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Reference Values for IGF-I throughout Childhood and Adolescence: A Model that Accounts Simultaneously for the Effect of Gender, Age, and Puberty

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We have constructed a reference model to facilitate comparison of serum IGF-I values among children, and thereby to improve the value of IGF-I measurements for diagnosis. The data set consists of serum values measured in 969 samples from 468 healthy children and adolescents (232 males, 236 females; ages, 1.1–18.3 yr). One sample per child was used for the model, each being selected so as to provide sufficient observations for each stage of puberty. The samples not selected were used to validate the reference data. The IGF-I values were log transformed, and multiple regression analysis was used in the model-building process. The best linear model, which converts serum IGF-I concentrations into SD scores and explains 66% of the variation in logIGF-I values, includes the variables of age, gender, and puberty, and takes the interactions among these variables into account. In prepubertal and early pubertal children, the relationship between age and logIGF-I was positive, with greater effect in girls older than 8 yr. In mid-puberty, logIGF-I values were higher in girls than in boys of the same age, up to 16 yr of age. Among boys, the most pronounced positive relationship between age and logIGF-I occurred in mid-puberty, whereas the relationship between age and logIGF-I among girls in mid-puberty is fairly constant. In late puberty, logIGF-I values were higher than earlier in puberty, and there was a negative relationship with age in both boys and girls. Instead of separate models for each combination of puberty and gender, estimating a single regression model permits simultaneous estimation of all explanatory variables and uses all observations in the data set, thereby making it easier to select those variables that have a significant effect on logIGF-I. Our model shows that IGF-I levels are related to age during each stage of puberty. The model also accounts for the fact that serum IGF-I concentrations during puberty are different for boys and girls. (*J Clin Endocrinol Metab* 86: 5870–5876, 2001)

THE CLINICAL USE of measurements of IGF-I has been focused primarily on diagnosing or excluding GH deficiency, and on monitoring GH therapy. IGF-I SD scores have been shown to relate to the GH_{max} in serum during provocative tests (1, 2). Although measurements of IGF-I are useful for diagnosis and follow-up of patients with acromegaly (3), the sensitivity and specificity of IGF-I or IGFBP-3 in the diagnosis of GH deficiency in children is a matter of controversy (4, 5). Because the liver is the principal source of IGF-I in the circulation (6), and because hepatic production of IGF-I is highly influenced by nutritional factors (7), it is possible that decrements in IGF-I expected with GH deficiency are modified by nutritional status and other factors, such that only severe GH deficiency produces a clear segregation of children who are deficient from those who are not (8). Also problematic is the marked variation found in healthy children, where IGF-I values may double or be reduced by half from one month to another (9).

Numerous reports indicate that the level of IGF-I is higher in older than in younger children (10–16). Also, puberty produces significant increments in IGF-I (17–25). These likely result from increased GH secretion mediated by sex hormone (*i.e.* estrogen) (10–16). In boys, aromatization of T to E2 appears to be important for the pubertal increase in GH secretion and IGF-I (24).

Abbreviations: CV, Coefficient of variation.

The objective of our study was to develop a childhood and adolescent model for converting serum concentrations of IGF-I to SD scores. We sought to develop a model that would explain as much of the variation in IGF-I as possible, and to include in the model the explanatory variables that have a significant effect on IGF-I concentrations. The variables selected were those shown in a preliminary exploratory study and in previously published studies to effect IGF-I concentrations. It was also important that the model be robust, as well as simple to use.

Subjects and Methods

Subjects

Our data originally consisted of 1022 measurements of IGF-I in serum from 663 children. Some children had IGF-I measurements only once; a large group had two measurements and some children had several measurements. Because we wished to use only one IGF-I measurement per child, we determined whether any systematic differences in IGF-I could be detected between the children with one measurement and those with several measurements. No such difference was observed (data not shown).

Because the reference model is cross-sectional, using only one observation per child, not all of the original observations could be used to produce the model. To construct a reference model for a normal population, the only children included were those with height and weight within ± 3 SD of the population mean (26). Because puberty is an important explanatory variable for IGF-I and the total number of measurements available within each pubertal stage differed considerably,

we selected observations in such a way as to provide sufficient information for each pubertal stage. The selection process was as follows:

Girls. The pubertal stage having the smallest number of children was early puberty (25 girls measured). If these girls had any measurements in pre-, mid-, or late puberty, these measurements were omitted from the data. The same procedure was thereafter applied to mid-puberty; that is, those girls who had a measurement in mid-puberty were omitted from prepuberty and late puberty. Thereafter, this procedure was applied to the prepubertal stage.

