

ORIGINAL

Reference Ranges for Serum IGF-1 and IGFBP-3 Levels in Chinese Children During Childhood and Adolescence

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Abstract. Serum levels of insulin-like growth factor-1(IGF-1) and insulin-like growth factor binding protein-3(IGFBP-3) reflect endogenous growth hormone secretion, and serum IGF-1 and IGFBP-3 values should be ethnic-specific, thus we established the reference ranges for serum IGF-1 and IGFBP-3 in Chinese children aged 6-18 yr according to age, sex, puberty stage and BMI. The study was included 837 children (age 6-18 yr, 416 boys and 421 girls) from different schools in Daqing, Beijing and Shanghai. Serum IGF-1 and IGFBP-3 were determined by a chemiluminescent assay system (IMMULITE 1000). The results show that IGF1 reached peak levels at around 13 yr in boys and 11 yr in girls while IGFBP-3 peaked at 14 yr in boys, and 11 yr in girls. Both IGF-1 and IGFBP-3 were at platform or decreased slightly after these ages. At each corresponding age, IGF-1 levels tended to be higher in boys compared to girls, while girls had higher IGFBP-3 levels than boys. A model for calculation of standard deviation scores of IGF-1 and IGFBP3 according to age, sex and pubertal stage was established. These normative data should facilitate child care, growth monitoring, clinical diagnosis and to follow up on GH treatment.

Key words: Insulin-like growth factor-1, Insulin-like growth factor binding protein-3, Reference values

GROWTH HORMONE (GH) release is pulsatile [1]. Serum levels of insulin-like growth factor-1(IGF-1) and insulin-like growth factor binding protein-3(IGFBP-3) reflect endogenous GH secretion in healthy children, and their serum levels are relatively stable with modest diurnal variation. Thus, serum IGF-1 and IGFBP-3 are widely accepted for diagnostic use and for monitoring of therapy in growth disorders. IGF-1 is a small peptide hormone, over 99% circulating IGF-1 are bound to serum proteins including IGFBP-3 and the acid labile subunit. However, both serum IGF-1 and IGFBP-3 levels are regulated by age, sex, pubertal stage, genetic factors, social factors, nutritional status and disease [2-3]. Numerous

reports indicate that serum concentrations of IGF-1 and IGFBP-3 increase through childhood [3-7]. Also, puberty produces significant increases in IGF-1 and IGFBP-3, possibly as a result of increased GH secretion mediated by sex steroids. On the other hand, timing of pubertal onset can be influenced by ethnicity, therefore the reference values of serum IGF-1 and IGFBP-3 should preferably be ethnic-specific and may not be simply adopted from other population. In this study, we established the reference ranges for serum IGF-1 and IGFBP-3 in Chinese children aged 6-18 yr according to age, sex, puberty stage and BMI.

Materials and Methods

Subjects selection and measurements

The study population was consisted of 837 children (age 6-18 yr, 416 boys and 421 girls) from different schools in difference provinces, including Daqing, Beijing and Shanghai. All subjects have had a routine

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physical examination, and blood samples collected. Children with any of the following conditions will not be recruited into the study: chronic medical illnesses (e.g. hepatic, renal and heart diseases), tumor, acute infection within two weeks of the study, precocious or delayed puberty, and height or weight greater than $\pm 2SD$ from mean.

All subjects had their heights and weight measured in schools. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Puberty staging was determined by endocrinologist according to Tanner stage criteria, with focus on breast development in girls and testicular volume in boys.

The blood was drawn from an antecubital vein in the morning with subjects fasting. Sera were separated after centrifugation of coagulated blood and stored at -20°C until analysis. IGF-1 and IGFBP-3 assays were carried out using an automated chemiluminescent assay system (IMMULITE 1000, Diagnostic Products Corp., Los Angeles, CA, USA).

This study was approved by Ethical Committee of Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine. Informed consent was obtained from the parents of each child.

