

## ORIGINAL ARTICLE

# Comparison of weight- vs body surface area-based growth hormone dosing for children: implications for response

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## Summary

**Objective** To compare weight (per kg)- vs body surface area (BSA, per m<sup>2</sup>)-based growth hormone (GH) dosing formats in children and to derive a useful conversion formula between the two formats.

**Patients and Design** Growth hormone doses (>33 000) from 1874 children were obtained from the national Australian database (OZGROW) and used to derive conversion formulae and to confirm the accuracy of a conversion formula based on a weight-only BSA estimate. A further 27 000 doses were used to test the accuracy of all formulae. The best conversion formula was used to compare weight- and surface area-based GH dosing, which included an analysis of first year response ( $\Delta$ SDS height or growth velocity, GV).

**Measurements** Growth hormone doses in mg/m<sup>2</sup>/wk and mg/kg/wk, dose estimates, residuals, first year  $\Delta$ SDS, first year GV.

**Results** The formula,

$$\text{Dose}_{\text{kg}} = \left( \frac{4W_{\text{tkg}} + 7}{W_{\text{tkg}} + 90} \right) \text{Dose}_{\text{m}^2} / W_{\text{tkg}},$$

based on a weight-only BSA estimate, provides accurate dose conversion (mean residual, 0.005 mg/kg/week). A constant mg/m<sup>2</sup>/week dose expressed in terms of mg/kg/week declines quickly with increasing body weight to approximately 15 kg after which the decline continues although less dramatically. For Australian patients, despite an increase in mean per m<sup>2</sup> dose with increased starting weight/age, the per kg dose decreased. This was associated with a greater decline in first year GV than estimated if a per kg dose had been maintained.

**Conclusions** Growth hormone doses can be accurately converted between formats. Surface area-based GH dosing is likely

to result in a reduced height response as children become heavier when compared with weight-based GH dosing.

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## Introduction

Paediatric growth hormone (GH) is prescribed either in terms of mg/m<sup>2</sup>/week of body surface area (BSA) or on a weight basis such as mg/kg/week or an equivalent, for example  $\mu$ g/kg/day. Australia,<sup>1</sup> New Zealand,<sup>2</sup> the Netherlands<sup>3</sup> and India<sup>4</sup> use BSA-based dosing, while paediatric endocrinologists in Japan,<sup>5</sup> China,<sup>6</sup> Canada,<sup>7</sup> the United States and most of Europe dose on a weight basis although consideration is given to BSA-based dosing in obese patients.<sup>8–10</sup> In a survey of European paediatric endocrinologists, 59% calculated GH dose on the basis of body weight, while 39% used BSA.<sup>11</sup> Which format is most appropriate for GH dosing is still considered an open debate although it is also generally assumed that differences between the two are only significant at the extremes of weight or in the very young.<sup>12</sup>

The choice of BSA over weight as the proportionality constant for GH dosing is made on the premise that metabolic rate per unit body weight decreases with increased body weight, but remains similar when calculated in terms of BSA.<sup>13</sup> Metabolic rate is proportional to drug redistribution and metabolism,<sup>14</sup> and the volume of drug distribution is closely associated with extracellular fluid volume, which is more highly correlated to BSA than to body weight.<sup>15</sup> Drugs primarily excreted via the kidneys are suited to dose scaling in terms of BSA; however, other factors such as hepatic metabolism can influence drug clearance.<sup>13</sup> The situation for GH is complex as it is eliminated via both hepatic and renal routes,<sup>16</sup> and the processes involved in drug metabolism change markedly throughout the neonatal and childhood periods.<sup>13</sup> Thus, there is no clear theoretical argument for BSA- or weight-based GH dosing, and it has been

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suggested that studies comparing therapeutic response and accuracy of growth response prediction between per kg and per m<sup>2</sup> dosing formats are indicated.<sup>17</sup>

Although the two dosing formats exist, most researchers and clinicians publish their work in either one or the other format rather than both, while some have attempted approximate conversions.<sup>18</sup> If BSA is known, it is a simple matter to convert doses. There are a number of different formulae published to estimate BSA, all but one of which require measures of both weight and height.<sup>19,20</sup> The BSA estimate used in Australia is that of Mosteller<sup>19</sup> and is given by,

$$BSA(m^2) = \sqrt{\frac{(\text{Height(cm)} \times \text{Weight(kg)})}{3600}}$$

As both weights and heights of patients are available, the GH doses used in Australia are routinely converted to per kg doses for publication<sup>21–23</sup> However, investigators rarely note the height of individual recipients when reporting GH doses in a per kg format to allow for a direct conversion to a per m<sup>2</sup> format. One BSA-estimating formula requiring only weight as a measure has been published and validated against the Mosteller's<sup>19</sup> formula.<sup>24,25</sup> If this formula performs well in patient populations receiving GH, it will allow for a simple per kg to per m<sup>2</sup> conversion. We tested the accuracy of this conversion formula using data from GH-treated children entered into the national Australian GH database (OZGROW). Conversion formulae were also derived empirically from the observed relationships between GH doses of each format in OZGROW. An accurate conversion formula will allow for direct comparisons of weight-based and BSA-based dosing formats, which will aid in studies designed to optimize GH therapy.

We have previously reported that in Australia, 11.9% of patients with GH (deficiency) GHD and 29.2% of patients with idiopathic short stature received dose increments between the first and second years of treatment (<sup>23</sup> Sup. Table 4) in reaction to nonattainment of specific response criteria<sup>1</sup> during the first year of treatment. This leads us to hypothesize that per m<sup>2</sup> dosing may be more effective at younger ages, and per kg dosing, more effective thereafter.<sup>23</sup> There are various possible causes for poor response to GH treatment.<sup>2,26,27</sup> Here, we describe the relationship between the two dose formats by use of the weight-only BSA-estimating formula and ask whether the dosing strategy used in Australia may also contribute to nonattainment of response criteria.

## Methods

### *Patients, doses and indications*

Doses, in both mg/m<sup>2</sup>/week and mg/kg/week, and information regarding gender, age and diagnosis/indication were obtained from patient records in the OZGROW database that comprises all patients receiving GH in Australia under the Pharmaceutical Benefits Scheme. A 'dose' was defined as the dose set each time the patient attended a growth clinic and was weighed and

measured. For most conditions, the Australian guidelines mandate a starting dose of 4.5 mg/m<sup>2</sup>/week, but that the dose can be increased by 1 mg/m<sup>2</sup>/week after 6 monthly reviews (total dose is also automatically adjusted for growth) to a maximum of 7.5 mg/m<sup>2</sup>/week (9.5 mg/m<sup>2</sup>/week for TS and CRI) if one or more response criteria are not met.<sup>1</sup> These criteria are as follows: (i) achievement of 50th percentile growth velocity for bone age, (ii) increase in height SDS for chronological age and (iii) growth velocity ≥4 cm/year.<sup>1</sup>

Doses (33 375) prescribed prior to 2008 constituted the training set upon which conversion formulae were derived. These were obtained for Turner syndrome (TS): 10 092 doses (570 patients); GH deficiency (GHD): 6584 doses (286 patients); Prader–Willi syndrome (PWS): 1983 doses (166 patients); the indication of 'short stature and slow growth' (SSSG): 12 373 doses (730 patients); cranial lesion/irradiation (CL/I): 1616 doses (77 patients); and chronic renal insufficiency (CRI): 727 doses (45 patients). A test set comprising 27,219 different doses recorded from the OZGROW database from 2008 to 2013 was used to test the derived conversion formulae. The test set of doses comprised TS: 3834 doses (403 patients); GHD: 5873 doses (541 patients); PWS: 1385 doses (167 patients); SSSG: 13 769 doses (1519 patients); CL/I: 1438 doses (171 patients); CRI: 779 doses (115 patients); and an additional diagnosis, short stature homeobox gene mutation (SHOX): 141 doses (16 patients). SHOX patients had molecular/cytogenetic evidence of SHOX mutation or deletion, a height below the 1st centile and growth velocity below the 25th centile.

