Daily online haemodiafiltration promotes catch-up growth in children on chronic dialysis

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Abstract

Background. In children, growth can be used as a measurable parameter of adequate nutrition and dialysis dose. Despite daily administration of recombinant human growth hormone (rhGH), growth retardation remains a frequent problem in children on chronic dialysis. Therefore, we performed an observational prospective non-randomized study of children on in-centre daily on line haemodiafiltration (D-OL-HDF) dialysis with the aim of promoting growth.

Patients and methods. Mean age at the start of the study was 8 years and 3 months, and all children had been receiving rhGH treatment for >12 months before enrolment. Mean follow-up time on D-OL-HDF was 20.5 ± 8 months (range, 11–39 months). Renal residual function was either <3 mL/
Introduction

Over the last few decades, the growth outcome for children with end stage renal failure has improved remarkably [1–3]. Nevertheless, even optimal care including daily administration of recombinant human growth hormone (rhGH) has proven inadequate in improving growth [4,5]. Indeed, several studies [1](rhGH) has proven inadequate in improving growth of children with end stage renal failure has improved remarkably [1–3]. Poor growth of children with end stage renal disease has been associated with an increased risk of hospital admissions and death [6,7], possibly related to their poor nutritional status, including both malnutrition and cachexia [3,8,9]. In children on chronic dialysis, malnutrition related to poor appetite and restrictive diet can be managed by dietary support [2,7]. However, this may not always solve the problem due to the cachexia and muscle wasting which occur in uraemic patients [8]. It is known that several uraemic factors can activate the ubiquitin proteasome system to degrade protein stores [8], such as metabolic acidosis, inflammation and uraemic toxin retention, which occur in haemodialyzed patients [10]. In children on chronic dialysis, growth may be used as a parameter to measure the optimal balance between nutrition, i.e. malnutrition and/or cachexia and adequate dialysis [9,11]. The three times a week programme (three times, 4 h) usually used in children on long-term dialysis does not allow for normal growth, therefore the case for an increased frequency was proposed [12,13]. However, intensive and daily dialysis is time consuming and so is not ideal in the paediatric population [14]. Knowing on the one hand the advantages of daily haemodialysis [15–18] and on the other hand the on line haemodiafiltration effects on uraemic toxin purification [19–21], we used in-centre daily on line haemodiafiltration (D-OL-HDF) in children [11,22,23], that was both daily dialysis and convective flow added to haemodialysis.

For this study, we prospectively collected data for growth in children on in-centre D-OL-HDF and assessed nutritional status and growth outcome with the hope of confirming our previous published data [11].

Materials and methods

This was a single centre, observational, prospective and non-randomized study. We included 15 children (Table 1) from September 2004 to April 2008, five of which had been included in previous publications [11]. Analysis of the data was performed in March 2009. The inclusion criteria were residual renal function <3 mL/min/1.73 m2 defined as the mean of Kmax and Kcr or anuria, prepubertal development stage (or early pubertal stage in three cases; Table 1), >6 months follow-up on D-OL-HDF and parents and child agreeing to in-centre daily dialysis. School lessons were provided by qualified teachers after discussion with the child’s own school for 2-h periods during each dialysis session. All had a journey time to the hospital of <1 h. The end point of D-OL-HDF follow-up was kidney transplantation, which was performed by the time of final analysis in 12/15 children, whilst 3/15 were still awaiting transplantation. During this study period, six children on D-OL-HDF were excluded from the analysis, as they underwent kidney transplantation before 6 months follow-up was complete. Only one child and his parents didn’t accept the daily schedule due to personal inconvenience despite the short travel time (<30 min) to hospital. The good acceptance rate of our daily in-centre dialysis programme was due to the child and care giver’s positive perceptions of the results seen over time. All children were on rhGH treatment with 1 IU/kg/week, by daily subcutaneous injections, started at least 12 months before the D-OL-HDF. At inclusion, their mean age was 8 years and 3 months (range, 3 years and 6 months to 14 years and 6 months). Before inclusion in the study, three children were on standard OL-HDF (4 h sessions three times a week), four were on chronic peritoneal dialysis (changed due to difficulties with diet, medications and dry weight achievement) and the remaining eight of them had started dialysis with D-OL-HDF. Vascular access was via a fistula (n = 13) or a central venous jugular catheter (n = 2). The dialysis schedule consisted of 3 hourly sessions six times a week (18 h/week), using highly permeable dialysers (FX 40 or FX 60, polysulfone, Fresenius), OL-HDF in a predilution mode, allowing a per session convective volume of 18 to 27 L/m2 body surface area (BSA), blood flow of 150 mL/min/m2 BSA adjusted to achieve a Kt/Vurea of at least 1.4 per session, on line measured (OCM, Fresenius, 4008 E machine) and dialysate flow of 500 mL/min. Dialysate and reinfusion fluid was bicarbonate buffered, 32 mmol/L with dextrose 1 gr/L. Pre-dialysis blood pressure was measured immediately before the dialysis session with an automated blood pressure monitor and was expressed as the systolic, diastolic and mean blood pressure. Tolerance during the dialysis session (i.e. hypertensive episodes and cramps) was recorded regularly. Post dialysis recovery time was recorded in minutes [24] (the time taken before the child was able to stand and walk after the end of the dialysis session). Diet was without restrictions and normal for age, the only limitation being the potassium intake especially in the day ‘off dialysis’ due to...
Table 1. Patients' demographic and medical histories

