Serum Insulin-like Growth Factor-1 (IGF-1) and Insulin-like Growth Factor Binding Protein-3 (IGFBP-3) in Healthy Thai Children and Adolescents: Relation to Age, Sex, and Stage of Puberty

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Abstract

The authors studied the serum concentrations of insulin-like growth factor-1 (IGF-1) and IGF-binding protein-3 (IGFBP-3) in 260 healthy children and adolescents (115 males, 145 females) aged 5-20 years. The subjects were divided into 12 groups according to age and sex. The serum IGF-1 and IGFBP-3 concentrations increased with age and peaked at age 13-15 years in males, and 11-13 years in females. After the peak concentration, IGF-1 and IGFBP-3 levels declined significantly in males, but were still high in females. Comparing between sexes, the concentrations of IGF-1 and IGFBP-3 were greater in females than males in all age groups. However, when subjects were divided according to the stage of puberty, the different concentrations between sexes were not significant, except for children within Tanner stage V where concentrations of IGF-1 and IGFBP-3 were significantly greater in females than males. Multiple regression analysis demonstrated the age, sex, and stage of puberty-dependent of IGF-1 concentration, and only the age and sex-dependent of IGFBP-3 concentration.

Key word : Growth, Insulin-like Growth Factor-1, IGF-1, Insulin-like Growth Factor Binding Protein-3, IGFBP-3, Puberty

Insulin-like growth factor-1 (IGF-1) is a growth hormone-dependent peptide that mediates the growth-promoting actions of growth hormone [1-3]. IGF-1 is synthesized by a variety of tissues, mainly by the liver. It circulates in plasma in a complex form with insulin-like growth factor binding proteins (IGFBP)[2-4]. The IGF-IGFBP complex acts as a reservoir and a buffer for the growth promoting action of IGF-1. To date, at least 6 IGFBPs have been demonstrated[1-4]. IGFBP-3 is the principal circulating IGFBPs and accounts for over 95 per cent binding of IGF-1 in serum[2-4]. Like

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IGF-1, IGFBP-3 is a growth hormone-dependent peptide and is mainly synthesized by the liver. IGF-1, as well as IGFBP-3, has a long half-life of 15-20 hours and shows minor circadian variation. With all these properties, the single measurement of IGF-1 and IGFBP-3 levels in serum is accepted as an alternative method in evaluating growth hormone secretion and has proven to be useful as a primary evaluation of growth-retarded children[5-8].

The levels of serum IGF-1 and IGFBP-3 have been widely studied in Western countries and Japan. However, these data are limited in Thai children. Recently, Wacharasindhu et al reported the levels of IGF-1 and IGFBP-3 in normal Thai children aged 0-18 years and demonstrated the age-dependent pattern[9]. It was our purpose to add more information of the concentrations of IGF-1 and IGFBP-3 in normal Thai children and adolescents according to age, sex, and stage of puberty and to study whether there is a relationship between these factors and the concentrations of IGF-1 and IGFBP-3.

SUBJECTS AND METHOD

Subjects

Two hundred and sixty children and adolescents aged 5-20 years participated in this study. One hundred and eighty-five subjects (71.2%) were normal children and adolescents who enrolled in a program of goiter survey. All of these subjects had a normal thyroid function test, negative thyroid antibodies, and had no history of thyroid disease in their family. Seventy-five subjects were children and adolescents who had a blood test for hepatitis before going abroad or before a hepatitis vaccination. All of the subjects had negative hepatitis antigen and had no liver disease.

The samples were collected in the morning between 9-12 a.m. without fasting. The sera were separated and stored at -20°C before the time of analysis.

Growth assessment

All subjects were in good health and had no history of chronic illness. Height was measured in a standing position using Harpenden stadiometer. Weight was measured on a light cloth using a beam balance scale. The detail of measurement was 0.1 cm for height and 0.1 kg for weight. All subjects had height and weight between the 10th and 90th centile of the standard growth chart of Thai children[10], and weight for height between 80 to 120 per cent. Puberty was assessed and recorded according to the method of Tanner[11].

All participants and their parents gave their informed consents. This study was approved by the Ethics Committee of Prince of Songkla University.