Turner syndrome patients were cytogenetically diagnosed, had an initial height below the TS-specific<sup>28</sup> 95th centile and were not exhibiting significant catch-up growth.<sup>1</sup> GHD patients recorded peak serum GH concentrations <10 mU/l following two pharmacological provocative tests or one pharmacological test <10 mU/l and other evidence of GHD in association with a height below the 1st centile.<sup>1</sup> PWS patients were defined by genetic diagnosis.<sup>1</sup> SSSG is defined as a current height below the 1st centile and growth velocity below the 25th centile for bone age.<sup>1</sup> Cranial lesion/irradiation patients were eligible for GH after 12 months of completing surgical, chemotherapy or irradiation treatment, in remission, and with evidence of GHD as previously defined with a growth velocity below the 25th centile for bone age.<sup>1</sup> Chronic renal insufficiency patients had a glomerular filtration rate <30 ml/min/1.73 m<sup>2</sup> with height and growth velocity less than the 25th centile.<sup>1</sup>

### *Evaluating relationships between dosing formats*

Each dose in the OZGROW database was recorded in both mg/m<sup>2</sup>/week and mg/kg/week formats and plotted separately against age and weight. These analyses demonstrate the relationship between mg/m<sup>2</sup>/week doses with advancing age or increased weight when GH is prescribed according to the Australian protocol. To more clearly show the effect of age or weight for a fixed mg/m<sup>2</sup>/week dose or mg/kg/week dose, graphs were constructed for each 1 mg/m<sup>2</sup>/week dose ranging from 2.00–2.99 mg/m<sup>2</sup>/week to 9.00–9.99 mg/m<sup>2</sup>/week in the training set of doses.

### Derivation of conversion formulae

A conversion formula was constructed using the weight-only BSA-estimating equation.<sup>24,25</sup> Conversion equations were also derived empirically from OZGROW doses as described in Supporting Information.

The accuracy of conversion equations was tested by calculating the mean of the residuals. A residual is the absolute value of the difference between the actual mg/kg/week dose and the estimate. Additionally, the mean of this value as a percentage,

$$100 \times \frac{\text{Abs (Actual - Estimate)}}{\text{Actual}},$$

was calculated. Residual analyses were applied to the training set and test set of doses.

### Correlation between Mosteller and weight-only BSA estimations

The linear correlation between BSA estimated from the Mosteller formula<sup>19</sup> and the weight-only BSA formula<sup>24</sup> was calculated in both training and test sets.

### Direct comparison between commonly used doses of each format

In Australia, the starting dose of GH is commonly 4.5 mg/m<sup>2</sup>/week with a maximum allowable dose of 7.5 mg/m<sup>2</sup>/week for most indications or 9.5 mg/m<sup>2</sup>/week for TS or CRF.<sup>1</sup> A brief review of the literature indicated that commonly used low, medium and high doses by body weight are 0.17, 0.24 and 0.37 mg/kg/week, respectively. These doses were directly compared by plotting each dose with increasing weight against dose in each format.

### The Effect of dose level or starting weight on first year response in height SDS

As the actual dose received by a patient depends on the format of dosing and their body weight, we investigated first year response in patients with SSSG, GHD and TS with respect to mean first year dose, in both formats, and starting weight. Doses and responses used were the same as those used in previous publications.<sup>22,23</sup> First year responses were compared, for SSSG and GHD at 10, 20 and 30 kg starting weights, with the growth velocity (GV) standards of Bakker *et al.*<sup>27</sup> GV predictions were also made using the equations of Ranke *et al.*<sup>29,30</sup> Identical parameters to the OZGROW data were used with equivalent or fixed mg/kg/week doses.

### Statistical analyses

Mean residuals were compared using *t*-tests, and the significance of regression slopes was determined through regression analysis. Regressions, *t*-tests and correlations were performed using Excel 2010 (Microsoft Corporation).

## Results

### Relationships between dosing formats

Figure 1 shows all doses since 2008. It is evident that doses in terms of mg/m<sup>2</sup>/week, the format in which they were originally prescribed, increase with increasing age or weight, while the equivalent mg/kg/week doses decrease with age or weight. Similar graphs were obtained using pre-2008 doses. The situation was similar for each indication (Supporting Information).

A better understanding of the relationship between dosing formats can be appreciated from Fig. 2 in which a 1 mg/m<sup>2</sup>/week range of doses, shown for 4–5 and 7–8 mg/m<sup>2</sup>/week, is converted to mg/kg/week doses. An essentially constant mg/m<sup>2</sup>/week dose is seen to be associated with a linearly decreasing mg/kg/week dose as age increases; for example,  $\text{Dose}_{\text{kg}} = -0.0062\text{Age}_{\text{Years}} + 0.2211$  for the 4–5 mg/m<sup>2</sup>/week band. In terms of increasing weight, however, the decrease in mg/kg/week dose for a fixed mg/m<sup>2</sup>/week dose is more extreme at lighter weights and is best described as a power relationship; for example,  $\text{Dose}_{\text{kg}} = 0.4545W_{\text{kg}}^{-0.319}$  for the 4–5 mg/m<sup>2</sup>/week band. It will also be noticed that the slope of the linear (age) relationship is steeper at the higher dose (7–8 mg/m<sup>2</sup>/week). Analysis of the adjusted mg/kg/week doses, used to derive conversion formulae, showed that there was a linear relationship between increasing dose and decreasing slope of the linear dose–age relationship.