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Underlying renal disease</th>
<th>Age at start</th>
<th>Pubertal status</th>
<th>RRF (\frac{K_{\text{urea}} + K_{\text{crea}}}{2})</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>Frasier syndrome</td>
<td>6 years and 10 months</td>
<td>Pre pubertal</td>
<td>Anuria</td>
<td>KT</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>Nephrotic syndrome</td>
<td>5 years and 8 months</td>
<td>Pre pubertal</td>
<td>&lt;3</td>
<td>KT</td>
</tr>
<tr>
<td>3–PD</td>
<td>F</td>
<td>Bardet Biedl/ciliopathy</td>
<td>9 years and 8 months</td>
<td>Pre pubertal</td>
<td>&lt;3</td>
<td>KT</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>Bardet Biedl/ciliopathy</td>
<td>7 years</td>
<td>Early pubertal: pre pubertal</td>
<td>&lt;3</td>
<td>On dialysis</td>
</tr>
<tr>
<td>5–PD</td>
<td>F</td>
<td>Bardet Biedl/ciliopathy</td>
<td>10 years and 6 months</td>
<td>Pre pubertal</td>
<td>Anuria</td>
<td>KT</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>Neurological bladder</td>
<td>11 years</td>
<td>Pre pubertal</td>
<td>Anuria</td>
<td>KT</td>
</tr>
<tr>
<td>7–PD</td>
<td>M</td>
<td>Nephronophthisis</td>
<td>7 years and 11 months</td>
<td>Pre pubertal</td>
<td>Anuria</td>
<td>KT</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>Renal hypoplasia</td>
<td>8 years and 2 months</td>
<td>Pre pubertal</td>
<td>Anuria</td>
<td>KT</td>
</tr>
<tr>
<td>9–HD</td>
<td>M</td>
<td>Posterior uretal valve</td>
<td>8 years and 1 month</td>
<td>Pre pubertal</td>
<td>&lt;3</td>
<td>KT</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>Henoch Schoenlein syndrome</td>
<td>9 years and 2 months</td>
<td>Pre pubertal</td>
<td>Anuria</td>
<td>KT</td>
</tr>
<tr>
<td>11–HD</td>
<td>M</td>
<td>Posterior uretal valve</td>
<td>14 years and 6 months</td>
<td>Pre pubertal</td>
<td>Anuria</td>
<td>KT</td>
</tr>
<tr>
<td>12–HD</td>
<td>F</td>
<td>Nephrotic syndrome</td>
<td>8 years and 2 months</td>
<td>Irregular periods</td>
<td>&lt;3</td>
<td>On dialysis</td>
</tr>
<tr>
<td>13–PD</td>
<td>F</td>
<td>Renal hypoplasia</td>
<td>3 years and 4 months</td>
<td>Pre pubertal</td>
<td>Anuria</td>
<td>KT</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>Neurological bladder</td>
<td>6 years</td>
<td>Pre pubertal</td>
<td>Anuria</td>
<td>KT</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>Renal hypoplasia</td>
<td>8 years</td>
<td>Pre pubertal</td>
<td>Anuria</td>
<td>KT</td>
</tr>
</tbody>
</table>

KT: kidney transplantation; PD, HD: peritoneal dialysis or haemodialysis before involved in D-OL-HDF; RRF: renal residual function.