Method

The procedure employed a two-site immunoradiometric assay (IRMA) described by Miles et al[12]. The DSL-5600 and DSL-6600 (Diagnostic Systems Laboratories, Texas, U.S.A.) were used for assays of IGF-1 and IGFBP-3, respectively. The IRMA is a non-competitive assay in which the analyte to be measured is sandwiched between two antibodies. The first antibody is immobilized to the inside wall of the tubes. The other antibody is radiolabelled for detection.

IGF-1 assay (DSL-5600)

The DSL-5600 IRMA includes an acid ethanol extraction step in which IGF-1 is separated from its binding protein in serum. This step is essential for accurate determination of IGF-1. Briefly, a serum sample of 100 µL was used and 400 µL of extraction solution was added. The mixture was incubated for 30 minutes at room temperature, then centrifuged at 2,500 rpm for 60 minutes at 4°C. The 100 µL clear supernatant was transferred to the second labelled tube and neutralized by 500 µL of neutralizing solution. The 50 µL neutralized sample extract was then used, with 200 µL of anti-IGF-1 added. After mixing by shaking gently, the mixture was incubated at room temperature for 3 hours on a shaker set at 180 rpm. The tube was decanted by simultaneous inversion with a spongy rack, then struck on absorbent material to facilitate complete drainage for 1-2 minutes. The tube was blotted to remove any droplets before returning to the upright position. After washing 3 times with 3 ml of deionized water, the tube was counted by a gamma counter for one minute.

IGFBP-3 assay (DSL-6600)

The sample was diluted 1 : 50 (10 µL serum + 500 µL IGFBP-3 sample diluent). The 50 µL of diluted solution was transferred and 200 µL of anti-IGFBP-3 was added. The mixture was incubated at room temperature overnight (18-24 hours) on a shaker set at 180 rpm. The tube was decanted by

simultaneous inversion with a spongy rack, struck on absorbent material and then blotted for 1-2 minutes to remove any droplets before returning to the upright position. After washing 3 times with 3 ml of deionized water, the tube was counted by a gamma counter for one minute. The result was multiplied by a dilution factor of 50.

Statistical analysis

Data were presented as mean ± standard deviation, and centile curves. Statistical comparisons were made with the student's *t* test. P values < 0.05 were considered significant. Multiple regression was used to analyse the factors affecting the concentrations of IGF-1 and IGFBP-3.

RESULTS

Age dependence of IGF-1 and IGFBP-3

The concentrations of serum IGF-1 and IGFBP-3 increased with age in both males and females as shown in Fig. 1 and 2 (centiles) and Table 1 (mean ± standard deviation). The peak concentration of IGF-1 occurred at 13-15 years in males and 11-13 years in females. Like IGF-1, IGFBP-3 levels reached the peak at an earlier age in females than in males (11-13 years in females and 15-17 years in males). After the age of peak concentration, IGF-1 and IGFBP-3 levels declined significantly in males, but were still high and not significantly different from the peak concentration in females.

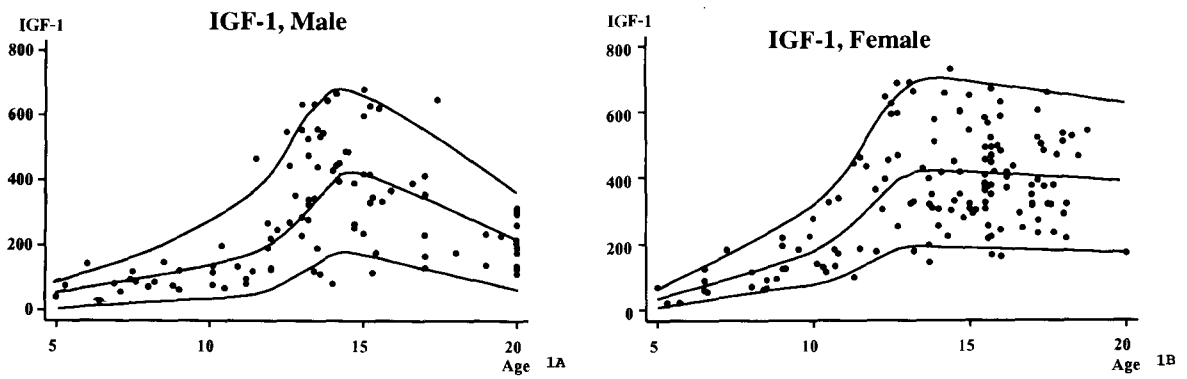

Fig. 1. The centile curves of IGF-1 concentrations in males (A) and females (B) The middle line showed the level of 50th centile. The lower and upper lines showed the 5th and 95th centile, respectively.