### Conversion formulae

The weight-only formula to estimate BSA<sup>24,25</sup> is

$$\text{BSA} = \frac{4W_{\text{kg}} + 7}{W_{\text{kg}} + 90}$$

Thus, conversion formulae will be

$$\text{Dose}_{\text{kg}} = \frac{\left(\frac{4W_{\text{kg}} + 7}{W_{\text{kg}} + 90}\right)\text{Dose}_{\text{m}^2}}{W_{\text{kg}}}$$

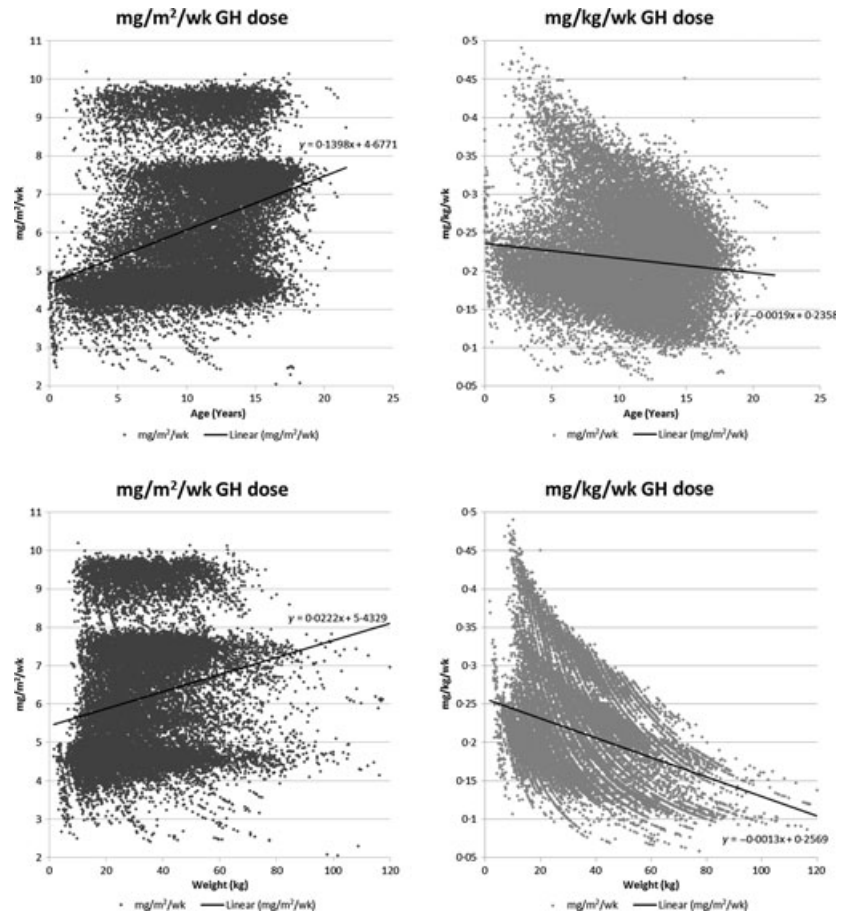
Or

$$\text{Dose}_{\text{m}^2} = \frac{\text{Dose}_{\text{kg}} W_{\text{kg}}}{\left(\frac{4W_{\text{kg}} + 7}{W_{\text{kg}} + 90}\right)}$$

All doses in the training set were used to derive empirical conversion equations as described in Supporting Information. A linear relationship with age was used to derive the following formula to estimate the mg/kg/week dose for a given mg/m<sup>2</sup>/week dose.

$$\text{Dose}_{\text{kg}} = \frac{\text{Dose}_{\text{m}^2}}{20 \cdot 4} + (-0 \cdot 0011(\text{Dose}_{\text{m}^2}) - 0 \cdot 0014)\text{Age}_{\text{Years}}$$

To convert a per kg dose to a per m<sup>2</sup> dose, this formula can be rearranged to give,



**Fig. 1** All doses (since 2008) shown in terms of mg/m<sup>2</sup>/week (left panels) and mg/kg/week (right panels) plotted against age (upper panels) or weight (lower panels). Trend lines are shown where  $y = \text{dose}$  (either format) and  $x = \text{age or weight}$ .

$$\text{Dose}_{\text{m}^2} = \frac{1000\text{Dose}_{\text{kg}} + 1.4\text{Age}_{\text{Years}}}{49.0 - 1.1\text{Age}_{\text{Years}}}$$

With respect to the power relationship between mg/kg/week dose and weight for fixed mg/m<sup>2</sup>/week dose, the following conversion formula was derived.

$$\text{Dose}_{\text{kg}} = (0.114\text{Dose}_{\text{m}^2} - 0.0546)W_{\text{kg}}^{(-0.0039\text{Dose}_{\text{m}^2} - 0.3046)}$$

The above formula cannot be simply rearranged to convert mg/kg/week doses to mg/m<sup>2</sup>/week doses. However, as the exponent term does not vary greatly, if the mean exponent value,  $-0.328$ , is used, an approximate conversion, below, can be found.

$$\text{Dose}_{\text{m}^2} = \frac{1}{572}(5000\text{Dose}_{\text{kg}}W_{\text{kg}}^{0.328} + 273)$$

Detailed residuals analyses were performed for all formulae on doses from the training set and from the test set. Results are shown in Table 1. In essentially all cases, the weight-only BSA-based equation was superior (had smaller mean residuals) to the empirically derived power or linear equations ( $P$ -values ranged from 0.043 for CL/I test set females to essentially 0 for 'all males' in both training and test sets). The exception was TS, in which the power equation provided smaller mean residuals (Table 1) with  $P = 3 \times 10^{-161}$  and  $P = 1 \times 10^{-40}$  for the

training and test sets, respectively. SHOX power-equation residuals were also smaller than the BSA-equation residuals, but not significantly so ( $P > 0.05$ ).

#### Correlation between Mosteller and weight-only BSA estimations

For the training set, the correlation between the Mosteller and weight-only estimates of BSA was  $r = 0.9955$  with a 95% confidence interval (CI) of 0.9954–0.9956. For the test set,  $r = 0.9956$  (CI 0.9955–0.9957).

#### Direct comparison between commonly used doses of each format

Not surprisingly, given the high correlations observed above, very small mean residuals were observed between actual GH mg/kg/week dose and dose estimates based on the weight-only BSA formula. We are therefore confident that common doses in each format can be directly compared by means of the weight-only BSA-estimating formula.<sup>24</sup> These comparisons are shown in (Fig. 3). The top panel shows doses in terms of mg/m<sup>2</sup>/week, and the bottom, in terms of mg/kg/week. It is evident that patients receive equivalently more GH under the per m<sup>2</sup> dosing format at lighter weights. Where dose curves intersect, the doses