Table 2. Patients SDS of height at the start of D-OL-HDF, achieved at the end of D-OL-HDF, and difference [(1)–(2)] between the SDS height achieved (1) and the SDS of the mid-parental target height (2)

<table>
<thead>
<tr>
<th>Patient (n = 15)</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (SDS)</td>
<td></td>
</tr>
<tr>
<td>Start of D-OL-HDF</td>
<td>– 1.5 ± 0.3</td>
</tr>
<tr>
<td>End of D-OL-HDF (1)</td>
<td>+ 0.2 ± 1.1*</td>
</tr>
<tr>
<td>Mid-parental target height (2)</td>
<td>– 0.3 ± 0.7</td>
</tr>
<tr>
<td>(1) – (2) (SDS)</td>
<td>+ 0.3 ± 0.7</td>
</tr>
<tr>
<td>Growth velocity (centimetres per year)</td>
<td></td>
</tr>
<tr>
<td>The year before daily</td>
<td>3.8 ± 1.1</td>
</tr>
<tr>
<td>First year of daily</td>
<td>14.3 ± 3.8*</td>
</tr>
<tr>
<td>Mean over daily</td>
<td>8.9 ± 2.2*</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td></td>
</tr>
<tr>
<td>At start of daily</td>
<td>16.5 ± 2.0*</td>
</tr>
<tr>
<td>End of daily</td>
<td>18.0 ± 2.4*</td>
</tr>
</tbody>
</table>

The mid-parental target height is equal to the sum of \(fater height (centimetres)\) and mother height (centimetres) \(± 13/2\), depending on the gender, + if male, – if female. Mean growth velocity (in centimetres per year): the year before D-OL-HDF, during the first year of D-OL-HDF, and the mean over all the duration of D-OL-HDF. Patient BMI expressed in weight over body surface area, i.e. kg/cm², and in percentile (%) at the start of D-OL-HDF and at the end. *P < 0.05 versus start; †, ‡P < 0.05 versus the year before daily; ††, ‡‡, ‰P < 0.05 versus start.

Results

The mean time on D-OL-HDF was 20.5 ± 8 months (11–39 months). No side effects were noted, in particular, no vascular access problems. Tolerance was good, with no significant post dialysis recovery time. The mean growth velocity (Table 2) was statistically lower the year before starting D-OL-HDF, 3.8 ± 1.1 cm/year (2.0–5.2 cm/year) than in comparison to the first year of treatment, 14.3 ± 3.8 cm/year (8.5–20.5 cm/year) and also when compared to the mean over the whole follow-up period, 8.9 ± 2.2 cm/year (4.7–14.7 cm/year). During the first year of D-OL-HDF, the growth velocity was statistically higher compared to the mean over the whole daily follow-up period. This growth velocity leads to a significant change in height SDS (Table 2), from the start of D-OL-HDF –1.5 ± 0.3 SDS (–3.5–0.0) to the end of daily +0.2 ± 1.1 SDS (–1.1 to +1.9), which resulted in the children achieving a mean height of just over the mid-parental target height by +0.3 ± 0.7 SDS (–1.3 to +1.6). The mean BMI increased (Table 2) from 16.5 ± 2.0 kg/m² (48 ± 24 in percentile) to 18.0 ± 2.4 kg/m² (65 ± 26 in percentile). Mean arterial blood pressure (mm Hg) decreased over D-OL-HDF at the start of the study, 99 ± 18 (Z score 2.3) and at the end of the study, 83 ± 12 (Z score 1.8). Only two children received one...
antihypertensive drug (patients 4 and 5). Mean pre dialysis haemoglobin (g/dL) showed no significant tendency to increase between the start of D-OL-HDF, 11.4 ± 1.2 and end of the study, 12.5 ± 0.9. The iPTH (pg/mL) didn’t change significantly, respectively, 143 ± 47 and 195 ± 89. Mean pre dialysis parameters are given in Table 3. Mean pre dialysis phosphate levels were in the normal range, 1.39 ± 0.05 mmol/L, despite a high protein intake, mean DPI of 2.5 ± 0.2 g/kg/day. A high mean CRP was noted in patients 4 and 5 having chronic bronchitis (respectively, 47 and 32 mg/L), which is under the suggested 25 mg/L pre dialysis threshold level. It could be speculated that the achievement of low antihypertensive drug levels, possibly due to free diet and good appetite. With the use of ultrapure dialysate, OL-HDF appears to be an optimal haemodialysis procedure at least in terms of both uraemic toxin removal and dialysis frequency and dialysis time, i.e. daily dialysis six times a week for 3 h and lastly, the absence of malnutrition, i.e. due to free dihydrapril. The impact of D-OL-HDF on catch-up growth, i.e. less resistance to rhGH in children on chronic dialysis, appears to be multifactorial, possibly due to the following factors: dialysis modality, i.e. OL-HDF (high convective dialysis flow and use of ultrapure dialysate), dialysis frequency and dialysis time, i.e. daily dialysis six times a week for 3 h and lastly, the absence of malnutrition, i.e. due to free diet and good appetite. With the use of ultrapure dialysate, OL-HDF appears to be an optimal haemodialysis procedure at least in terms of both uraemic toxin removal and of reduced dialysis induced inflammation [21], two factors which potentially limit uraemic protein wasting [8,10] and so may promote growth for children despite being on chronic dialysis [9]. Haemodiafiltration applied daily improves renal blood purification [30–32].

