Cardiovascular risk, growth and patient-related outcome measures in children with end-stage kidney disease: an observational comparison of hemodiafiltration to conventional hemodialysis – the HDF, Heart and Height (3H) study

Supplemental section

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Statistical analysis

Based on a parallel study investigating cardiovascular disease progression in children on HD[1], the sample size was 69 children per group at 90% power and 2.5% Type I error (Bonferroni correction to account for the co-primary endpoints), with 76 subjects per group after accounting for a 10% dropout rate. All analyses were decided *a priori* in a statistical analysis plan[1]. *Per protocol* analysis (at least 90% of all dialysis sessions must be in the assigned group) was performed, however only 4 children switched from HDF to HD, so intention to treat analysis yielded similar results. The co-primary endpoints of annualized change in cIMT-SDS and height-SDS were calculated, and compared between the HD and HDF cohorts using unpaired t-tests.

As the data are observational, adjustment for potential confounders were made through the construction of propensity scores derived from a logistic regression, as detailed in Fu et al[2]. These propensity scores represent the likelihood (i.e. probability) of receiving HDF rather than HD, based on a child's characteristics. The pre-specified predictors included in the construction of the propensity scores were identified by the expert treating clinicians in the study group as factors known to be predictors of dialysis modality choice (age, sex, country [Turkey vs others], blood flow rate adjusted for body surface area and water quality [pure vs ultra-pure]). This propensity score was then included as a predictor in a multivariable model, as a method to account for potential confounding. The regression analysis was also repeated using propensity score weighting, using each subject's propensity score to create a weighted dataset (pseudo-population) in which no confounding is present.

Sensitivity analyses were performed to ensure robustness of results, adjusting for a wide range of potential confounders through a multivariable linear regression model. All variables with $p<0.2$ in univariable analysis were included in multivariable analysis. In addition, dialysis modality (HD vs HDF) was included in every model regardless of its statistical significance, as this was the primary independent variable of interest in the study. This inclusion rule was chosen *a priori* in the statistical analysis plan, to exclude biased selection of which variables to include and to ensure consistency between the different multivariable models performed.

The annual change in secondary endpoints (PWV-SDS, MAP-SDS and LVMI) were investigated similarly. Predictors of the vascular measures at 12-months were similarly investigated. Factors associated with the outcomes at 12 months were conducted in an identical way to the sensitivity analyses considering change from baseline to 12 months (i.e. a linear regression, using a $p<0.2$ cut-off rule for selection in multivariable analysis). Changes in biomarkers between baseline and 12 months were compared between HD and HDF groups using Mann-Whitney U tests. The Kruskal-Wallis test was used to compare the median blood flow rate as well as convective volume in each vascular access group. Patient outcomes for health-related quality of life measures were compared using Fisher's exact tests. Determinants of post-dialysis recovery time were further investigated using ordinal logistic regression. A Bonferroni correction was pre-specified for the two co-primary endpoints, and so a p-value of <0.025 was required to indicate statistical significance for these two comparisons. No other formal adjustments for multiple testing were made, as the study was powered to assess the co-primary endpoints, and all other analyses are post-hoc secondary analyses. All analyses were performed in SAS Version 9.4 (SAS Institute Inc, Cary, NC). All analyses were two-sided, and $p<0.05$ was considered statistically significant for the post-hoc secondary analyses.

Reference List

1. Shroff R, Bayazit A, Stefanidis CJ, Askiti V, Azukaitis K, Canpolat N, Agbas A, Anarat A, Aoun B, Bakkaloglu S, Bhowruth D, Borzych-Duzalka D, Bulut IK, Buscher R, Dempster C, Duzova A, Habbig S, Hayes W, Hegde S, Krid S, Licht C, Litwin M, Mayes M, Mir S, Nemec R, Obrycki L, Paglialonga F, Picca S, Ranchin B, Samaille C, Shenoy M, Sinha M, Smith C, Spasojevic B, Vidal E, Vondrak K, Yilmaz A, Zaloszyc A, Fischbach M, Schaefer F, Schmitt CP: Effect of haemodiafiltration vs conventional haemodialysis on growth and cardiovascular outcomes in children - the HDF, heart and height (3H) study. *BMC Nephrol* 19:199, 2018