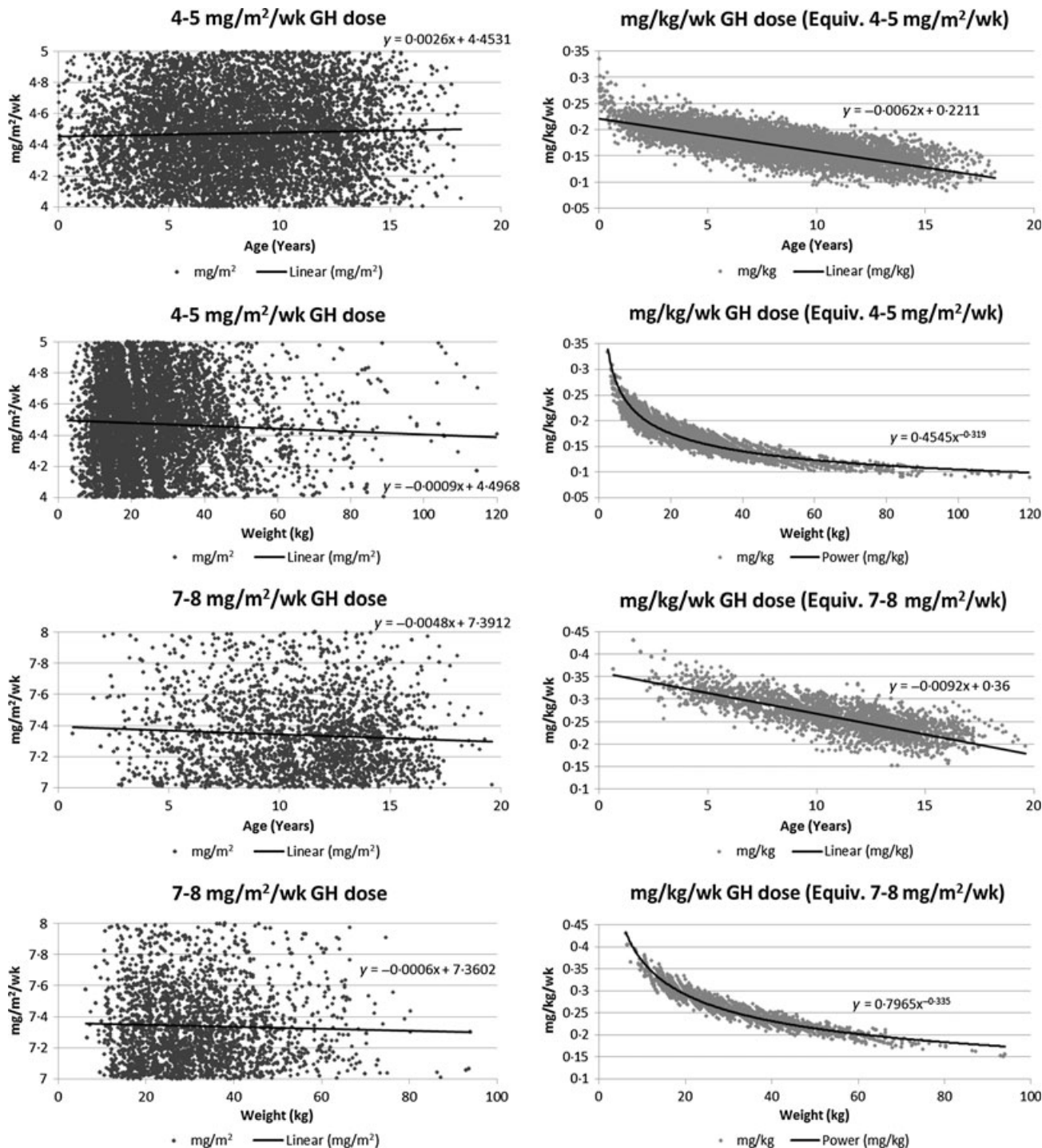


Fig. 2 Examples of the relationship between mg/m<sup>2</sup>/week doses and mg/kg/week doses for relatively narrow 1 mg/m<sup>2</sup>/week ranges. 4–5 and 7–8 mg/m<sup>2</sup>/week are shown as they include commonly used doses of 4.5 and 7.5 mg/m<sup>2</sup>/week. Trend lines are shown where  $y = \text{dose}$  (either format) and  $x = \text{age}$  or weight. The value by which  $x$  is multiplied is the slope of the linear relationship or, for a power relationship, the mg/kg/week dose if the patient weighed 1 kg.

are equivalent. Thus, the common starting dose in Australia of 4.5 mg/m<sup>2</sup>/week becomes equivalent to the lowest used per kg dose (0.17 mg/kg/week) at 25 kg body weight and thereafter is less. The more common international starting dose of 0.24 mg/kg/week is equivalent to the Australian starting dose at approximately 6 kg and thereafter becomes progressively greater.

#### *The effect of dose level or starting weight on first year height response*

For GHD, there is little variation in first year dose (Fig. 4, mean = 4.26 mg/m<sup>2</sup>/week, 0.171 mg/kg/week), and thus, a dose response is difficult to identify ( $P = 0.12, 0.10$ , mg/m<sup>2</sup>/week and

**Table 1.** Mean residuals and % residuals for equations estimating mg/kg/week doses for given mg/m<sup>2</sup>/week doses

Equation Population	Training set						Test set					
	BSA (Wt)*		Linear (Age)†		Power (Wt)‡		BSA (Wt)*		Linear (Age)†		Power (Wt)‡	
	Res.	%	Res.	%	Res.	%	Res.	%	Res.	%	Res.	%
All	0.0050	2.49	0.0146	7.76	0.0054	3.02	0.0049	2.30	0.0171	8.39	0.0055	2.65
All males	0.0042	2.35	0.0134	7.71	0.0055	3.36	0.0041	2.11	0.0161	8.34	0.0054	2.72
All females	0.0058	2.63	0.0159	7.63	0.0052	2.67	0.0057	2.55	0.0184	8.47	0.0056	2.56
GHD	0.0040	2.45	0.0136	8.52	0.0051	3.19	0.0042	2.39	0.0157	9.10	0.0048	2.65
GHD males	0.0037	2.42	0.0124	8.21	0.0047	2.92	0.0039	2.28	0.0157	9.20	0.0048	2.56
GHD females	0.0043	2.50	0.0154	9.02	0.0057	3.65	0.0047	2.54	0.0158	8.96	0.0048	2.71
SSSG	0.0044	2.20	0.0146	7.35	0.0051	2.82	0.0044	2.04	0.0169	7.96	0.0055	2.60
SSSG males	0.0041	2.07	0.0134	6.90	0.0048	2.77	0.0041	1.95	0.0164	7.90	0.0056	2.53
SSSG females	0.0051	2.46	0.0169	8.26	0.0057	2.91	0.0050	2.23	0.0180	8.07	0.0055	2.64
TS	0.0067	2.84	0.0168	7.23	0.0049	2.22	0.0076	2.75	0.0215	7.81	0.0061	2.09
PWS	0.0053	3.23	0.0162	10.70	0.0055	3.71	0.0053	3.47	0.0175	13.18	0.0057	4.59
PWS males	0.0047	3.00	0.0158	10.40	0.0049	3.22	0.0049	3.16	0.0174	12.45	0.0055	4.03
PWS females	0.0060	3.51	0.0167	11.06	0.0062	4.33	0.0057	3.80	0.0177	13.97	0.0060	5.18
CRI	0.0047	2.04	0.0129	5.76	0.0056	2.33	0.0056	2.05	0.0156	5.78	0.0075	2.65
CRI males	0.0049	2.17	0.0141	6.40	0.0057	2.44	0.0054	1.90	0.0152	5.82	0.0080	2.75
CRI females	0.0043	1.79	0.0106	4.51	0.0052	2.11	0.0060	2.37	0.0166	6.22	0.0064	2.45
CL/I	0.0043	2.90	0.0129	9.08	0.0039	2.63	0.0039	2.35	0.0127	8.04	0.0043	2.51
CL/I males	0.0043	3.05	0.0122	6.95	0.0040	2.78	0.0038	2.28	0.0127	8.06	0.0043	2.48
CL/I females	0.0043	2.52	0.0132	9.88	0.0038	2.22	0.0039	2.44	0.0126	8.02	0.0043	2.56
SHOX	–	–	–	–	–	–	0.0066	2.20	0.0185	6.13	0.0062	2.06
SHOX males	–	–	–	–	–	–	0.0075	2.52	0.0206	6.90	0.0061	1.98
SHOX females	–	–	–	–	–	–	0.0048	1.57	0.0145	4.65	0.0062	2.10