Boys. The omission procedure described above was applied to data from the boys, in the following order for the pubertal stages: mid, early, and late.

Pubertal stage. Puberty in girls was classified into four stages according to breast development: pre- (breast stage 1), early (breast stage 2), mid- (breast stage 3–4) and late (breast stage 5). Puberty in boys was also classified into four stages according to testicular volume: pre- (testis 1–3 ml), early (testis 4–8 ml), mid- (testis 9–19 ml), and late (testis > 20 ml).

The characteristics of the group of children used to produce the model are given in Table 1a.

The Ethical Committees of the Medical Faculty of the University of Göteborg approved the study. Informed consent was obtained from the parents of each child and from the child if old enough.

When a preliminary exploratory analysis was performed on the children in prepuberty, the distribution of height SD was found to be highly skewed, with a mean height of −1.45 SD, *i.e.* the majority of children were below average height. Because the aim was to construct a reference model for a normal population, a portion of IGF-I measurements from prepubertal children with a height SD between −1 SD and −3 SD had to be excluded from the model. One hundred seventy-one IGF-I values were therefore omitted in randomized manner. Thus, the cross-sectional data used for estimating and validating the reference model was obtained from 468 children (236 girls, 232 boys) from a cohort of 969 serum samples (Table 1).

The data used come from children involved in three different studies, here denoted groups A, B, and C

Group A. 1–18 yr of age (n = 176). These were siblings of children with short stature, relatives or friends of employees at our research center, or children seen in pediatric endocrine outpatient clinics and subsequently regarded as healthy, and as normal in terms of height and growth.

TABLE 1a. Characteristics of the children included in the normal reference group. Age and SD height, SD weight and SD weight/height are given for the children split into puberty stage

Puberty		Age		SD Height		SD Weight		SD Height/weight	
		Boy	Girl	Boy	Girl	Boy	Girl	Boy	Girl
Prepubertal	Mean	9.42	8.45	−0.56	0.10	−0.26	0.01	0.16	0.03
	Minimum	1.10	2.60	−2.94	−2.97	−2.91	−2.82	−1.74	−2.14
	Maximum	13.90	12.50	2.26	2.99	2.71	2.86	2.11	2.29
	Count	72	43	72	43	72	43	72	43
Early puberty	Mean	13.32	12.15	−0.91	−0.23	−0.79	−0.41	−0.13	−0.35
	Minimum	11.40	9.90	−2.82	−2.87	2.87	−2.23	−2.19	−2.03
	Maximum	18.10	15.50	2.23	2.63	2.36	2.04	1.96	1.83
	Count	35	24	35	24	35	24	35	24
Mid puberty	Mean	14.24	14.89	−0.26	0.55	−0.12	0.16	0.05	−0.18
	Minimum	10.90	11.00	−2.67	−2.10	−2.30	−2.93	−2.13	−2.34
	Maximum	16.30	18.30	3.00	2.92	2.83	2.35	1.67	2.30
	Count	39	108	39	108	39	108	39	108
Late puberty	Mean	16.38	16.46	0.20	0.00	0.58	0.33	0.55	0.40
	Minimum	13.90	14.30	−2.47	−2.68	−2.25	−2.67	−1.84	−2.20
	Maximum	18.30	18.20	2.31	2.57	2.67	2.81	2.62	2.73
	Count	86	61	86	61	61	86	86	61

TABLE 1b. Characteristics of the children included in the validation group. Age and SD height, SD weight and SD weight/height are given for the children split into puberty stage