Statistical analysis

Data were presented as *mean*, $\pm 1SD$, $\pm 2SD$. IGF-1 and IGFBP-3 values above or below the detection limit were calculated as detection limit for the statistical analysis. IGF-1 and IGFBP-3 levels exhibited Gaussian distribution, and no transformation was required. *T* test was used to compare levels in boys and girls of the same age group.

Due to the different variances within the Tanner groups, a weighted linear regression analysis was performed, using weights equal to the reciprocal variance around regression lines for each combination of sex and Tanner stage of puberty. Age-related regression lines and the corresponding 95% confidence intervals (equal to $\pm 2SD$) were constructed for each sex and puberty stage. According to sex and Tanner stage, coefficients α (intercept) and β (slope) were used to determine the age-, sex- and puberty-corrected IGF-1 & IGFBP-3 levels based on the formula: $y = \beta \times \text{age} + \alpha$ where y = IGF-1 or IGFBP-3 levels. The SDS of IGF-1 and IGFBP-3 were calculated as follows: $SDS(IGF-1) = (IGF-1 \text{ value} - y) / SD$; $SDS(IGFBP-3) = (IGFBP-3 \text{ value} - y) / SD$. Multiple linear regression analysis was performed to evaluate the influence

of age, sex, puberty and BMI on serum IGF-1 and IGFBP-3 concentrations. The relative importance of the variables was indicated by standardized coefficients β , which were calculated for each variable. $p < 0.05$ was considered statistically significant. The statistical package SPSS 15.0 (SPSS, Inc., Chicago, IL) was used for the analysis.

Results

Age dependence of serum IGF-1 and IGFBP-3 levels

Serum levels of IGF-1 and IGFBP-3 increased from early childhood into adolescence. In late puberty, IGF-1 and IGFBP-3 levels were maintained at platform or decreased slightly with increasing age. The serum IGF1 reached peak level around 13 yr in boys, and 11 yr in girls, just compatible to reported age of peak height velocity (table 1). The general pattern of IGFBP-3 changes was similar to IGF-1 and increased with age (table 2).

Sexual differences in IGF-1 and IGFBP-3

IGF-1 levels tended to be higher in boys compared to girls at the corresponding ages except for 9-12 yr when lots of girls had gone into early puberty. But the differences were statistically significant only in some pubertal ages ($p = 0.002$ for age 9; $p = 0.025$ for age 10; $p \leq 0.001$ for age 11, 13, 14; $p = 0.045$ for age 16).

IGFBP-3 levels in girls are higher than boys at the same ages, and differences almost were statistically significant ($p = 0.004$ for age 6; $p \leq 0.001$ for age 7, 8, 9, 10, 11, 12, 13, 15, 16, 17, 18; $p = 0.003$ for age 14).

Effect of puberty on IGF-1 and IGFBP-3

Reference curves for serum IGF-1 and IGFBP-3 levels of each age, sex and puberty stage were determined and were constructed as 95% confidence intervals (fig. 1, 2). A prediction model for calculating the standard deviation scores of IGF-1, IGFBP-3 according to age in certain puberty stage was proposed (table 3, 4). Multiple linear regression analysis demonstrated that age, sex and puberty stage all have significant influences on serum IGF-1 levels. However, IGFBP-3 levels seemed only correlated with age in boys and girls (Table 5, 6).

BMI and serum IGF-1, IGFBP-3

Removed the confounding effects of age and puberty stage, BMI has no statistically significant effects on

Table 1. Normal ranges for total IGF-1 serum levels (ng/mL) in 6 to 18 years children.

