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## Ambulatory Hypertension in Children with Kidney Failure on Maintenance Dialysis

Dear Editor,

Cardiovascular (CV) disease is the leading cause of death in children with advanced chronic kidney disease (CKD).<sup>1</sup> Indian children with CKD have a higher prevalence of CV morbidity compared to the Western pediatric CKD cohort.<sup>2</sup> Limited data are available on the prevalence of hypertension (HTN) in children with kidney failure on maintenance dialysis.

Traditionally, blood pressure (BP) in children on dialysis is measured manually in the clinic, which may be inaccurate due to fluctuations in fluid status and diurnal variations.<sup>3</sup> Ambulatory BP monitoring (ABPM) has the advantage of detecting diurnal variations in BP over a 24-h period. The objectives of this study were to determine the prevalence of uncontrolled HTN by ABPM versus clinic BP measurement alone in children with kidney failure on maintenance dialysis, to assess the diurnal variation of ambulatory BP and to determine factors associated with ambulatory HTN. For detailed description of methods refer to the Supplementary Material.

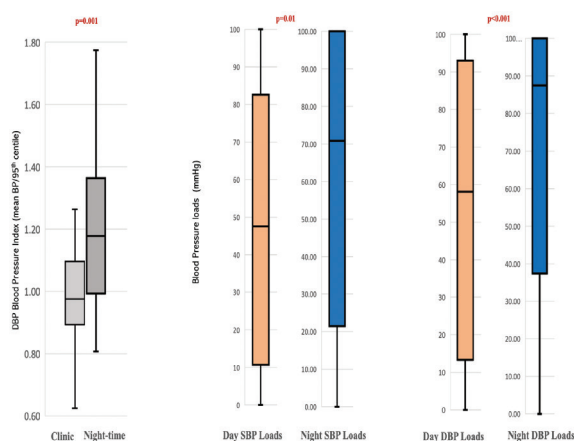
Twenty-seven patients (12 ± 2.6 years) consisting of 13 (48%) girls, with 18 (67%) on peritoneal dialysis (PD), having a median dialysis vintage of 17 months (10–35 months) were included. Residual kidney function was present in 16 patients (59%). Concentric left ventricular hypertrophy (LVH) was present in 19 (70%) patients. Twenty-six patients (96%) already had a diagnosis of HTN and were on treatment, with a median of three antihypertensive medications. The patient characteristics are described in Table 1.

**Table 1: Clinical characteristics of children with kidney failure on maintenance dialysis**

Characteristic	Value
Total patients	27
Girls	13 (48%)
Patients on PD	18 (67%)
Age (years)	12 (±2.6)
Dry wt z-score	−3.2 (±2.3)
Ht z-score	−3.18 (±1.9)
Non-glomerular native kidney disease	17 (63%)
Dialysis vintage (months)	17 (10-35)
IDWG (wt gain above the dry weight as a percentage of body weight)	2.5% (±2.16%)
Patients with LVH	19 (70%)
HTN by clinic BP alone	17 (63%)
HTN by ABPM	22 (81%)
Isolated nocturnal HTN, n (%)	4 (18%)
Blunted nocturnal dip, n (%)	24 (89%)

Data presented as n (%), mean (±SD), or median (IQR). ABPM = ambulatory blood pressure monitoring, DBP = diastolic blood pressure, HTN = hypertension, IDWG = intradialytic weight gain, LVH = left ventricular hypertrophy, PD = peritoneal dialysis, SBP = systolic blood pressure, wt: weight.

Despite the patients being on antihypertensive medication, ABPM identified uncontrolled HTN in 22 (85%) patients and one patient had a newly diagnosed HTN. In contrast, clinic BP monitoring detected uncontrolled HTN in only 17 patients (65%). Therefore, in five patients, HTN was diagnosed only by ABPM (four had masked uncontrolled HTN and one was newly diagnosed). The level of



**Figure 1:** Diurnal variation of ambulatory blood pressure indices and BP loads. DBP = diastolic blood pressure, SBP = systolic blood pressure.

agreement between the clinic BP and ABPM to detect HTN was only moderate ( $k = 0.5$ ).

All patients with ambulatory HTN were treated with changes in their dialysis prescription or modification of medications.

Mean night-time diastolic BP index was greater than day-time indices (1.19 vs. 0.98,  $P = 0.001$ ). Night-time BP loads were greater than day-time values (52% vs. 42%,  $P = 0.01$ ) for systolic BP and (89% vs. 58%,  $P < 0.001$ ) diastolic BP [Figure 1]. Nocturnal HTN (high night-time BP) was present in 21 patients (78%). Isolated nocturnal HTN was present in 4 (18%) patients. The nocturnal dip was blunted in 24 (89%) patients, with a reversal of dip (higher BP at night-time) found in five of these. The severity of ambulatory HTN did not differ by native kidney disease, dialysis modality, weight gain as a percentage of their dry weight, residual kidney function, or presence of LVH (all  $P > 0.05$ ).

In our study, we found that 96% of children had clinical diagnoses of HTN and were on salt- and water-restricted diets, regular hemodialysis (HD) or PD, and also antihypertensive medications. Despite these standard clinical measures, uncontrolled HTN persisted in 85% of these patients. The clinical relevance of uncontrolled HTN is likely indicated by the high prevalence of CV morbidity – 70% had concentric LVH (LVH is a known preclinical marker of CV disease in children).

This is the first study in India looking at the ambulatory pattern of HTN in children on dialysis. Prevalence of HTN in our study is higher than that noted in the North American Pediatric Renal Transplant Cooperative Study,<sup>4</sup> and the prevalence of uncontrolled HTN is also higher than that of Western pediatric dialysis patients.<sup>5</sup> In addition, it is noteworthy that neither of these studies used ABPM.