Puberty		Age		SD Height		SD Weight		SD Height/weight	
		Boy	Girl	Boy	Girl	Boy	Girl	Boy	Girl
Prepubertal	Mean	10.41	9.78	−0.29	0.37	−0.12	0.59	−0.01	−0.78
	Minimum	7.40	8.10	−2.99	−2.19	−2.61	−1.52	−1.94	−2.54
	Maximum	16.10	11.20	2.66	2.91	2.21	2.68	1.86	0.57
	Count	32	15	32	15	32	15	32	15
Early puberty	Mean	12.48		−0.13		−0.09		0.02	
	Minimum	11.10		−2.01		−2.58		−2.15	
	Maximum	13.80		2.48		2.86		1.47	
	Count	5		5		5		5	
Mid puberty	Mean	14.46	15.19	0.96	0.55	0.51	−0.10	−0.18	−0.50
	Minimum	13.20	11.70	−1.30	−0.93	−0.72	−1.76	−1.21	−2.30
	Maximum	16.80	17.30	2.49	2.89	2.06	1.91	0.68	1.88
	Count	7	26	7	26	7	26	7	26
Late puberty	Mean	16.49	16.55	0.20	0.26	0.45	0.25	0.41	0.13
	Minimum	15.30	14.10	−1.95	−2.58	−2.59	−1.95	−1.91	−2.15
	Maximum	17.40	17.90	2.37	2.55	2.95	2.44	2.44	2.28
	Count	68	90	68	90	68	90	68	90

Group B. 8–13 yr of age (n = 80). These were children from one primary school who had participated in a study to determine the mean intraindividual monthly coefficient of variation of serum IGF-I concentrations (9).

Group C. 15–18 yr of age (n = 212). These were children from several schools in Göteborg who had participated in a follow-up assessment of a study involving iron supplementation in flour.

When data from several studies are combined, the results sometimes produce biased estimates. Therefore, tests were performed to uncover systematic differences between groups. No evidence of such deviations was found (data not shown).

Cross-sectional validation group. More than 50% of the 468 children whose samples were used in the reference model had more than one IGF-I measurement. For these children, one of their serum samples that was not used in the reference model was randomly selected (n = 268) and used to validate the reference model (Table 1b).

Longitudinal validation group. Factors that must be accounted for in a longitudinal reference model are intraindividual variation and dependence. For 153 children (79 boys and 74 girls) who had at least 2 IGF-I samples measured in the same pubertal stage, an exploratory analysis was performed to determine their change in logIGF-I over time. The mean changes for each combination of gender and pubertal stage were then compared with the regression coefficients given by the multiple regression (see *Results—Estimated regression model*). To determine the effect of using the cross-sectional reference model on longitudinal data, we used IGF-I data from a small group of children with measurements in at least three pubertal stages. The reference model was used with the assumptions that the intraindividual development was the same as the over-time development, and that observations from the same person can be regarded as approximately independent. This group consisted of 21 children: 10 girls and 11 boys with height and weight within ± 2 SD.

Residual analysis. Residual analysis was performed, the residuals were tested for normality (skewness), and exploratory analysis was used to check the assumption of homoscedastisity (*i.e.* constant variance of the residuals).

Hormone measurements. Concentrations of IGF-I were measured in duplicate by an IGF binding-protein blocked RIA, without extraction and in the presence of an approximately 250-fold excess of IGF-II (Mediagnost GmbH, Tübingen, Germany) (27). The intraassay coefficients of variations (CVs) were 8.1, 4.4, and 4.5% at concentrations of 55, 219, and 479 μg/liter, respectively, and the interassay CVs were 10.4, 7.7, and 5.3% at concentrations of 55, 219, and 479 μg/liter, respectively.

Auxology. Heights and weights were transformed into SD scores for sex and age according to Swedish reference values (26).

Statistical evaluation. The statistical package SPSS (SPSS, Inc., Chicago, IL) was used for the analysis.

When selecting the parameters to include in the reference model, the significance and the variables found to be biologically relevant in our exploratory study and in earlier studies were taken into account. Only variables that are significant (gender, age, and pubertal stage) are included in the final model.

Results

The analysis was performed after transformation of IGF-I values (Fig. 1, *left panel*) to logarithmic values (*right panel*). R^2 measures the proportion of the variation in outcome that is explained by the combination of the explanatory variables in the model. In multiple regression analysis, an adjusted R^2 is used, with a correction for degrees of freedom. The adjusted R^2 was found to be 0.66 for the reference group. An ANOVA was performed, and the resulting *F* test showed a highly significant regression relationship between logIGF-I and at least one of the explanatory variables ($P < 0.001$). The estimated regression model for the normal reference group is shown in Fig. 2 and Table 2.