Age (yr)	Boys						Girls					
	N	-2SD	-1SD	Mean	1SD	2SD	N	-2SD	-1SD	Mean	1SD	2SD
6	20	52.71	128.21	203.71	279.21	354.71	30	64.31	126.30	188.29	250.28	312.27
7	30	52.29	144.18	236.07	327.96	419.85	27	68.62	139.51	210.40	281.29	352.18
8	35	108.38	192.46	276.54	360.58	444.66	35	110.08	185.87	261.66	337.45	413.24
9	34	83.84	152.87	221.90	290.93	359.96	35	83.58	186.52	289.46	392.40	495.34
10	35	122.23	223.13	323.83	424.53	525.23	34	100.01	247.80	395.59	543.38	691.17
11	35	174.61	283.43	392.25	501.07	609.89	33	284.32	427.52	570.72	713.92	857.12
12	35	204.18	359.38	514.58	669.78	824.98	36	245.40	385.59	525.78	665.97	806.16
13	35	343.50	512.36	681.22	850.08	1018.94	34	358.53	447.84	537.15	626.46	715.77
14	35	350.89	475.78	600.67	725.56	850.45	31	221.39	335.18	448.97	562.76	676.55
15	35	282.86	444.83	606.80	768.77	930.74	32	258.67	411.32	563.97	716.62	869.27
16	36	334.14	479.64	625.14	770.64	916.14	33	341.54	447.54	553.54	659.54	765.54
17	35	280.48	427.44	574.40	721.36	868.32	31	266.59	408.60	550.61	692.62	834.63
18	16	224.72	382.05	539.38	696.71	854.04	30	229.50	398.19	566.88	735.57	904.26

Table 2. Normal ranges for IGFBP-3 serum levels ($\mu\text{g/mL}$) in 6 to 18 years children.

Age (yr)	Boys						Girls					
	N	-2SD	-1SD	Mean	1SD	2SD	N	-2SD	-1SD	Mean	1SD	2SD
6	20	2.65	3.96	5.27	6.58	7.89	30	2.39	4.59	6.79	8.99	11.19
7	30	3.34	4.42	5.50	6.58	7.66	27	3.49	5.54	7.57	9.62	11.67
8	35	3.35	4.55	5.75	6.95	8.15	35	4.06	5.94	7.82	9.70	11.58
9	34	2.32	3.59	4.86	6.13	7.40	35	3.39	5.50	7.61	9.72	11.83
10	35	2.63	4.08	5.53	6.98	8.43	34	4.33	6.31	8.29	10.27	12.25
11	35	2.84	4.25	5.66	7.04	8.48	33	6.60	8.40	10.20	12.00	13.80
12	35	3.67	4.87	6.07	7.27	8.47	36	6.34	7.32	8.30	9.82	10.80
13	35	3.77	5.31	6.85	8.39	9.93	34	5.24	6.92	8.60	10.28	11.96
14	35	4.19	5.65	7.11	8.57	10.03	31	5.11	6.63	8.15	9.67	11.19
15	35	4.09	5.41	6.73	8.05	9.37	32	5.00	6.74	8.48	10.22	11.96
16	36	3.75	5.29	6.83	8.37	9.91	33	6.52	8.24	9.96	11.68	13.40
17	35	3.70	5.26	6.82	8.38	9.94	31	5.99	7.96	9.93	11.90	13.87
18	16	4.07	5.55	7.03	8.51	9.99	30	5.92	7.88	9.84	11.80	13.76

serum IGF-1 and IGFBP-3 in both sexes (table 5, 6).

Discussion

In this survey, the reference values for serum IGF-1 and IGFBP-3 levels were established in a cohort of healthy Chinese children during childhood and adolescence aged 6-18 yr. Agreeing with the data from previous studies for other populations including German, Trukese, Swedes, Danes, and Japanese etc [4, 6-9], our results also show that age, sex, and puberty stage were important factors for determining serum levels of IGF-1 and IGFBP-3.

Serum levels of IGF-1 and IGFBP-3 were low during early childhood, and increased with age, reaching peak values during sexual maturation. Review

the normative data published before, serum IGF-1 high values occurred around 13-15 yr in girls and 14-16 yr in boys and IGFBP-3 peak level occurred from 13 yr to 15 yr in both sexes (Fig 3, 4) [4-10,12]. In our study, IGF-1 peaked at 13 yr and fell thereafter in boys, while plateauing off after reaching peak at 11 yr in girls. These peak serum IGF-1 levels correspond to peak height velocity, implying that the significant increase in IGF-1 contribute to the accelerated bone growth in puberty. Such correlation between peak IGF-1 concentrations and peak height velocity has been reported [8]. The changes in IGFBP-3 were similar to IGF-1, peaked at 14 yr in boys and 11 yr in girls then fluctuated around the peak level with increasing age [11]. This trend has also been shown in some longitudinal studies [12-14].