\*Equation based on BSA estimate.  $\text{Dose}_{\text{kg}} = \left( \frac{4W_{\text{kg}} + 7}{W_{\text{kg}} + 90} \right) \text{Dose}_{\text{m}^2} / W_{\text{kg}}$

†Equation based on linear relationship with age.  $\text{Dose}_{\text{kg}} = \frac{\text{Dose}_{\text{m}^2}}{24} + (-0.0011(\text{Dose}_{\text{m}^2}) - 0.0014)\text{Age}_{\text{Years}}$

‡Equation based on power relationship with weight.  $\text{Dose}_{\text{kg}} = (0.114\text{Dose}_{\text{m}^2} - 0.0546)W_{\text{kg}}^{(-0.0039\text{Dose}_{\text{m}^2} - 0.3046)}$

mg/kg/week, respectively). For SSSG, there is a significant ( $P = 0.0007$ ) decrease in response for increasing mg/m<sup>2</sup>/week dose (mean = 4.80), but a nonsignificant increase ( $P = 0.19$ ) with mg/kg/week dose (mean = 0.195). This likely reflects a dose increment of 1 mg/m<sup>2</sup>/week applied to poor responders after 6 months of treatment (see criteria). For TS, there is greater scope for starting dose variation,<sup>1</sup> and in both formats, increasing dose is associated with increasing response ( $P = 5.1 \times 10^{-7}$ ,  $P = 2.1 \times 10^{-5}$ , mg/m<sup>2</sup>/week and mg/kg/week, respectively). It is particularly apparent in each of the GHD, SSSG and TS cohorts that starting GH at a heavier body weight is associated with a poorer first year response. This is highly significant for GHD ( $P = 3.5 \times 10^{-7}$ ) and SSSG ( $1.8 \times 10^{-22}$ ). For TS, due to the variation in starting dose, response with respect to starting weight is demonstrated separately for high (8.00–9.99 mg/m<sup>2</sup>/week), medium (5.50–7.99 mg/m<sup>2</sup>/week) and low (4.00–5.49 mg/m<sup>2</sup>/week) starting doses (Fig. 4). A decreasing response with increasing starting weight is seen at medium and high doses, but not at low doses. However, none of these associations were found to be significant. Figure 5 summarizes mean doses and GV<sub>1</sub> in the first year of treatment for starting weights of 10, 20 and 30 kg (and equivalent ages) compared with those published by Bakker

*et al.*<sup>27</sup> and estimated from prediction equations of Ranke *et al.*<sup>29,30</sup> Table S1 of Supporting Information shows complete results. In all cases, the decline in GV with increasing starting weight (age) is greatest for the Australian data for which the mg/kg/week dose decreases compared with the fixed mg/kg/week models of Bakker *et al.*<sup>27</sup> or Ranke *et al.*<sup>29,30</sup> The difference is greater for GHD than for SSSG.

## Discussion

We have demonstrated that BSA-based dosing, in comparison with weight-based dosing, is associated with relatively less GH being prescribed for the majority of childhood and that this declines progressively as children grow heavier. We have also shown that first year response to treatment similarly declines with increasing body weight. It should also be noted, however, that even when using a fixed per kg dose, Bakker *et al.*'s<sup>27</sup> and Ranke's groups<sup>12,29,30</sup> have clearly demonstrated that mean first year response declines as age at GH commencement increases. Given that GH dose is consistently associated with first year height response,<sup>12,27,29–31</sup> it is likely that at least a portion of the observed decrease in first year height response is attributable to the BSA-based dosing format used

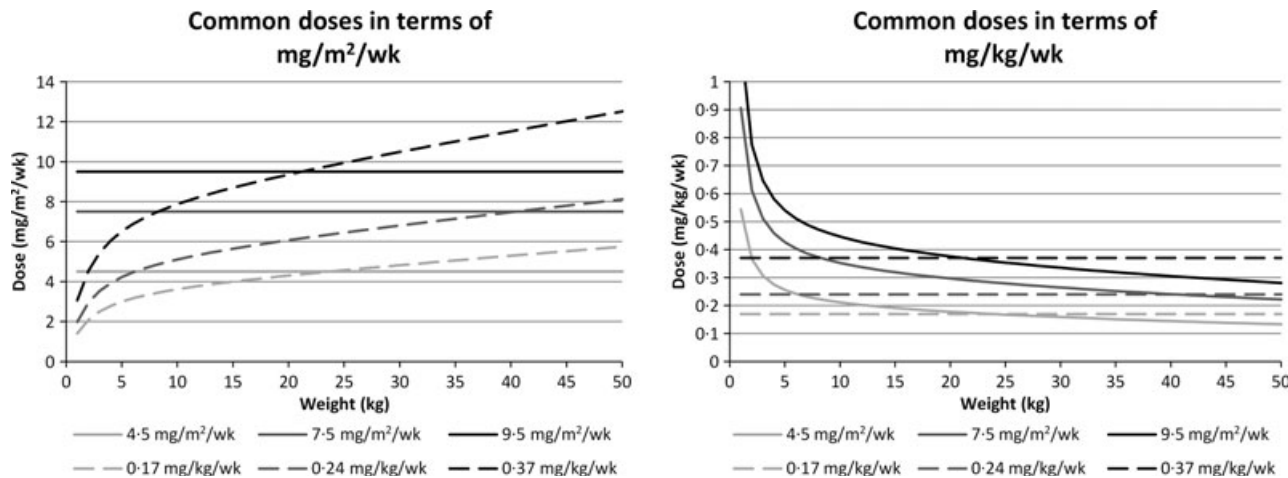


Fig. 3 Comparison between commonly used low (4.5 mg/m<sup>2</sup>/week and 0.17 mg/kg/week), medium (7.5 mg/m<sup>2</sup>/week and 0.24 mg/kg/week) and high (9.5 mg/m<sup>2</sup>/week and 0.37 mg/kg/week) doses of growth hormone (GH) with increasing weight of the patient. The top panel shows doses in terms of mg/m<sup>2</sup>/week, and the bottom panel, in terms of mg/kg/week. GH doses are equivalent where graph lines intersect.