Interpretation of the variables in Table 2 for the prepubertal children reveals that the relationship between their age and logIGF-I is positive, with the regression coefficient b ($b_{Age*Pre}$) = 0.0325 ($P < 0.001$). This means that older prepubertal children had higher logIGF-I values compared with younger prepubertal children. For girls above 8 yr of age, the relationship between age and logIGF-I is somewhat more pronounced ($b_{Sex*Age*Pre\ (>8\ yr)\ Early} = 0.0089$; $P < 0.001$) than that observed in boys of the same age. Also in early puberty the relationship between age and logIGF-I is positive and again a bit more pronounced in girls than in boys. In mid-

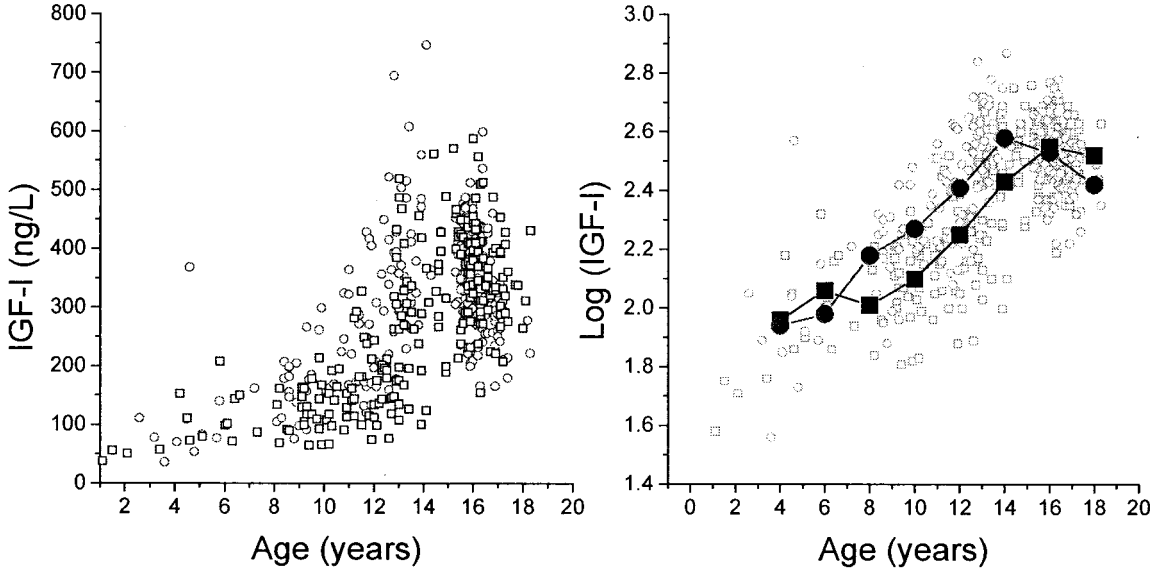

FIG. 1. Cross-sectional measurements of IGF-I in 468 children (boys, □ and girls, ○) whose heights and weights were within ± 3 SD of Swedish norms (*left panel*). The logarithmic transformation is shown in the *right panel*, with the mean values given at 2-yr intervals for boys (-■-) and girls (-●-).