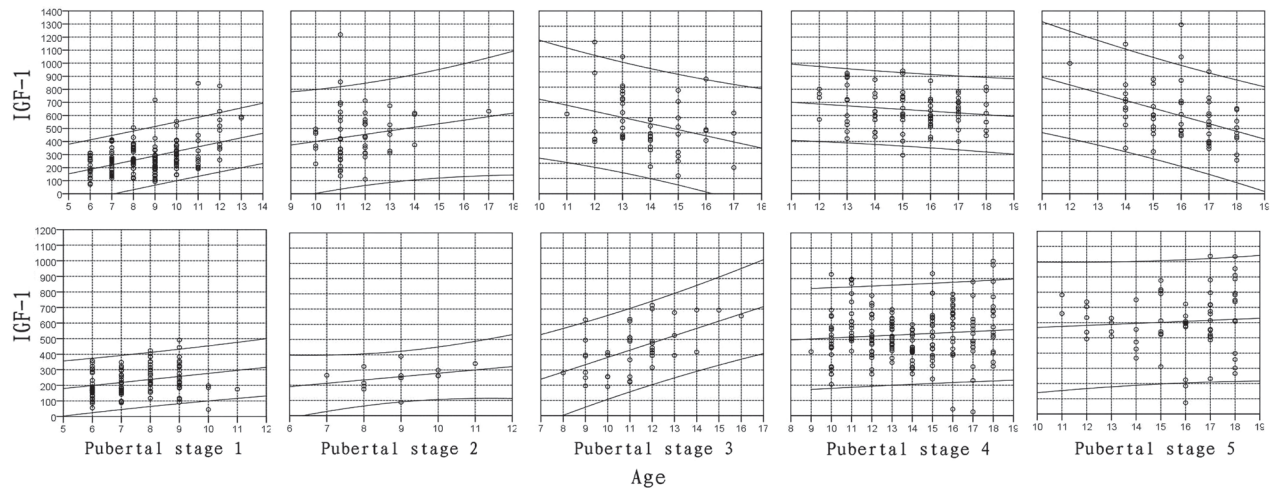


Fig.1. Serum IGF-1 levels (ng/mL) in boys (upper panels) and girls (lower panels) according to the chronological age and pubertal stage. Regression lines represent 95% confidence intervals.