In our D-OL-HDF study, not only is TADurea low but it is also a marker of middle molecule weight uraemic toxins, for example β₂ microglobulin, which is under the suggested 25 mg/L ‘optimal’ pre dialysis threshold level [20]. It could be speculated that the achievement of low β₂ microglobulin levels in our study, i.e. 15.3 ± 3.3 mg/L should be a surrogate marker for the elimination of other

**Table 3. Mean (±SDS) mid-week pre dialysis parameters**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid-week pre dialysis</td>
<td></td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>15.5 ± 2.6</td>
</tr>
<tr>
<td>Phosphate (mmol/L)</td>
<td>1.39 ± 0.05</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)</td>
<td>23.6 ± 0.5</td>
</tr>
<tr>
<td>Kt/Vurea</td>
<td>1.4 ± 0.1</td>
</tr>
<tr>
<td>nPNA (g/kg/day)</td>
<td>1.35 ± 0.12</td>
</tr>
<tr>
<td>Protein diet intake (g/kg/day)</td>
<td>2.5 ± 0.2</td>
</tr>
<tr>
<td>TAD</td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>2.5 ± 0.4</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>0.64 ± 13</td>
</tr>
<tr>
<td>β₂ microglobulin (mg/L)</td>
<td>15.3 ± 33</td>
</tr>
</tbody>
</table>

All parameters were assessed weekly except for β₂ microglobulin determined each third month.
Patient 1, a boy on daily online hemodiafiltration.
Protein diet intake (g/kg/d): 2.7 ± 0.2; protein nitrogen appearance (g/kg/d): 1.44 ± 0.15
Mean growth velocity (cm/year): 10.4
Achieved height versus mid parental target height (SDS): +0.2

Patient 14, a girl on daily online hemodiafiltration.
Protein diet intake (g/kg/d): 2.4 ± 0.4; protein nitrogen appearance (g/kg/d): 1.3 ± 0.14
Mean growth velocity (cm/year): 9.6
Achieved height versus mid parental target height (SDS): +0.3

Fig. 1. Examples of growth charts (height and weight chart; growth velocity chart in centimetres per year; body mass under chart) of two patients on D-OL-HDF (start indicated by bars). TC on height chart is the familial target height in centimetres.
middle molecular uremic toxins as well [20,21]. Despite the daily OL-HDF which involves not only a process of diffusion but also a significant convective mass transfer, i.e. 18–27 L/m² BSA per session, we didn't observe any signs of malnutrition despite a potential for albumin loss in the dialysate [33] as may be associated with intensive convective dialysis regimes. Moreover, it could be speculated that this presumed enhanced albumin loss in the dialysate [33] observed during D-OL-HDF could actually be a positive side effect due to the increased excretion of toxic uraemic molecules which are albumin bound such as indoxyl sulphate [20]. Also of importance is the low CRP noted, a marker of inflammation. In almost all our cases, CRP was <4 mg/L. Interestingly, in cases 4 and 5, the elevated CRP related at least in part to their chronic lung disease and did not impair the growth velocity induced by D-OL-HDF. Pre dialysis bicarbonate levels were within the normal range. Interestingly, we noted a very low D-OL-HDF. Pre dialysis bicarbonate levels were within the normal range. Interestingly, we noted a very low D-OL-HDF. Pre dialysis bicarbonate levels were within the normal range. Interestingly, we noted a very low D-OL-HDF. Pre dialysis bicarbonate levels were within the normal range. Interestingly, we noted a very low D-OL-HDF. Pre dialysis bicarbonate levels were within the normal range. Interestingly, we noted a very low D-OL-HDF. Pre dialysis bicarbonate levels were within the normal range. Interestingly, we noted a very low D-OL-HDF. Pre dialysis bicarbonate levels were within the normal range. Interestingly, we noted a very low D-OL-HDF. Pre dialysis bicarbonate levels were within the normal range. Interestingly, we noted a very low D-OL-HDF. Pre dialysis bicarbonate levels were within the normal range. Interestingly, we noted a very low D-OL-HDF. Pre dialysis bicarbonate levels were within the normal range. Interestingly, we noted a very low D-OL-HDF. Pre dialysis bicarbonate levels were within the normal range. Interestingly, we noted a very low D-OL-HDF. Pre dialysis bicarbonate levels were within the normal range. Interestingly, we noted a very low D-OL-HDF. Pre dialysis bicarbonate levels were within the normal range. Interestingly, we noted a very low D-OL-HDF. Pre dialysis bicarbonate levels were within the normal range. Interestingly, we noted a very low D-OL-HDF. Pre dialysis bicarbonate levels were within