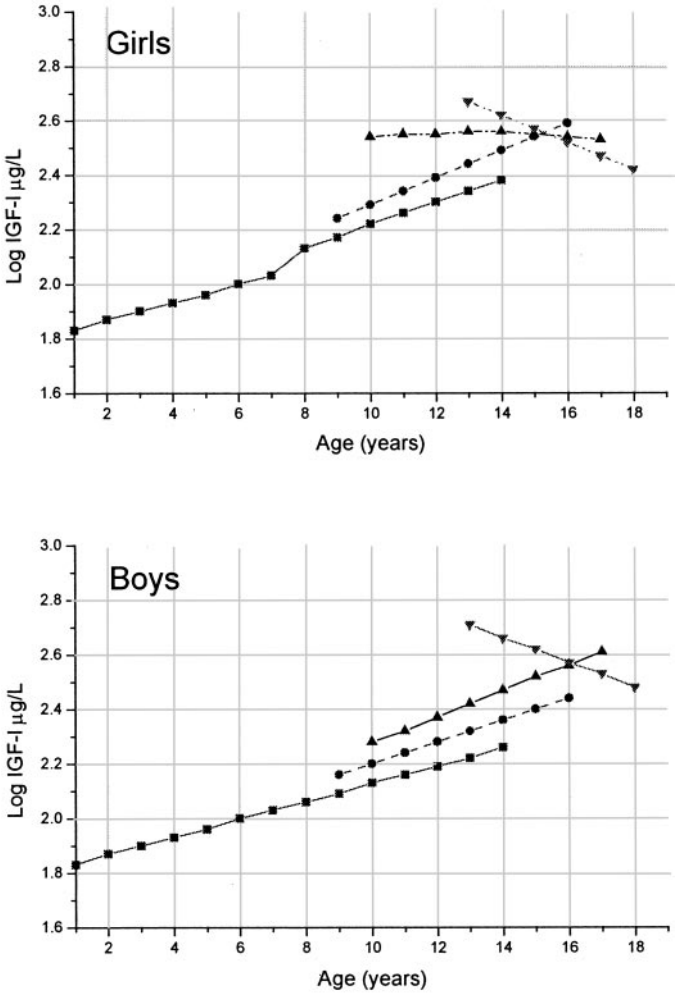

FIG. 2. Estimated mean regression equation for each combination of gender and puberty. Girls (*top panel*) were classified into four stages according to breast development (see *Subjects and Methods*) and boys (*bottom panel*) according to testicular volume: (pre -■-), early (-●-), mid (-▲-), late (-▼-).

puberty, the relationship between age and logIGF-I is different for girls and boys. Virtually no age-effect is observed in girls, whereas an age-effect is present in boys. The logIGF-I values are higher for mid-pubertal girls, compared with boys. Finally, in late puberty there is a negative relationship between age and logIGF-I, somewhat more pronounced in girls than in boys.

Estimated regression model

The estimated multiple regression model in Table 2 can be used for estimating the value of logIGF-I, given the age, sex, and puberty. In the multiple regression model, the effects of all of the explanatory variables included are taken into account simultaneously. To simplify the comparison between gender and pubertal stage, the estimated regression equations for each combination of gender and puberty are presented below, using the appropriate coefficients from Table 2. Use of these equations facilitates visual illustration of the reference ranges for each gender and pubertal stage, as seen in Fig. 3.

TABLE 2. The reference model (*i.e.* estimated regression model) includes the variables of age, gender and puberty, and takes the interactions among these variables into account simultaneously

Variable	Coefficient b	SE	*P* value
(Constant)	1.8010	0.041	<0.001
Age*Pre	0.0325	0.004	<0.001
Age*Early	0.0401	0.003	<0.001
Age*Midpub	0.0476	0.003	<0.001
Age*Late	−0.0464	0.016	<0.005
Sex*Age*[Pre (>8 yr) Early]	0.0089	0.002	<0.001
Age**2 Midpub*Sex	−0.0018	0.000	<0.001
Midpub*Sex	0.4410	0.070	<0.001
Sex*Age*Late	−0.0035	0.001	<0.010
Late	1.5130	0.269	<0.001

Dependent variable, $\log_{10}$IGF-I.

1, variable is included in the model; 0, variable is not included. Thus, an interaction variable must not include any 0 in order to be included in the model. A simplified estimated regression equation for each combination of gender and puberty are presented under *Results.*

Age**2: Years squared.

Pre: 1, if puberty stage prepubertal, 0, otherwise.

Early: 1, if puberty stage early puberty, 0, otherwise.

Midpub: 1, if puberty stage mid-puberty, 0, otherwise.

Late: 1, if puberty stage late puberty, 0, otherwise.

[Pre (>8 y) Early]: 1, if puberty stage prepubertal and older than 8 yr; 1, if puberty stage early; 0, otherwise.

Sex: 1, if girl; 0, otherwise.