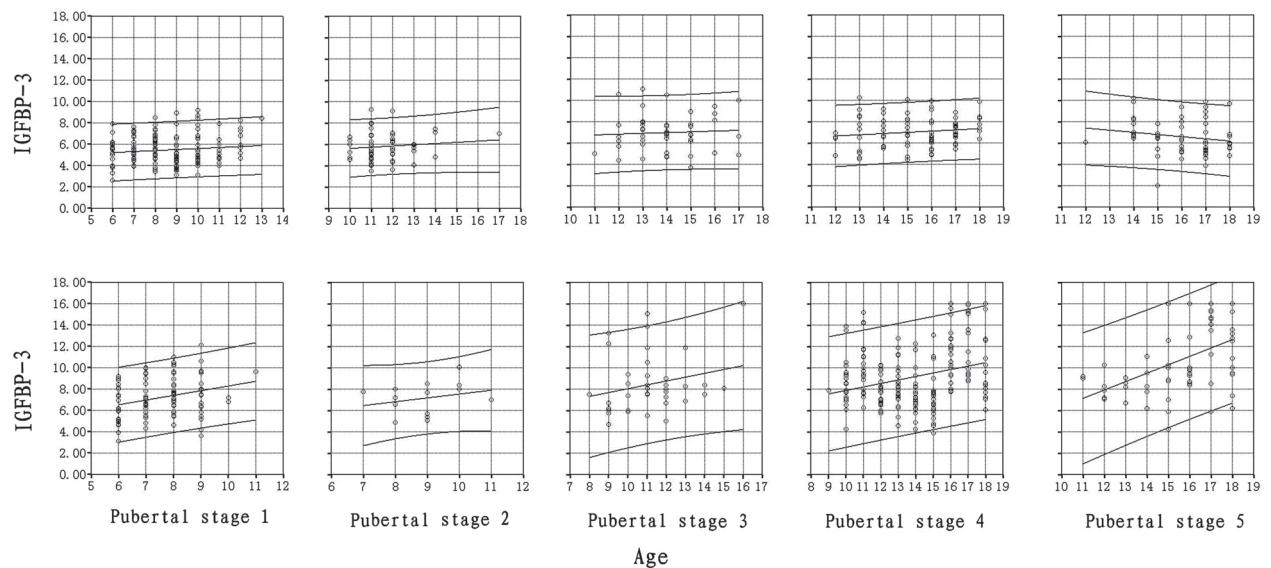


Fig.2. Serum IGFBP-3 levels ($\mu\text{g/mL}$) in boys (upper panels) and girls (lower panels) according to the chronological age and pubertal stage. Regression lines represent 95% confidence intervals.

IGF-1 and IGFBP-3 peak values in girls appear approximately 1-2 yr earlier than boys. It agreed with the observation that girls enter puberty earlier than boys, and hence have puberty growth spurt 1-2 yr earlier than boys. IGF-1 levels tended to be higher in boys compared to girls of the same ages, while IGFBP-3 levels in girls are higher than boys of the same ages as previously demonstrated in normal children [8, 15-16]. It may be in line with that there are well known direct negative effects of estrogens on GH-regulated IGF-1 production with potentially di-

vergent effects of androgens [17-19].

Apart from age and sex, puberty stage influenced serum levels of IGF-1 and IGFBP-3, probably because of the sex steroids-induced increase in GH secretion in the pubertal years [12, 20]. IGF-1 and IGFBP-3 varied with age within the same puberty stage. IGF-1 increased with increasing age in prepubertal children, but decreased with increasing age of children from puberty stage III (in boys) or V (in girls). It revealed that the older a child reached the final puberty stages, the lower IGF-1 levels. IGFBP-3 increased with in-

Table 3. Linear regression data for the age distribution of IGF-1 levels in each puberty stage for both sexes. $y=\beta \times \text{age} + \alpha$ (SE: standard errors; β : slopes; α : intercepts; SD: standard deviations)

Puberty stage	α (SE)	β (SE)	SD	p	n	r
Boys						
I	-144.01(34.56)	50.27(3.79)	118.60	<0.001	170	0.736
II	-192.13(144.44)	51.26(12.81)	145.47	<0.001	54	0.456
III	638.95(202.01)	-1.52(14.94)	154.30	0.920	49	0.015
IV	838.22(135.49)	-13.01(8.75)	137.15	0.141	82	0.027
V	1252.61(244.40)	-42.65(15.11)	167.17	0.007	61	0.353
Girls						
I	148.0(45.18)	9.70(5.78)	88.73	0.096	112	0.160
II	31.01(183.75)	24.30(19.63)	74.73	0.244	14	0.365
III	-80.43(179.08)	47.54(16.15)	145.45	0.006	40	0.446
IV	464.36(58.51)	4.11(4.19)	133.38	0.329	190	0.072
V	600.51(140.82)	-1.47(9.14)	146.17	0.873	65	0.022

Table 4. Linear regression data for the age distribution of IGFBP-3 levels in each puberty stage for both sexes. $y=\beta \times \text{age} + \alpha$ (SE: standard errors; β : slopes; α : intercepts; SD: standard deviations)

Puberty stage	α (SE)	β (SE)	SD	p	n	r
Boys						
I	1.126(0.353)	0.553(0.030)	1.310	<0.001	170	0.838
II	4.603(1.767)	0.090(0.156)	1.436	0.567	54	0.072
III	4.914(2.349)	0.139(0.170)	1.532	0.416	49	0.123
IV	4.731(1.305)	0.150(0.084)	1.386	0.078	82	0.197
V	11.219(2.244)	-0.284(0.140)	1.523	0.048	60	0.263
Girls						
I	6.532(1.129)	0.112(0.144)	2.056	0.439	112	0.077
II	-2.167(4.706)	1.051(0.523)	1.570	0.072	14	0.536
III	8.376(2.656)	-0.026(0.228)	2.344	0.911	40	0.019
IV	5.524(1.018)	0.249(0.074)	2.491	0.001	190	0.241
V	-1.543(2.099)	0.758(0.134)	2.598	<0.001	65	0.596