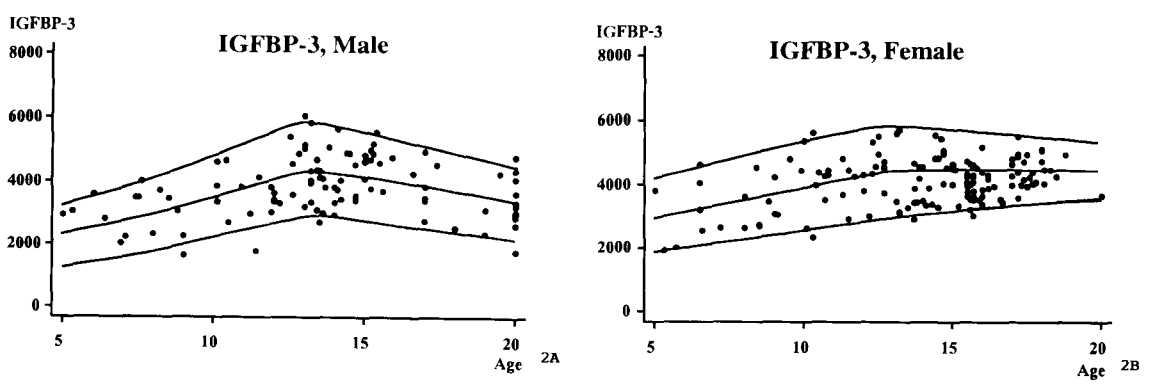

Fig. 2. The centile curves of IGFBP-3 concentrations in males (A) and females (B).

Table 1. The levels (mean ± standard deviation) of serum IGF-1 (ng/ml) and IGFBP-3 (ng/ml) of males and females in different age groups.

Age	Male			Female		
	N	IGF-1	IGFBP-3	N	IGF-1	IGFBP-3
5.1-9.0	13	85.6 ± 9.7	3085 ± 169	14	80.7 ± 11.1	3188 ± 232
9.1-11.0	19	115.2 ± 15.9*	3360 ± 387	16	189.0 ± 17.8*	4051 ± 228
11.1-13.0	14	254.5 ± 39.7*	3639 ± 243#	17	422.2 ± 42.5*	4330 ± 172#
13.1-15.0	31	404.9 ± 29.0	4151 ± 158	29	416.9 ± 32.5	4186 ± 160
15.1-17.0	15	399.9 ± 43.3	4560 ± 141##	42	401.0 ± 19.8	4034 ± 75##
17.1-20.0	23	244.5 ± 24.6*	3409 ± 168##	27	395.4 ± 24.3*	4261 ± 92##

* $p < 0.01$ for IGF-1 between males and females
\# $p = 0.025$ for IGFBP-3 between males and females
\## $p < 0.001$ for IGFBP-3 between males and females