Girls. Prepubertal 1–8 yr: logIGF-I = 1.8010 + 0.0325*Age; prepubertal 8–14 yr: logIGF-I = 1.8010 + 0.0325*Age + 0.0089* Age; early 9–15.5 yr: logIGF-I = 1.8010 + 0.0401*Age + 0.0089*Age; mid 10–18 yr: logIGF-I = 2.2420 + 0.0476*Age − 0.0018*Age2; late 13–19.5 yr: logIGF-I = 3.3140–0.0499*Age.

Boys. Prepubertal 1–14 yr: logIGF-I = 1.8010 + 0.0325*Age; early 9–15.5 yr: logIGF-I = 1.8010 + 0.0401*Age; mid 10–18 yr: logIGF-I = 1.8010 + 0.0476*Age; late 13–19.5 yr: logIGF-I = 3.3140 − 0.0464*Age.

To calculate the SD score, the SE of the predicted value of logIGF-I must also be estimated. The SE varies with the values of the explanatory variables. In the reference group, the mean of the SE was 0.1373 and the range was 0.1366–0.1425. There was very little variation among the mean of the SE for the different combinations of gender and pubertal stage.

To illustrate how to use an equation: A 9-yr-old prepubertal girl has an IGF-I measurement of 219 μg/liter. To calculate her SD score, the following formula should be used.

$$\text{SD score, IGF-I} = \frac{(y - \hat{y})}{\text{SE}} = \frac{(2.3404 - 2.1736)}{0.1373} = 1.21$$

where y is the logarithmic value of her IGF-I measurement: that, y = log 219 = 2.3404. $\hat{y}$ is calculated from the estimated regression equations: that is $\hat{y}$ = 1.8010 + (0.0325*9) + (0.0089*9) = 2.1736 and the mean SE value (0.1373) is used.

Validation of the model

Distribution of SD scores. The distribution of SD scores for the reference group and the validation group are compared in Fig. 4, *top* and *bottom*. The graphs show that the reference model gives a distribution of SD scores for the validation group that is similar to that for the reference group.