2. Fu EL, Groenwold RHH, Zoccali C, Jager KJ, van DM, Dekker FW: Merits and caveats of propensity scores to adjust for confounding. *Nephrol Dial Transplant* 2018

Supplemental Table 1 Fluid status and vascular measures in HD and HDF patients

	HD (n = 78)			HDF (n = 55)			P*	P**
	Baseline	12-months	p	Baseline	12-months	p		
Interdialytic weight gain (%)	4.9 (3.4 – 6.3)	5.2 (3.6 – 6.5)	0.36	3.8 (1.9– 5.5)	3.8 (1.8 – 4.8)	0.30	0.001	<0.001
Ultrafiltration per session ml/kg/hour	8.9 (5.3- 10.6)	9.3 (6.9 – 11.2)	0.07	7.5 (4.1 – 8.7)	7.7 (4.6 – 8.9)	0.58	0.03	0.01
Vascular measures								
Carotid intima-media thickness (cIMT; mm)	0.48 (0.45 – 0.52)	0.50 (0.47 – 0.55)	<0.0001	0.46 (0.40 – 0.53)	0.46 (0.43 – 0.56)	0.78	0.24	0.003
cIMT-SDS	2.05 (1.3 – 2.7)	2.52 (1.7 – 3.4)	0.02	1.81 (0.5 – 3.1)	1.61 (0.9 – 3.1)	0.89	0.36	0.009
Pulse Wave Velocity (PWV; m/sec)	5.7 (4.8 – 6.4)	5.8 (4.9 – 6.5)	0.09	4.8 (4.6 – 5.4)	4.9 (4.6 – 5.5)	0.94	0.0002	0.0002
PWV-SDS	2.07 (1.2 – 3.2)	1.43 (-0.4 – 2.7)	0.01	0.68 (-0.45 – 2.3)	-0.31 (-1.0 – 0.9)	0.006	0.002	0.0008
24-hour Mean Arterial Pressure (MAP; mmHg)	90 (83 – 92)	96 (89 – 100)	0.05	78 (72 – 84)	80 (72 – 86)	0.07	0.004	<0.0001
24-hour ambulatory BP MAP-SDS	2.75 (2.0 – 3.8)	3.74 (2.9 – 5.4)	<0.0001	0.98 (0.18 – 2.1)	1.38 (0.3 – 2.6)	0.35	<0.0001	<0.0001
Left Ventricular Mass Index (g/[$m^{2.16}$+0.09])	42.76 (34.7 – 58.2)	47.38 (36.6 – 56.5)	0.40	39.05 (28.4 – 48.9)	39.3 (27.0 – 50.4)	0.55	0.07	0.02
Intra-individual change from baseline (absolute values)								
	HD (n = 78)			HDF (n = 55)			p	
cIMT (mm)	0.025 (0 – 0.045)			0 (-0.01 – 0.019)			0.0004	
cIMT-SDS	0.41 (-0.09 – 0.93)			-0.07 (-0.35 – 0.37)			0.02	
PWV (m/sec)	0.1 (-0.43 – 0.42)			0 (-0.4 – 0.35)			0.44	
PWV-SDS	-0.74 (-1.43 - 0.22)			-0.70 (-1.67 – 0.04)			0.87	
24-hour MAP (mmHg)	5 (3 – 8)			2 (-2 – 5)			<0.0001	
24-hour MAP-SDS	0.99 (0.58 – 1.98)			0.31 (-0.42 – 0.84)			<0.0001	
LVMI (g/[$m^{2.16}$+0.09])	4.3 (-3.8 – 9.61)			0.88 (-3.63 – 7.34)			0.21	

All values are described as median and interquartile range unless specified otherwise. SDS – standard deviation score.
P - compares baseline vs 12-month values within HD or HDF groups (paired t-test)

P* - compares vascular measures at baseline between HD and HDF groups (unpaired t-test)
P** - compares vascular measures at 12-months between HD and HDF groups (unpaired t-test)

Supplemental Table 2 Laboratory results, medications and changes in measures in HD and HDF patients