mean TADbicarbonate, thus a limited acidosis

the normal range. Interestingly, we noted a very low

D-OL-HDF. Pre dialysis bicarbonate levels were within

CRP related at least in part to their chronic lung disease

marker of inflammation. In almost all our cases, CRP

molecules which are albumin bound such as indoxyl sul-

side effect due to the increased excretion of toxic uraemic

wave both during the dialysis sessions and between the
dialysis sessions. This profile presumed to be a better
correction of the dialysis acidosis/alkalosis waves usually

for a three times a week dialysis schedule [15,28],
should potentially impact on patient nutrition (review in [10]) possibly via the ubiquitin proteasome system reduc-

protein wasting, i.e. cachexia (review in [8]). In fact,

we noted in our study a significant discrepancy between

the measured DPI and the calculated nPNA. The nPNA
formula used [26] was applied the same day of the week

for all patients, mid-week as recommended [10]. It is

known that nPNA does not reflect daily protein intake
alone but also protein turnover [10]. Better correction
of metabolic acidosis in dialysed patients as achieved
in our study by applying D-OL-HDF should reduce protein
catabolism and muscle wasting, presumably resulting

in less growth hormone resistance [8,10,28]. Nevertheless,
we have to remark that from our study we cannot propose
a change in the recommended optimal pre dialysis serum
bicarbonate level, i.e. 20–22 mmol/L [10]. The reported in-
crease in growth velocity with BMI gain over D-OL-HDF
Xis also likely to be attributable in part to less malnutri-
tion, i.e. optimized food intake. Despite the absence of di-
etary restrictions, control of both phosphate and potassium

serum levels was easily achieved, with only a limited need
to prescribe chelators, in particular only potassium chela-
tors the day ‘off dialysis’. This optimal control is likely to

be not only related to purification parameters, i.e. removal
capacities of D-OL-HDF, but presumably [8,10,29] are als-
so in part secondary to the induced anabolic state. It could
be speculated that optimized phosphate levels should posi-
tively impact on the cardiovascular morbidity/mortality
outcome [34,35].

The reported catch-up growth achieved in children re-
ceiving chronic dialysis on the in-centre D-OL-HDF
programme should be recognized as being a result of sev-
eral potential factors which contribute towards patient care
and management [36]: on the one hand, free diet and good
appetite result in less malnutrition, and on the other hand,
daily convective dialysis modality purification, reduced in-
flammation and no metabolic acidosis lead to less uraemic
protein wasting. The impact of increased daily activity due
to less fatigue in children on daily dialysis presumably may
also be presumed to play a role in explaining this growth
pattern and body mass increase [37,38]. At present, it is
not well known if all the different available daily dialysis
modalities are equivalent in terms of catch-up growth
[14,39]. Some may have specific benefits but also relative
disadvantages such as the major cost increase of daily in-
centre versus conventional in-centre dialysis or daily at
home dialysis and the impact on social integration and ac-
tivities of daily living of daily in-centre versus nocturnal
dialysis sessions [14,40]. Nevertheless, daily haemodialy-
sis regimens should not just be thought of as a rescue mo-
dality [16] but should also be considered in children facing
long waiting times on chronic dialysis [14]. Ongoing paed-
iatric daily dialysis registry [41] should help in clarifying
the optimal ‘daily haemodialysis’ regime, daily nocturnal,
daily at home or in-centre OL-HDF delivered daily [14,39],
taking into account the potential benefits, the important
cost increase and the economical resources available.

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Conflict of interest statement. None declared.

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Use of spent dialysate analysis to estimate blood levels of uraemic solutes without blood sampling: urea

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Abstract

Background. Urea kinetic modelling-based methods are widely used to assess dialysis efficacy. However, they require blood sampling and are susceptible to a number of errors, mainly from the calculated parameters (particularly V). Spent dialysate determinations have been used and have been shown to be reliable and simple to use. In this study, we associated dialysate-based and clear-