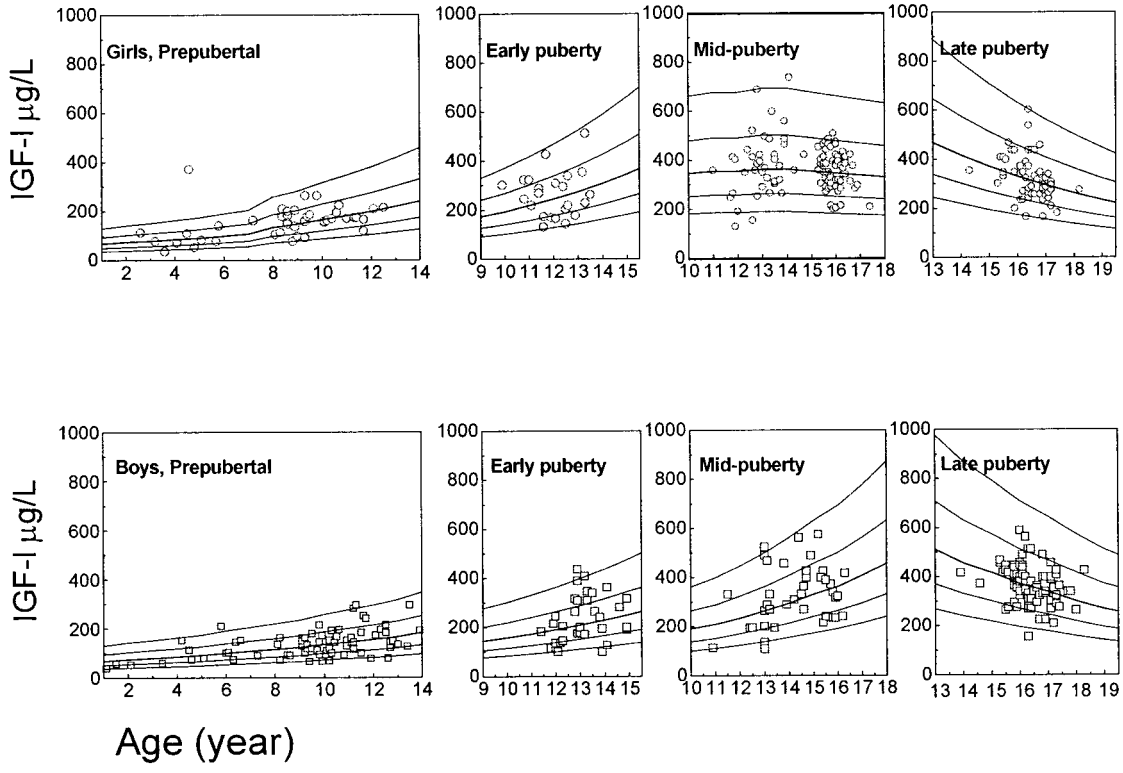

FIG. 3. The reference model is illustrated using in-sample data, segregated by gender and pubertal stage (girls, *top panel*; boys, *bottom panel*). The five reference lines indicate regression line ± 1 SD and ± 2 SD.

Residuals. The residuals for the reference group are illustrated in Fig. 5. This shows that the assumption of a constant variance for logIGF-I was fulfilled.

Longitudinal validation group

The exploratory analysis for the 153 children in the longitudinal validation group showed that the change in IGF-I with age was positive in prepuberty and early puberty among both boys and girls. In late puberty, the change in IGF-I with age was negative for boys. In mid- (for girls above 15 yr of age) and late puberty, the change in IGF-I with age was negative for girls. These observations agree with the results from the reference model. Taking the data from the 21 healthy subjects (10 girls and 11 boys) followed longitudinally and using it in our cross-sectional reference model showed mean range variation of 0.9 IGF-I SD scores with all logIGF-I SD scores within the range of ± 2 SD.

Discussion

We have developed a model that can be used in children for relating serum IGF-I levels to age, puberty, and gender simultaneously, thus enabling comparisons between different groups of children without using matched controls. These reference values should improve the accuracy of diagnosis for individual children. The model is the first that can be used to convert IGF-I serum concentrations into SD scores from infancy to adulthood with a high degree of accuracy.

Our results confirm previous studies (10–16) showing that the relationship between age and serum IGF-I levels is positive in prepubertal and early pubertal children and that the relationship between age and IGF-I concentrations is negative in late puberty. For children in mid-puberty, no reference values have been available. Juul *et al.* (28) did not report a prediction range for children in Tanner stage 3, and for girls in Tanner stage 2 (equivalent to our early stage of puberty) and in stage 4 no significance value is given for the prediction intervals. Our study shows that in mid-puberty the relationship between age and IGF-I was different for girls and boys, with a positive age effect in boys and a fairly constant effect in girls. The IGF-I values were higher for mid-pubertal girls, compared with boys. These gender differences agree with the observation that girls have peak height velocity and concurrent elevation of serum IGF-I earlier than boys (28). Some girls do not reach stage 5 of breast development. When this occurs in a girl who has reached final height and/or had menarche more than 2 yr previously, she should be classified as being in late puberty.

In this report, one regression model was fitted to all observations, instead of dividing the sample into subgroups and fitting separate regression models for each subgroup. The advantage of using one model is that it permits simultaneous estimation of all explanatory variables and uses all observations in the estimation process. The power of a test increases with the number of observations (the number of degrees of freedom). With an increased number of observations, it is easier to obtain significant results for the exploratory variables that are important.

The reference model presented in this report was constructed from cross-sectional, not longitudinal data. A longitudinal study would be subject to the variation between