	HD (n = 78)			HDF (n = 55)			P*	P**
	Baseline	**12-months**	**p**	**Baseline**	**12-months**	**p**		
Laboratory results								
KTV	1.7 (1.4 – 1.9)	1.78 (1.5 - 2.04)	0.25	1.84 (1.6 - 2.0)	1.89 (1.6 - 2.2)	0.11	0.06	0.09
Urea Reduction Rate (URR; %)	76 (71 – 81)	76.4 (71.6 – 81.9)	0.63	78.7 (74.6 – 83)	80 (74.6 – 83.6)	0.20	0.13	0.37
Beta-2 microglobulin (mg/L)	36.8 (29.6 - 46.6)	36.8 (30.9 – 48.9)	0.57	26.6 (23.5 - 30.8)	23.1 (21.4 - 26.4)	0.02	<0.0001	<0.0001
High-sensitivity CRP (mg/L)	2.6 (1.05 - 6.1)	3.9 (1.5 - 8.8)	0.009	0.9 (0.5 - 2.4)	0.95 (0.4 - 2.7)	0.88	0.002	<0.0001
Serum Albumin (g/L)	41 (39 - 43)	40 (37 - 43)	0.06	40 (37 - 42)	41 (39 - 43)	0.26	0.30	0.47
Serum Sodium (mMol/L)	138 (134 – 142)	137 (134 – 141)	0.49	137 (133 – 142)	138 (133 – 142)	0.58	0.82	0.79
Serum Potassium (mMol/L)	5.1 (4.7 – 6.6)	4.8 (4.4 - 6.4)	0.53	5.0 (4.5 - 6.1)	5.2 (4.6 – 6.2)	0.72	0.81	0.70
Serum bicarbonate (mMol/L)	21.5 (18.1 - 23.6)	22 (19.8 - 24.7)	0.26	22.0 (19.9 - 23.6)	23 (21 – 24.5)	0.21	0.10	0.31
Serum Phosphate (mMol/L)	1.60 (1.28 - 2.22)	1.71 (1.27 - 2.22)	0.67	1.82 (1.64 - 2.1)	1.74 (1.59 - 2.18)	0.85	0.09	0.10
Parathyroid hormone (pmol/L)	282 (108 – 759)	365 (155 – 853)	0.13	249 (46 – 400)	86 (38 – 349)	0.03	0.3	0.004
25-hydroxyvitamin D (nMol/L)	28.3 (19.0 - 37.7)	31.8 (17.4 - 44.8)	0.06	36.0 (22.4 - 44.6)	35.0 (21.0 - 52.0)	0.66	0.06	0.36
Haemoglobin (g/dL)	10.3 (9.7 - 11.7)	10.4 (9.5 - 12.1)	0.60	10.9 (9.6 - 12)	12.0 (10.8 - 13.0)	0.001	0.41	0.001
Ferritin (ng/ml)	294 (152 - 539)	358 (186 - 543)	0.23	241 (116 - 482)	372 (163 - 566)	0.16	0.44	0.90
Medications								
Growth Hormone; n (%)	12 (15.4)	9 (11.5)	0.64	14 (25.5)	13 (23.6)	0.99	0.18	0.09
CKD-MBD treatment: Ca based /			0.87			0.91	0.78	0.83

Sevelamer/Lanthanum / Ca based +sevelamer / Ca based + Lanthanum / none Cinacalcet	41 / 11 / 0 / 21 / 0 / 5 2	37 / 14 / 1 / 24 / 1 / 1 3	 -	28 / 4 / 1 / 19 / 1/ 2 2	25 / 4 / 1 / 21 / 2/ 2 2	 -	 -	 -
Erythropoetin stimulating agents - none / EPO / Darbe / Cera - EPO dose (IU/kg/wk) Darbe dose(µg/kg/wk)	 8 / 37 / 33 / 0 145 (96 – 215) 1.09 (0.7 – 2.1)	 2 / 43 / 33 / 0 146 (95 – 190) 1.06 (0.53 – 1.97)	 0.09 0.87 0.65	 3 / 18 / 33 / 1 171 (93 – 219) 0.73 (0.42 – 0.94)	 2 / 11 / 38 / 4 160 (138 - 212) 0.55 (0.43 – 0.79)	 0.64 0.42 0.26	 0.13 0.85 0.01	 0.002 0.33 0.005
Iron supplements - None / Oral / IV - Intravenous iron dose (/kg/week)	 18 / 13 / 47 1.64 (1.07 – 2.03)	 19 / 10 / 49 1.42 (0.91 – 2.55)	 0.79 0.46	 19 / 5 / 40 1.2 (0.89 – 1.67)	 11 / 1 / 43 1.28 (0.85 – 2.18)	 0.25 0.21	 0.29 0.06	 0.06 0.55
Anti-Hypertensives: None / 1 / 2 /3 *Types* (%): ACEi or ARB / Ca channel blocker / beta blocker / diuretic / others	 35 / 11 / 22 / 10 33 / 37 / 16 / 8 / 6	 39 / 8 / 6 / 2 33 / 36 / 21 / 8 / 2	 0.93 -	 28 / 16 / 24 / 10 38 / 37 / 16 / 5 /4	 37 / 10 / 7 / 1 41 / 29 / 21 / 7 /2	 0.97 -	 0.11 -	 0.38 -