Table 5. Multiple regression analysis with serum IGF-1 levels as dependent variables, and age, puberty stage, sex and BMI as independent variables.

Variables	β	p
Age	0.244	<0.001
Puberty stage	0.462	<0.001
BMI	0.026	0.316
Sex	0.131	0.000

$R=0.676$; $R^2=0.458$; $p=0.000$ (β : standardized coefficients β)

Table 6. Multiple regression analysis with serum IGFBP-3 levels as dependent variables, and age, puberty stage, sex and BMI as independent variables.

Variables	β	p
Age	0.328	<0.001
Puberty stage	0.035	0.541
BMI	0.013	0.663
Sex	0.454	0.000

$R=0.538$; $R^2=0.289$; $p=0.000$ (β : standardized coefficients β)

creasing age till stage IV in boys. However, in girls, IGFBP-3 parameters increased with age in all five stages. These results have a little difference from previous reports [21]. It is possibly because of the judgment for puberty stage with different clinicians, and ethnic disparity.

In this study, we have developed a model that can be used in Chinese children for relating serum IGF-1 and IGFBP-3 levels to age, puberty stage, and sex si-

multaneously. From this formula, we can calculate the standard deviation scores of IGF-1, IGFBP-3 according to age in certain puberty stage. A similar model has been proposed in several studies such as for Trukese population.

Using multiple regression analysis, we observed a strong relationship between IGF-1 and age, puberty stage, sex. However, only age but not puberty stage has significant positive effect on IGFBP-3. This

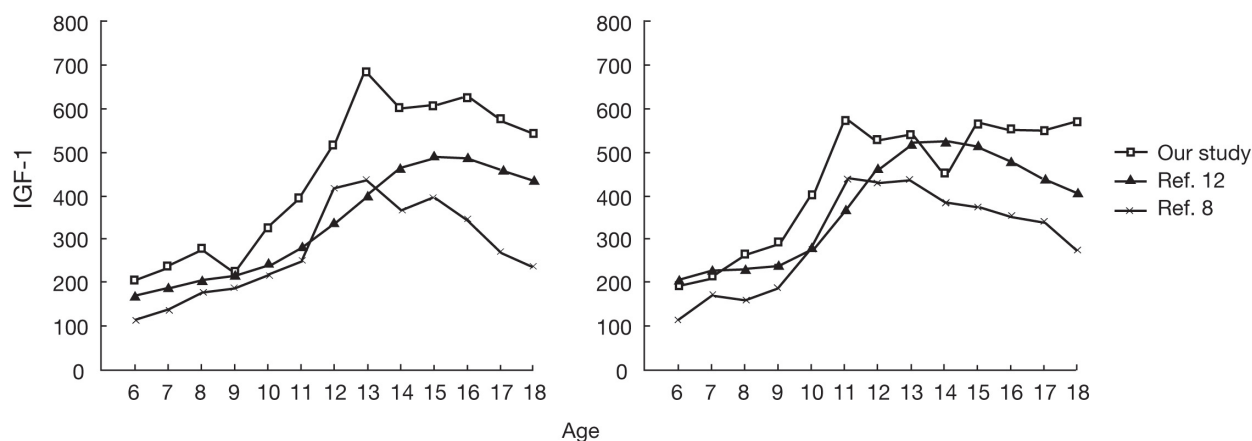


Fig. 3. Serum IGF-1 mean levels (ng/mL) in different population in Ref.8, 12 and our study, comparing the boys (left panel) and girls (right panel) subjects.