In our study, almost 20% of patients would have been incorrectly diagnosed with controlled BP if they had been

assessed by clinic BP alone. ABPM is better than routine manual BP monitoring at detecting uncontrolled HTN as it reveals nocturnal HTN that is highly prevalent (78%) even in pediatric dialysis patients. Nocturnal HTN occurs in children with secondary HTN, such as those on dialysis, and is an independent risk factor for CV morbidity.<sup>6</sup> Thus, we believe that ABPM has an important role in management, even in children who have already been diagnosed with HTN.

Even though native kidney disease, residual kidney function, and weight gain (as a percentage of dry weight) are known to affect ambulatory BP, we could not find statistical associations of these variables with ambulatory HTN in our patients. It is possible that in children on dialysis, HTN is multifactorial, similar to adults, and less affected by factors affecting HTN in earlier stages of CKD.

Due to its retrospective nature, we did not have access to ultrafiltration volumes of the HD or PD sessions preceding the 24-h ABPM period. In an attempt to address the role of salt and water retention as a cause for uncontrolled HTN, we used weight gain (as a percentage of dry weight) as a surrogate marker of fluid overload.

In conclusion, despite the universal use of antihypertensive medication in children on maintenance dialysis, ABPM detected uncontrolled HTN in 85% of patients. ABPM is superior to clinical BP in detecting uncontrolled HTN due to the high prevalence of nocturnal HTN. In this high-risk cohort, studies targeting better nocturnal control of BP are needed to reduce CV risk.

#### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

#### Conflicts of interest

There are no conflicts of interest.

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## Evaluation of Relationship between Copper and Insulin Resistance by Hyperinsulinemic Clamp

Dear Editor,

Trace elements are essential micronutrients required for the normal functioning of the body. Patients on hemodialysis (HD) exhibit altered levels of essential trace elements, predisposing them to oxidative stress, inflammation, and immune abnormalities. In particular, patients undergoing HD have disruption of zinc (Zn) and copper (Cu) levels, which has been suggested as a cause of clinical deterioration and adverse outcomes in HD patients.<sup>1</sup> Zn and Cu have been suggested to affect oxidative stress and to be associated with abnormal glucose tolerance and diabetes mellitus.<sup>2</sup> Cu is an essential trace element and a major constituent of the respiratory enzyme complex cytochrome *c* oxidase; Cu is also found in superoxide dismutase, which decreases oxidative stress. Oxidative stress is thought to promote the development of insulin resistance (IR) and diabetes.<sup>2</sup> IR is considered a substantial risk factor for the development of excessive vascular stiffening and consequent adverse cardiovascular disease events.<sup>3</sup> Strategies aimed at preventing or improving IR may represent novel interventions to improve poor clinical outcomes in HD patients. The hyperinsulinemic euglycemic clamp is the gold standard for the index of IR, but the technique is complicated because it requires time for equipment and inspection, making it difficult to use in daily medical treatment and large-scale clinical studies.<sup>4</sup> Since there is a lack of evidence in this area, we evaluated the relationship between IR and trace elements such as Zn and Cu in HD patients using an artificial pancreas.

The hyperinsulinemic euglycemic clamp was performed with an artificial pancreas (STG-55; Nikkiso, Shizuoka, Japan). In brief, human regular insulin was automatically injected intravenously by the artificial pancreas at a rate of 1.25 mU/kg/min to achieve a blood glucose level of 95 mg/dL. The mean glucose infusion rate (GIR; mg/kg/min) over the last 30 min of the 120-min clamp represents insulin sensitivity. The high GIR means low IR because insulin is functioning well.

This study and all its protocols were reviewed and

approved by the International University of Health and Welfare Ethics Committee (approval no. 21-NR-060). Written informed consent was obtained from the patient for this study. In seven HD patients, GIR was measured by the hyperinsulinemic euglycemic clamp on two occasions, 6 weeks apart, before dialysis at the beginning of the week. The hyperinsulinemic euglycemic clamp requires two catheters, one for continuous blood collection and the other for glucose and insulin administration. In this study, the two indwelling needles used in subsequent HD were used as routes.

Normality of data was evaluated with the Shapiro–Wilk test. Data are presented as the mean  $\pm$  standard deviation (SD) or the median (25%–75% interquartile range), unless otherwise indicated. The relation between two variables was assessed with Pearson’s correlation coefficient for normal distribution and Spearman’s rank correlation coefficient for non-normal distribution. All statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) software. A *P* value of  $<0.05$  was considered statistically significant.

Table 1 summarizes the demographic and clinical characteristics of the seven patients included in this study. Results showed correlation between Cu and GIR ( $r = -0.55$ ,  $P = 0.042$ ), but no correlation between Zn and GIR ( $r = 0.31$ ,  $P = 0.280$ ) [Figure 1]. Trace elements have received increasing attention in relation to the prevalence of diabetes, and Cu is one such element. Cu is a crucial component of a variety of metalloenzymes and plays an important role in the redox reaction. Cu contributes to increased oxidative stress by enhancing the formation of reactive oxygen species (ROS) through Haber–Weiss and Fenton-like reactions and by catalytically participating in the generation of hydroxyl radicals by hydrogen abstraction.<sup>5</sup> These consequences are thought to lead to IR, and our results are consistent with this hypothesis. Zn is an essential micronutrient in the metabolism, which regulates more than 300 enzymes for protein folding, gene expression, and the