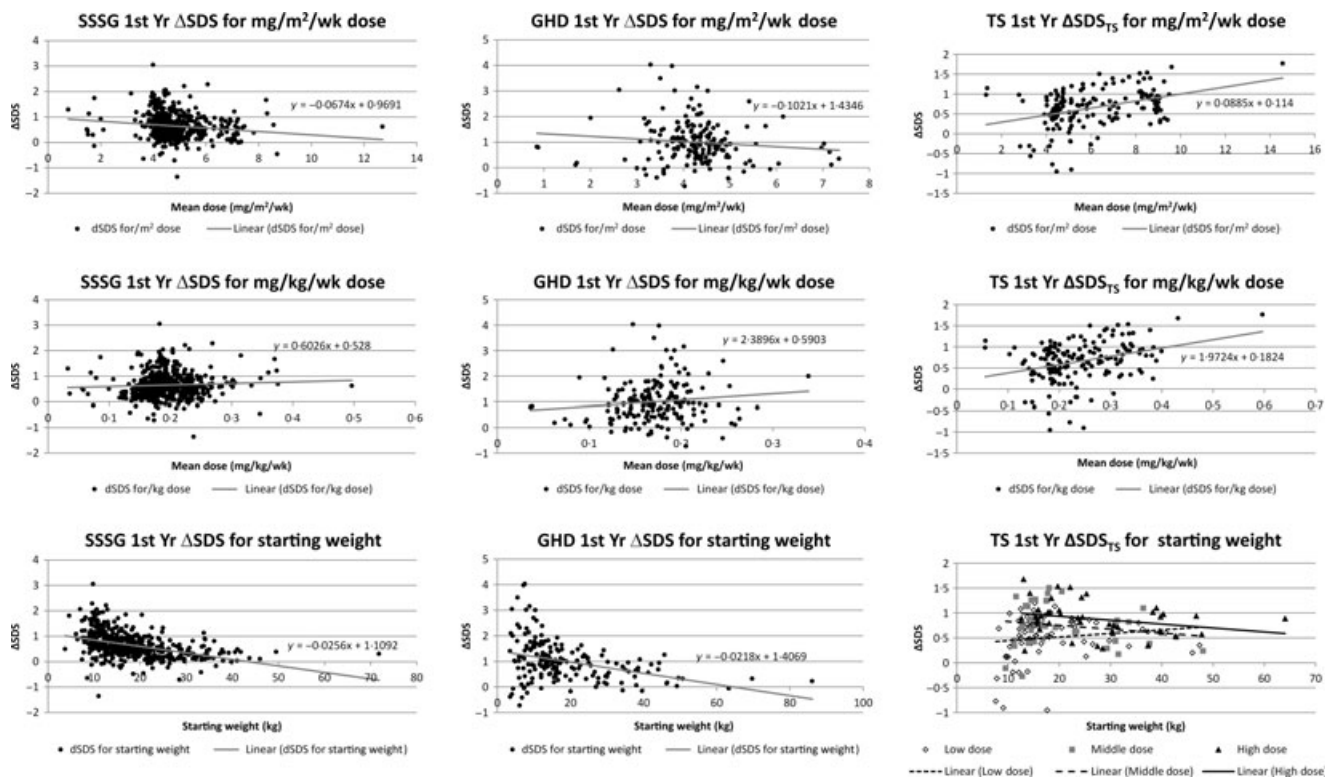


Fig. 4 Change in height SDS ( $\Delta$ SDS) in the first year of treatment for SSSG, GHD and TS with respect to mean 1st year dose (mg/m<sup>2</sup>/week and mg/kg/wk) and weight at start of the treatment. For TS,  $\Delta$ SDS is TS specific.<sup>22</sup> Regression lines are shown for each relationship. For TS, regression lines are shown for mean 1st year doses (mg/m<sup>2</sup>/week) designated as high (8.00–9.99), medium (5.50–7.99) and low (4.00–5.49).

in Australia. This is illustrated in Fig. 5 (and Supporting Information Table S1). In the Australian cohort, despite an increase in mean per m<sup>2</sup> dose with increased starting weight/age, the per kg dose decreased. This was associated with a greater decline in first year GV than estimated if a fixed per kg dose had been maintained. The results shown here and estimates using the Ranke models<sup>29,30</sup> suggest for GHD at

least a 3% greater decline in GV from 10 kg to 30 kg starting weights for the declining Australian doses (1% for SSSG) than if the original per kg dose had been maintained. Specific research is now required to validate and quantify the effect and its significance.

We were able to make these observations by first demonstrating that BSA estimates from a weight-only formula described by



