>55\text{mg}^2/\text{dl}^2$) while only 6.6% of KTX group experienced this biochemical abnormality. Similar results were published by Becker-Cohen et al. (2006). They reported very low incidence (1.6%) of increased CA X Po₄ ($>55\text{mg}^2/\text{dl}^2$) among their transplanted children.

Markers of chronic inflammation

Chronic uremia is considered a pro-inflammatory state associated with increased CV morbidity and mortality (Stompor et al., 2003). In the present study; N/L and HsCRP were evaluated in ESKD children. N/L was reported to be independently related to ED and could predict composite CV endpoints independent of traditional confounding factors in patients with moderate to severe CKD (Solak et al., 2013). We found that N/L is elevated in presence of LVH ($p=0.048$) and high degree of nocturnal fall in diastolic BP ($p=0.025$) in HD patients. Additionally; significant positive correlation was detected between N/L and HsCRP and with total cholesterol level. In the present study; mean (\pm SD) N/L of KTX group [2.3 (± 1.1)] was less than that of HD group ($p<0.001$) signifying less chronic inflammatory state and less CV risk. Moreover; high N/L associated with uncontrolled 24 hours diastolic BP in KTX patients.

CRP is known to be an excellent marker of systemic inflammation. In the present study the mean (\pm SD) serum HsCRP in HD group was 6.9 (± 5.1) mg/L with 40% of HD patients have HsCRP $>10\text{mg/L}$. Our value is near to Elshamaa et al., study as the authors reported HsCRP values of 6.57 ± 5.57 mg/l, with raised HsCRP concentrations (>10 mg/l) was found in 30% of their HD patients (Elshamaa et al., 2009). We detected a difference in HsCRP level between ESKD patients and KTX group with more levels detected in KTX ($p<0.001$). Our finding does not go

with the adult study conducted by Yilmaz et al., (2015). They reported that there is substantial reduction in HsCRP level after KTX. On the other hand; Kocak et al., (2006) found in their study that Hs-CRP levels was high in both KTX same as HD patients. HsCRP level is associated with development of hypertension, which means that hypertension is, in part, an inflammatory disorder (Sesso et al., 2003). Moreover, HsCRP and BP are both independent determinants of future CV disease, and their predictive value is additive (Blake et al., 2003). In the present study; we detected a direct significant correlation between HsCRP and 24hrs systolic, diastolic BP, 24hrs MAP and nocturnal MAP in KTX group ($p=0.047$, 0.037 , 0.032 and 0.036 respectively). Moreover; HsCRP was significantly high in uncontrolled systolic pressure and MAP above 95th percentile ($p=0.018$, 0.009 respectively). Although specific therapies to lower the serum levels of inflammatory markers are not yet warranted for preventing CVD, lowering of serum concentrations of CRP in patients treated with statin for hyperlipidemia is associated with an independent beneficial effect on the risk of CVD events (Ridker et al., 2005).

Netrin1 is most likely produced by the endothelium (Ly et al., 2005), when atherosclerosis progresses, Netrin-1 expression by the (inflamed) endothelium is decreased, which leads to decreased Netrin-1 plasma concentrations (Bruikman et al., 2020). In the present study; we investigated netrin1 as an emerging CV parameter to be evaluated by comparing it with risk factors of CVD and markers of ED. Netrin-1 has been shown to play an important role in atherosclerosis by acting as a cardio-protective agent (Passacquale et al., 2015). In the present study; we reported a significant negative correlation between Netrin1 and each of tested markers of chronic inflammation (HsCRP and N/L) among HD group, signifying it's an anti-inflammatory role. Similar finding was reported by few years ago (Liu et al., 2019). Endothelial Netrin-1 expression is increased by atheroprotective laminar flow and decreased by inflammatory cytokines (Lin et al., 2018). The plasma lipid profile was also improved by netrin-1. While total cholesterol and triglyceride levels were drastically reduced in netrin-1 infused animals, HDL-cholesterol did not change (Bandeali and Farmer, 2012). In the present study, transplant group showed inverse significant relations between serum netrin1 and total cholesterol, LDL and triglyceride with no relation with HDL cholesterol. We reported elevated Netrin-1 levels in HD patients without LVH. In Wang et al., 2016 study, the authors found that netrin-1-mediated the protection against cardiac hypertrophy and heart failure in experimental mice. The patients with low netrin-1 level tended to have higher BP, triglycerides and have higher prevalence of history of hypertension than those with high netrin-1 level (Guo et al., 2020). In the present study, the median serum netrin1 level was 562.5 pg/ml in HD group and 586.1 pg/ml in KTX group (both were less than controls; 650.2 pg/ml). We found that lower netrin1 levels were insignificantly associated with uncontrolled systolic hypertension ($p=0.75$) in HD group beside significant lower level with higher serum total cholesterol ($p<0.001$), LDL ($p=0.003$) and TAG ($p=0.009$) in KTX group.

Similar to previous study conducted in our Center (Fadel et al., 2018); we reported less CV risk in ESKD children after KTX than those on HD by this study. Our new results showed significant higher prevalence of hypertension, higher number of patients with 24hrs BP > 95th percentile by ABPM, more prevalence of

nocturnal non-dipping BP, higher percentage of obese and overweight patients, worse biochemical analysis, higher chance of medical calcification by higher Po_4 and $\text{Ca} \times \text{Po}_4$, higher triglyceride level and lower HDL level and higher N/Lin HD than KTX group.

The points of strength in this study are

Sticking out the importance of using ABPM in HD and KTX patients to detect masked hypertension and follow up response to antihypertensive drugs to maintain controlled BP and graft function after KTX. Raising the CV beneficial effect of KTX in children in comparison to regular HD. This study outcrops the importance cardiovascular predictive value of anti-inflammatory markers.

The limitations of this study are

Being single center with small sample size. Steroid use in KTX group may affect both lymphocyte and neutrophil counts or HsCRP due to steroid anti-inflammatory effect.

Conclusion

Hypertension, LVH, dyslipidemia and CKD-MBD considered common CV risk factors in patients with ESKD. The lower level of plasma Netrin-1 level could predict the CV risk in ESKD children. Netrin-1 has anti-inflammatory effect (lower level of netrin1 associated with high level of HsCRP and N/L in HD patients). KTX has positive impact of decreasing CV risk encountered by ESKD children. Transplanted patients have less prevalence of hypertension by AMBP monitoring, nocturnal non-dipping BP, and less markers of chronic inflammation than HD patients. Markers of chronic inflammation have prognostic value for CV risk, being well correlated to LVH and nocturnal fall in DBP (N/L).

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