All values are described as median and interquartile range unless specified otherwise. SDS – standard deviation score.

P - compares baseline vs 12-month values within HD or HDF groups (paired t-test or chi-square test)

P* - compares vascular measures at baseline between HD and HDF groups (unpaired t-test or chi-square test)

P** - compares vascular measures at 12-months between HD and HDF groups (unpaired t-test or chi-square test)

Supplemental Table 3 Sensitivity analyses for factors associated with annualized change in vascular measures, using a standard multivariable adjustment approach

Standard adjustment[a]	Delta cIMT-SDS				Delta PWV-SDS				Delta MAP-SDS				Delta LVMI			
	Univariable		**Multivariable**		**Univariable**		**Multivariable**		**Univariable**		**Multivariable**		**Univariable**		**Multivariable**	
	β (95% CI)	**p**	**β (95% CI)**	**P**	**β (95% CI)**	**p**	**β (95% CI)**	**P**	**β (95% CI)**	**p**	**β (95% CI)**	**p**	**β (95% CI)**	**p**	**β (95% CI)**	**p**
Dialysis modality ***HD vs HDF***	**0.54** **0.22, 0.86**	**0.001**	**0.44** **0.11, 0.77**	**0.01**	**0.11** **-0.51, 0.73**	**0.73**	**-0.18** **-0.51, 0.87**	**0.60**	**0.88** **0.50, 1.27**	**<0.0001**	**0.54** **0.04, 1.03**	**0.03**	**2.20** **(-2.83, 7.22)**	**0.39**	**2.77** **-2.33, 7.88**	**0.29**
Prevalent vs Incident status	**-0.66 (-0.5, 0.18)**	**0.64**			**0.10 (-0.53, 0.73)**	**0.75**			**0.26 (-0.16, 0.69)**	**0.23**			**-0.99 (-6.22, 4.25)**	**0.71**		
Serum phosphate *Per 0.3 higher*	0.00 -0.10, 0.10	0.98			0.09 -0.10, 0.28	0.35			-0.08 -0.21, 0.05	0.23			0.33 -1.17, 1.83	0.66		
PTH *Per 10 higher*	0.00 0.00, 0.00	0.22			0.00 0.00, 0.01	0.76			0.00 0.00, 0.01	0.01	0.0 0..0, 0.0	0.29	0.00 -0.04, 0.03	0.87		
Urine group 0 0-200 201-500 501+	 0.16 -0.24, 0.56 0.16 -0.33, 0.65 0.04 -0.48, 0.56 Ref.	 0.85			 -0.11 -0.87, 0.64 0.08 -0.81, 0.97 0.29 -0.69, 1.27 Ref.	 0.86			 0.20 -0.30, 0.71 0.50 -0.11, 1.11 0.22 -0.44, 0.89 Ref.	 0.47			 1.24 -4.91, 7.39 3.02 -4.63, 10.67 -1.07 -8.96, 6.83 Ref.	 0.80		
Haemoglobin *per 1 higher*	-0.06 -0.15, 0.03	0.21			-0.02 -0.20, 0.16	0.85			-0.03 -0.15, 0.08	0.56			0.62 -0.81, 2.04	0.40		
Inter-dialytic weight gain percentage *per 1 higher*	0.06 -0.01, 0.12	0.11	0.01 -0.06, 0.09	0.74	0.05 -0.07, 0.18	0.41			0.05 -0.03, 0.14	0.20	0.02 -0.08, 0.13	0.64	0.50 -0.54, 1.54	0.35		
MAP SDS *per 1 higher*	-0.04 -0.14, 0.05	0.37			-0.12 -0.31, 0.06	0.18	-0.14 -0.34, 0.05	0.15	-	-			0.15 -1.33, 1.63	0.84		
Systolic BP SDS *per 1 higher*	0.00 -0.10, 0.11	0.95			-0.10 -0.30, 0.10	0.32			0.01 -0.12, 0.13	0.93			0.67 -0.88, 2.22	0.40		
Diastolic BP SDS *per 1 higher*	0.04 -0.10, 0.17	0.60			0.10 -0.16, 0.38	0.42			0.02 -0.15, 0.19	0.80			1.43 -0.60, 3.46	0.17	1.17 -0.86, 3.20	0.26
BMI SDS *per 1 higher*	0.08 -0.04, 0.19	0.20	0.07 -0.05, 0.18	0.25	-0.19 -0.40, 0.03	0.09	-0.23 -0.46, -0.01	0.04	0.12 -0.02, 0.27	0.10	0.07	0.30	0.65 -1.20, 2.50	0.49		