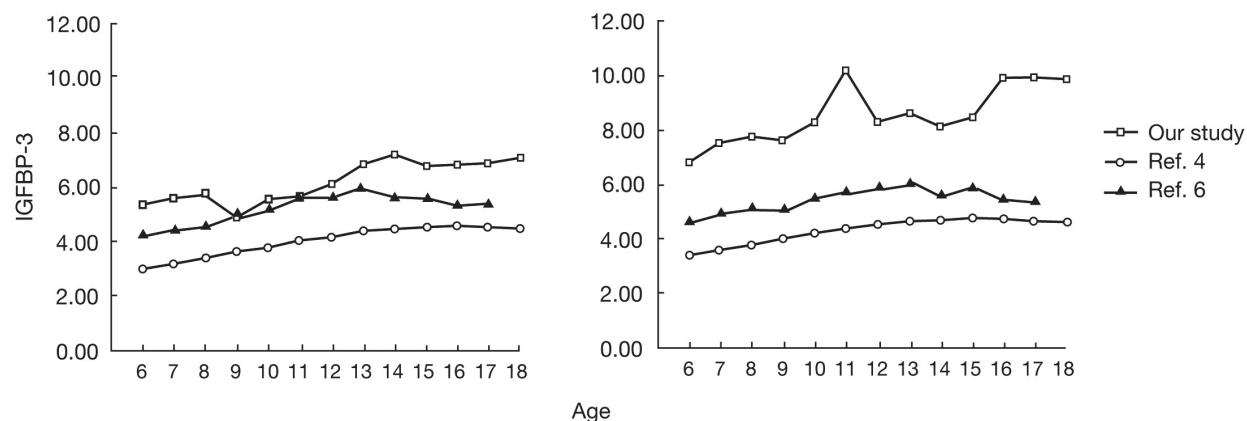


Fig. 4. Serum IGFBP-3 mean levels ($\mu\text{g/mL}$) in different population in Ref.4, 6 and our study, comparing the boys (left panel) and girls (right panel) subjects.

might be explained that IGF-1 levels are more sensitive to GH regulation than IGFBP-3. And the impact of pubertal development is stronger on IGF-1 than on IGFBP-3. The multiple regression analysis showed that BMI has no statistically significant effects on serum IGF-1 and IGFBP-3 values in boys and girls. This result is in line with previous studies in healthy children [12, 15]. We concluded that height or weight have strong positive linear association with age, and when age variable is included in consideration, height, weight, or BMI would not increase the explanatory power of the models. In studies covering over- and underweight patients, body composition influences IGF-1 secretion was found in these patients [22].

Despite using the similar methodology (eg. chemiluminescent assays), even the same commercial kits, the reference values of serum IGF-1 and IGFBP-3

may be different from different laboratories [23]. In our opinion, differences come from genetic background, nutritional status, and preanalytical influences like sample collection and storage, as well as differences between laboratories.

Compared to published reference data, we reached the following conclusions: (1) Serum IGF1 reached peak level around 13 yr in boys, and 11 yr in girls. IGFBP-3 peaked at 14 yr in boys, and 11 yr in girls. This time is about 1-2 yr earlier than previous studies. After peak, IGF-1 and IGFBP-3 decrease slightly or maintain the levels on peak with increasing age. (2) IGF-1 levels tended to be higher in boys compared to girls at the same ages, while IGFBP-3 levels in girls are higher than boys at the same ages. (3) The impact of pubertal development is stronger on IGF-1 than on IGFBP-3. (4) Correcting for the confounding effects

of age, sex and puberty stage, there is a lack of correlation between serum IGF-1 & IGFBP-3 and BMI in healthy children.

This study established age-, sex-, pubertal stage-specific reference values for IGF-1 and IGFBP-3 in Chinese children, revealed the relationship between age, sex, pubertal, BMI and IGF-1, IGFBP-3, and also constructed a model formula to calculate the standard deviation scores of IGF-1, IGFBP-3 according to age in certain puberty stage. These normative data should facilitate child care and growth monitoring for healthy children, also it could aid research worker and clinical

to assess, manage and study GH-IGF-axis-related metabolic disorders.

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