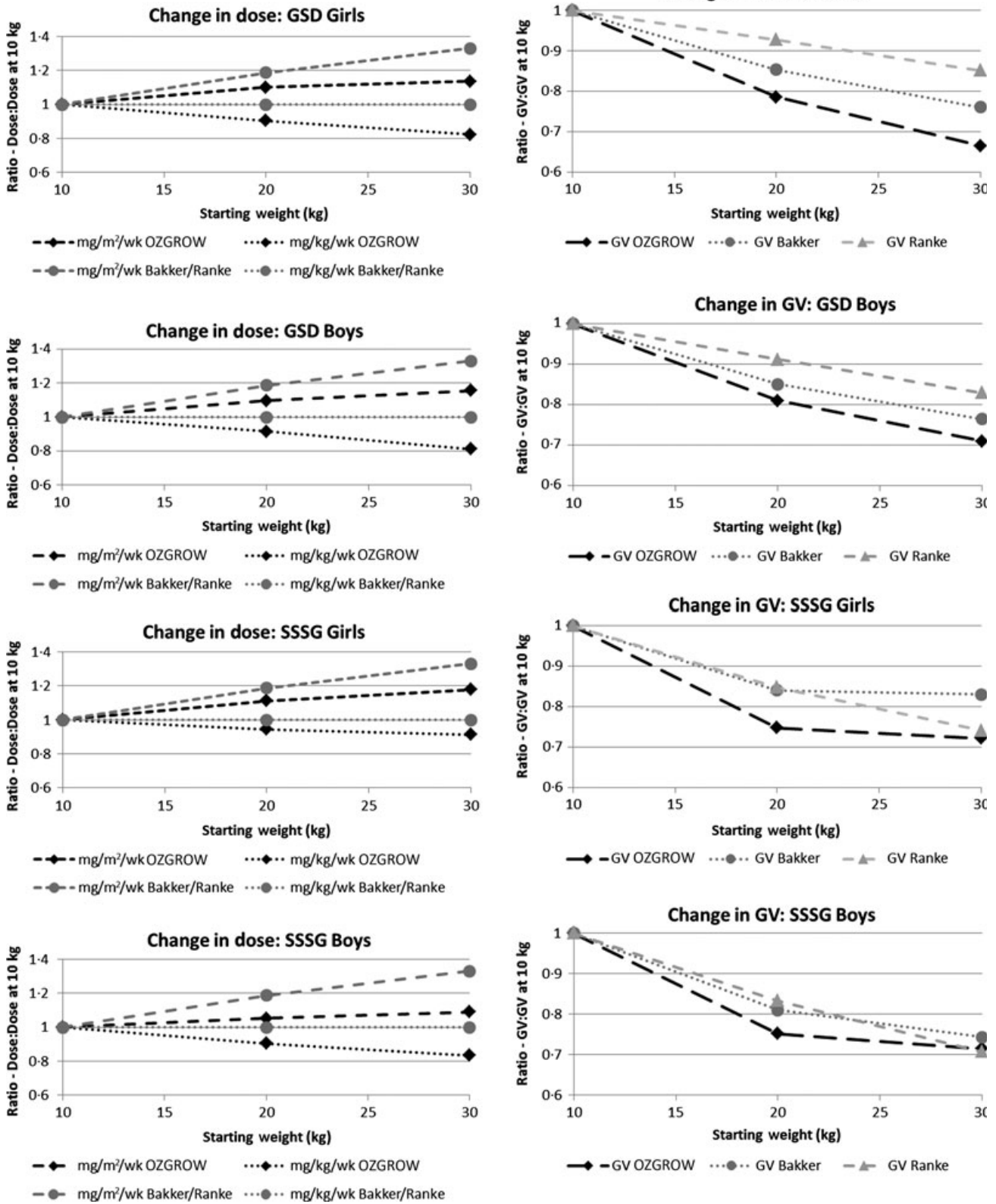


Fig. 5 Comparisons of first year growth velocity (GV) for starting weights of 10, 20 and 30 kg (or equivalent mean ages) between OZGROW data (this study) and those published by Bakker *et al.*<sup>27</sup> and from prediction equations of Ranke *et al.*<sup>29,30</sup> Changes in dose in mg/m<sup>2</sup>/wk and mg/kg/wk are also shown. Changes in dose or GV are shown as a proportion of the value observed/calculated for a starting weight of 10 kg. The dose used by Bakker *et al.* was 0.3 mg/kg/wk for all weights/ages. Ranke calculations used a mg/kg/wk dose fixed at that used at the 10 kg starting weight in the OZGROW data. Details are provided in Table S1 of 'Supporting Information'.



Furqan and Haque<sup>24,25</sup> are very highly correlated to estimates obtained from the Mosteller formula<sup>14,19</sup> used to calculate GH doses in Australia.<sup>1</sup> Correlations of 0.9955 and 0.9956 using data from the OZGROW database prior to and since 2008, respectively, are essentially the same as the correlation of 0.9955 reported by Furqan and Haque for children undergoing cardiovascular surgery.<sup>24,25</sup> Further, it was shown that this formula could be used to convert mg/m<sup>2</sup>/week doses to mg/kg/week doses with a very high degree of accuracy for all GH indications and was superior to empirically derived equations. The one exception was TS for which a power relationship with weight was found to model the dose conversion best. Although significant, the improvement in mean residual was <0.002 mg/kg/week and does not detract from the general utility of the weight-only formula. This means that it is now possible to express GH doses in either format simply and accurately using these conversion formulae, and we encourage workers in the field to do so when presenting research or making clinical recommendations. While we described the conversion of doses originally prescribed in a per m<sup>2</sup> format, it is anticipated that conversion of doses originally prescribed in the per kg format to per m<sup>2</sup> will be equally accurate, but suggest appropriate validation studies be undertaken.

An important consequence of accurate dose conversion using the weight-only BSA estimate is that it allows for direct comparison of the two GH dosing formats. Figure 3 clearly demonstrates this relationship. A constant mg/m<sup>2</sup>/week dose expressed in terms of mg/kg/week declines rapidly with increasing body weight to 10–15 kg after which the decline continues, although less dramatically. This finding is contrary to the understanding of the relationship articulated in a recent review in which the authors state, ‘...the difference between the two approaches is only significant at the extremes of weight and in very young children...’.<sup>12</sup> It might be considered that a ‘significant’ dose increase would be 1 mg/m<sup>2</sup>/week as this is the dose increment recommended in Australia.<sup>1</sup> Then, if a 6 kg child receives a dose of 5.5 mg/m<sup>2</sup>/week, which is equivalent to 0.296 mg/kg/week and that this mg/kg/week dose is maintained, the child would receive 6.6 mg/m<sup>2</sup>/week at 12 kg, 7.5 mg/m<sup>2</sup>/week at 20 kg, 8.5 mg/m<sup>2</sup>/week at 31 kg and 9.5 mg/m<sup>2</sup>/week at 44 kg.

The fact that mg/m<sup>2</sup>/week doses are seen to increase with age (Fig. 1) suggests that a significant proportion of patients have their doses incremented as a consequence of not meeting response criteria (see Methods). Indeed, we have reported that 11.9% of patients with GHD and 29.2% of patients with idiopathic short stature received dose increments, due to poor response, between the first and second years of treatment.<sup>23</sup> However, we have also reported that the first year response of GH-treated children in Australia is similar to that in other countries, but that commencement age is generally younger.<sup>22,23</sup> These observations may be explained by the nature of the relationship between the mg/m<sup>2</sup>/week and mg/kg/week doses and response (Fig. 3). The equivalence of first year growth response in Australian GH-treated children with international response data may arise from the fact that a BSA-based dosing strategy results in a GH dose that is equivalent to or greater than a weight-based dose in younger, lighter patients.

Thus, it would appear that mg/m<sup>2</sup>/week dosing is effective in very young children, but requires doses to be regularly adjusted upward to remain so. It can be concluded that the mg/m<sup>2</sup>/week dosing format is associated with a relative decrease in GH administered with increasing weight, which is likely to compound the well-described decline in response to age with fixed mg/kg/week doses.

Finally, in addition to dosing format, there are many other factors to consider when assessing patients’ response to GH treatment. These include diagnosis, safety, catch-up growth, compliance/adherence, cost-effectiveness, pubertal timing and adult height in relation to target height. Further, dosing on the basis of body size is not the only approach that may be taken in GH treatment. For example, markers of response such as IGF-1 and IGFBP-3<sup>32,33</sup> and predicted height<sup>34,35</sup> have been used to titrate GH treatment. However, as GH dosing by body size is likely to remain a practical and continuing strategy, this study makes a valuable contribution as it demonstrates that weight-based and BSA-based dosing formats can be directly compared and that doses can easily be presented in both formats. Most importantly, it has highlighted practical differences and possible implications for height response to GH treatment between the two formats.

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## Conflict of interest

Nothing to declare.

## References

- 1 Australian-Government. Guidelines for the Availability of Human Growth Hormone (hGH) as a Pharmaceutical Benefit. Australian Government. Department of Health and Ageing, 2012; Available from: <http://health.gov.au/internet/main/publishing.nsf/Content/health-pbs-general-supply-hghapplication#Guidelines>.
- 2 Cutfield, W.S., Derraik, J.G., Gunn, A.J. *et al.* (2011) Non-compliance with growth hormone treatment in children is common and impairs linear growth. *PLoS One*, **6**, e16223.
- 3 Renes, J.S., de Ridder, M.A., Breukhoven, P.E. *et al.* (2012) Methylphenidate and the response to growth hormone treatment in short children born small for gestational age. *PLoS One*, **7**, e53164.
- 4 Ekbote, V.H., Rustagi, V.T., Khadilkar, V.V. *et al.* (2011) Evaluation of insulin-like growth factor-1 in Indian growth hormone-deficient children on growth hormone therapy. *Endocrine Research*, **36**, 109–115.
- 5 Seino, Y., Yamashita, S., Morisaki, Y. *et al.* (2012) Japanese growth prediction model for prepubertal children with growth