											-0.07, 0.21					
Access type *AVF vs CVL*	-0.14 -0.47, 0.20	0.42			0.12 -0.52, 0.75	0.72			0.12 -0.30, 0.54	0.57			0.10 -5.02, 5.23	0.97		
Dialysate sodium level *per 1 higher*	-0.02 -0.12, 0.08	0.71			-0.10 -0.29, 0.08	0.26			-0.07 -0.19, 0.05	0.26			0.32 -1.19, 1.83	0.67		
Beta 2 microglobulin *per 10 higher*	0.09 -0.06, 0.23	0.26			0.03 -0.26, 0.31	0.85			0.26 0.08, 0.44	0.006	0.12 -0.09, 0.32	0.26	1.04 -1.22, 3.29	0.37		
Blood flow BSA *per 100 higher*	-001 -0.30, 0.29	0.97			-0.16 -0.72, 0.39	0.56			0.20 -0.18, 0.58	0.31			-5.48 -9.92, -1.02	0.02	-4.92 -9.47, -0.37	0.04
Ultrafiltration BSA *per 1 higher*	0.09 -0.06, 0.24	0.22			0.04 -0.24, 0.32	0.78			0.06 -0.14, 0.25	0.57			0.84 -1.45, 3.13	0.47		
hsCRP *per 1 higher*	0.00 -0.03, 0.02	0.64			0.04 0.00, 0.07	0.06	0.04 0.01, 0.08	0.02	0.01 -0.02, 0.04	0.46			-0.09 -0.40, 0.22	0.57		
Convective volume[b] *Per 1 l/m² BSA*	-0.02 -0.07, 0.02	0.32														
Dialyser type[c] *Low flux vs high flux* *Medium vs high*	0.11 -0.47, 0.68 -0.40 -1.02, 0.23	0.40														
Water quality[c] *Pure vs ultra pure*	0.15 -0.26, 0.56	0.48														

Results from a linear regression model, with potential confounders identified in univariable analysis with p<0.2 included as covariates in a multivariable analysis

[a]Standard adjustment multivariable models additionally adjusted for country [Turkey vs other].

[b]Subgroup of patients receiving HDF only

[c]Subgroup of patients receiving HD only

Supplemental Table 4 Comparison of study results, when using different propensity score methods to adjust for potential confounders

	Delta cIMT-SDS		Delta PWV-SDS		Delta MAP-SDS		Delta LVMI	
Dialysis modality: ***HD vs HDF***	**β (95% CI)**	**p**	**β (95% CI)**	**p**	**β (95% CI)**	**P**	**β (95% CI)**	**p**
Propensity score included as predictor in model (primary study results)	0.47 0.07, 0.87	0.02	0.58 -0.2, 1.36	0.15	0.65 0.16, 1.13	0.01	5.6 -0.79, 11.99	0.09
Propensity score weighting	0.59 0.15, 1.02	0.009	-0.15 -0.93, 0.64	0.72	0.89 0.49, 1.28	<0.0001	2.49 -2.71, 7.89	0.35