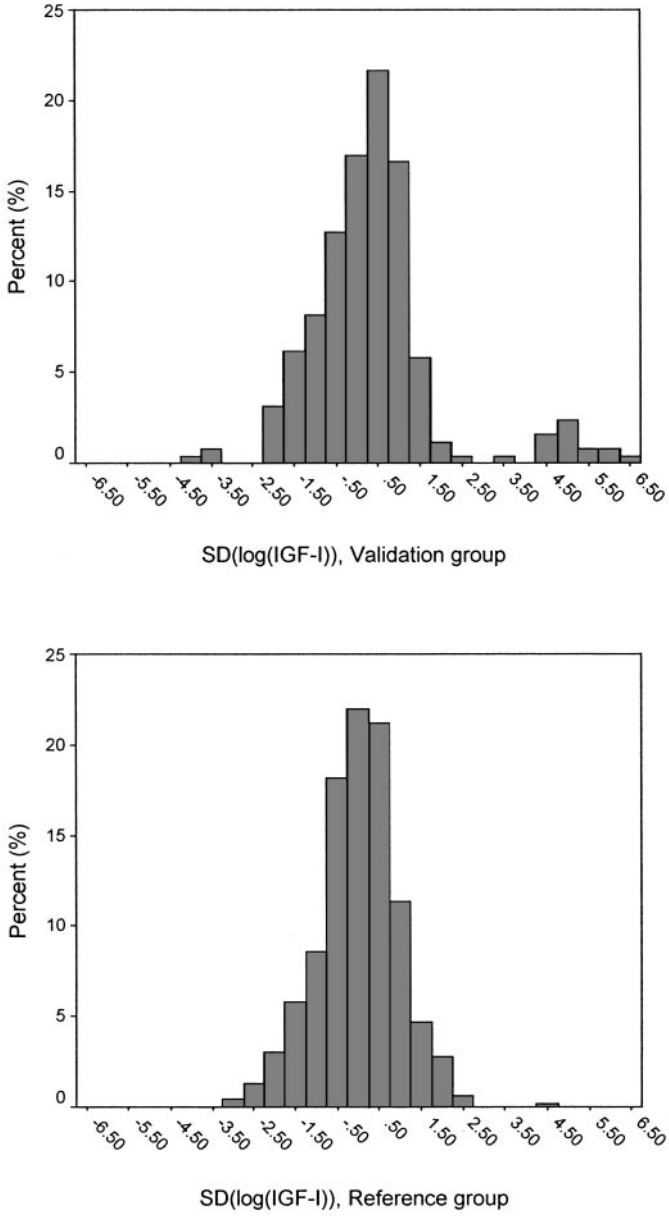

FIG. 4. Histogram of the distribution of SD scores for the reference group (n = 468) (*bottom panel*) and for the validation group (n = 268) (*top panel*).

children and the variation within each child. In normal children, repeated measurements of IGF-I have been shown to cluster around a level dependent on the size of the child, although the mean intraindividual monthly CV for IGF-I was found to be 16% (9). Constructing a longitudinal reference model would require repeated blood sampling from the same healthy children over a prolonged interval, for as long as 20 yr. In this study, an exploratory analysis of longitudinal data was conducted on a small number of children for the purpose of comparing the intraindividual development with the development given by the cross-sectional reference model. This analysis showed that the within-individual changes in IGF-I follow the same pattern as that exhibited by the reference model. Preliminary results using the reference

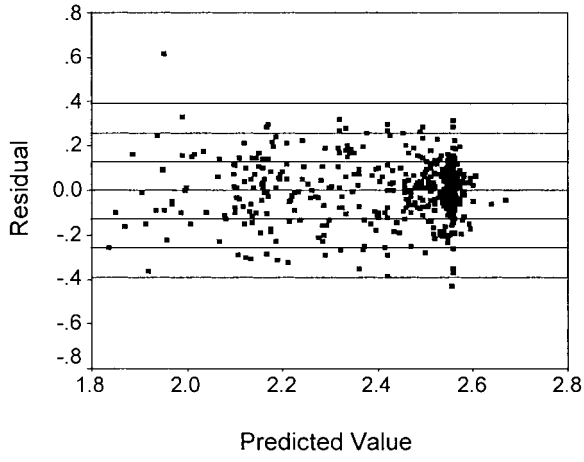

FIG. 5. The residuals for the reference group (n = 468). The *horizontal lines* each indicate 1 SD.

model showed that the longitudinal measurements for each of the normal healthy children varied considerably, but were within the normal range given by the model (±2 SD).

Based on the very good correlation we have seen when comparing results from different IGF-I assays, we believe that this model is also suitable for use with other IGF-I assays. Nevertheless, it is important for each individual laboratory to determine whether their assays give similar measured IGF-I levels as the Mediagnost assay or whether a conversion factor is required.

Our model shows that serum IGF-I concentrations are related to age throughout puberty. The model also accounts for the difference in IGF-I for boys and girls during puberty. The results of the study provide a tool to optimize the evaluation of IGF-I in the diagnosis of GH insufficiency and to follow up on GH treatment.

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