- hormone deficiency. *Journal of Pediatric Endocrinology and Metabolism* **25**, 909–915.
- 6 Lu, W., Shen, S., Luo, X. *et al.* (2013) Comparative evaluation of short-term biomarker response to treatment for growth hormone deficiency in Chinese children with growth hormone deficiency born small for or appropriate for gestational age: a randomized phase IV open-label study. *Therapeutic advances in endocrinology and metabolism*, **4**, 41–49.
  - 7 Fillion, M., Deal, C. & Van Vliet, G. (2009) Retrospective study of the potential benefits and adverse events during growth hormone treatment in children with Prader-Willi syndrome. *Journal of Pediatrics*, **154**, 230–233.
  - 8 GH Research Society. (2000) Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. *Journal of Clinical Endocrinology and Metabolism* **85**; 3990–3993.
  - 9 Wit, J.M., Reiter, E.O., Ross, J.L. *et al.* (2008) Idiopathic short stature: management and growth hormone treatment. *Growth Hormone & IGF Research*, **18**, 111–135.
  - 10 Cohen, P., Rogol, A.D., Deal, C.L. *et al.* (2008) Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. *Journal of Clinical Endocrinology and Metabolism*, **93**, 4210–4217.
  - 11 Juul, A., Bernasconi, S., Clayton, P.E. *et al.* (2002) European audit of current practice in diagnosis and treatment of childhood growth hormone deficiency. *Hormone Research*, **58**, 233–241.
  - 12 Ranke, M.B., Lindberg, A., Mullis, P.E. *et al.* (2013) Towards optimal treatment with growth hormone in short children and adolescents: evidence and theses. *Hormone research in paediatrics* **79**; 51–67.
  - 13 Sharma, V. & McNeill, J.H. (2009) To scale or not to scale: the principles of dose extrapolation. *British Journal of Pharmacology*, **157**, 907–921.
  - 14 El Edelbi, R., Lindemalm, S. & Eksborg, S. (2012) Estimation of body surface area in various childhood ages—validation of the Mosteller formula. *Acta Paediatrica*, **101**, 540–544.
  - 15 Thomson, A.H. (2004) Introduction to Clinical Pharmacodynamics. *Paediatric and Perinatal Drug Therapy*, **4**, 3–11.
  - 16 Denson, L.A. (2008) Growth hormone therapy in children and adolescents: pharmacokinetic/pharmacodynamic considerations and emerging indications. *Expert opinion on drug metabolism & toxicology*, **4**, 1569–1580.
  - 17 Grimberg, A. & Cohen, P. (1997) Optimizing growth hormone therapy in children. *Hormone Research*, **48**(Suppl 5), 11–15.
  - 18 Wit, J.M. (2007) Optimizing growth hormone therapy in growth hormone deficient children: what to do in the absence of hard evidence? Commentary on Rachmiel *et al.*: Final height in children with idiopathic growth hormone deficiency treated with a fixed dose of recombinant growth hormone (Horm Res 2007;68:236–243). *Hormone Research*, **68**, 244–247.
  - 19 Mosteller, R.D. (1987) Simplified calculation of body-surface area. *New England Journal of Medicine*, **317**, 1098.
  - 20 Lack, J.A. & Stuart-Taylor, M.E. (1997) Calculation of drug dosage and body surface area of children. *British Journal of Anaesthesia*, **78**, 601–605.
  - 21 Hughes, I.P., Choong, C.S., Cotterill, A. *et al.* (2010) Gender bias in children receiving growth hormone treatment. *Journal of Clinical Endocrinology and Metabolism*, **95**, 1191–1198.
  - 22 Hughes, I.P., Choong, C.S., Harris, M. *et al.* (2011) Growth hormone treatment for Turner syndrome in Australia reveals that younger age and increased dose interact to improve response. *Clinical endocrinology*, **74**, 473–480.
  - 23 Hughes, I.P., Harris, M., Choong, C.S. *et al.* (2010) Growth hormone regimens in Australia: analysis of the first 3 years of treatment for idiopathic growth hormone deficiency and idiopathic short stature. *Clinical endocrinology*, **77**, 62–71.
  - 24 Silverman, B.K. (2006) Practical information. In: G.R. Fleisher, S. Ludwig, F.M. Henretig eds. *Textbook of Pediatric Emergency Medicine*, 5th edn. Philadelphia, Lippincott, Williams, and Wilkins, 2013.
  - 25 Furqan, M. & Haque, A. (2009) Surface area in children: a simple formula. *Indian Pediatrics*, **46**, 1085–1087.
  - 26 Rosenfeld, R.G. & Bakker, B. (2008) Compliance and persistence in pediatric and adult patients receiving growth hormone therapy. *Endocrine practice*, **14**, 143–154.
  - 27 Bakker, B., Frane, J., Anhalt, H. *et al.* (2008) Height velocity targets from the national cooperative growth study for first-year growth hormone responses in short children. *Journal of Clinical Endocrinology and Metabolism*, **93**, 352–357.
  - 28 Lyon, A.J., Preece, M.A. & Grant, D.B. (1985) Growth curve for girls with Turner syndrome. *Archives of Disease in Childhood*, **60**, 932–935.
  - 29 Ranke, M.B., Lindberg, A., Brosz, M. *et al.* (2012) Accurate long-term prediction of height during the first four years of growth hormone treatment in prepubertal children with growth hormone deficiency or Turner Syndrome. *Hormone research in paediatrics*, **78**, 8–17.
  - 30 Ranke, M.B., Lindberg, A., Price, D.A. *et al.* (2007) Age at growth hormone therapy start and first-year responsiveness to growth hormone are major determinants of height outcome in idiopathic short stature. *Hormone Research*, **68**, 53–62.
  - 31 Wit, J.M., Rekers-Mombarg, L.T., Cutler, G.B. *et al.* (2005) Growth hormone (GH) treatment to final height in children with idiopathic short stature: evidence for a dose effect. *The Journal of pediatrics* **146**, 45–53.
  - 32 Park, P. & Cohen, P. (2005) Insulin-like growth factor I (IGF-I) measurements in growth hormone (GH) therapy of idiopathic short stature (ISS). *Growth Hormone & IGF Research* **15**(Suppl A), S13–S20.
  - 33 Ranke, M.B., Traunecker, R., Martin, D.D. *et al.* (2005) IGF-I and IGF binding protein-3 levels during initial GH dosage step-up are indicators of GH sensitivity in GH-deficient children and short children born small for gestational age. *Hormone Research*, **64**, 68–76.
  - 34 Kristrom, B., Aronson, A.S., Dahlgren, J. *et al.* (2009) Growth hormone (GH) dosing during catch-up growth guided by individual responsiveness decreases growth response variability in prepubertal children with GH deficiency or idiopathic short stature. *Journal of Clinical Endocrinology and Metabolism*, **94**, 483–490.
  - 35 Jung, H., Land, C., Nicolay, C. *et al.* (2009) Growth response to an individualized versus fixed dose GH treatment in short children born small for gestational age: the OPTIMA study. *European Journal of Endocrinology*, **160**, 149–156.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Data S1.** Derivation of empirical conversion formulae.

**Figure S1.** Doses (pre 2008) for the indications of GH deficiency (GHD), short stature and slow growth (SSSG), and Turner syndrome (TS) in  $\text{mg}/\text{m}^2/\text{week}$  and  $\text{mg}/\text{kg}/\text{week}$  plotted.

**Table S1.** Examples of changes in mean first year GH dose and response to treatment for different starting weights. Compared to published mean responses from Bakker *et al.*<sup>26</sup> and predicted responses from Ranke *et al.*<sup>29,30</sup> at equivalent starting ages and other relevant parameters.