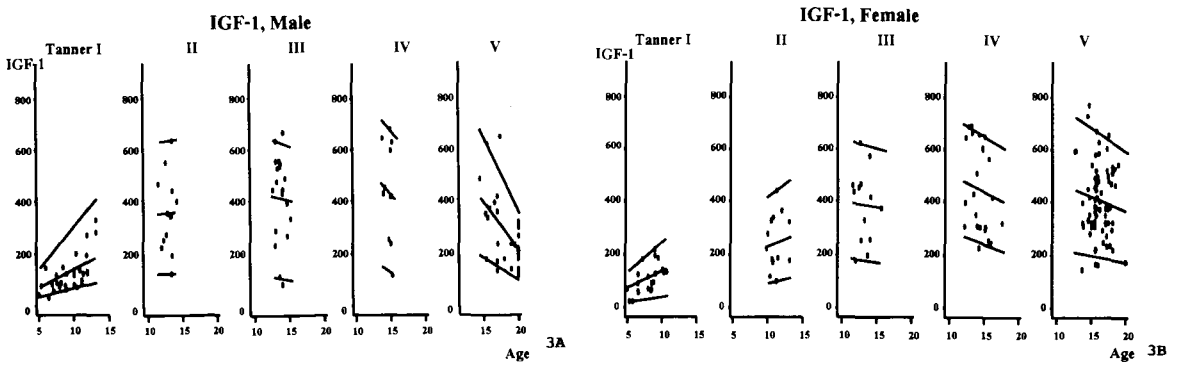

Fig. 3. The centile curves of IGF-1 concentrations according to the Tanner stage of puberty in males (A) and females (B).

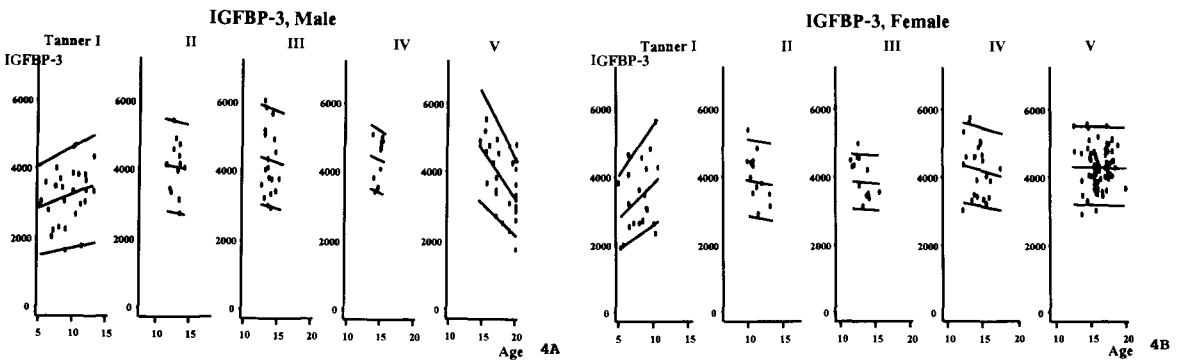

Fig. 4. The centile curves of IGFBP-3 concentrations according to the Tanner stage of puberty in males (A) and females (B).

Table 2. The mean ages (years) and the levels (mean ± standard deviation) of serum IGF-1 (ng/ml) and IGFBP-3 (ng/ml) of males and females in different stages of puberty.

Stage puberty (M/F)	Male			Female		
	Age	IGF-1	IGFBP-3	Age	IGF-1	IGFBP-3
I (34/30)	8.5±0.7	114.5±11.8	3152±133	7.2±0.5	98.4±9.5	3163±182
II (13/13)	12.9±1.0+	321.8±40.4*	4063±209	11.1±0.8+	242.0±28.8*	4029±192
III (20/13)	13.9±1.2+	406.1±36.1	4211±212	12.5±09+	395.4±38.4	4005±159
IV (18/23)	14.8±0.5	443.3±55.8	4431±179	13.5±0.7	452.1±34.8	4252±165
V (30/66)	18.2±1.0+	278.2±24.7**	3711±171#	16.7±0.8+	408.1±16.0**	4189±69#

\+ $p < 0.02$ for age between males and females
* $p = 0.04$ for IGF-1 level between males and females
** $p < 0.001$ for IGF-1 level between males and females
\# $p = 0.003$ for IGFBP-3 level between males and females

Sex dependence of IGF-1 and IGFBP-3

In prepubertal children, the concentrations of IGF-1 and IGFBP-3 were not significantly different between males and females. After age 9, the levels of IGF-1 and IGFBP-3 were greater in females than in males with a statistical difference at age 9-11 years, 11-13 years, and 17-20 years for IGF-1 and at age 11-13 years, 15-17 years, and 17-20 years for IGFBP-3.

Relation to stage of puberty

To demonstrate the effect of puberty on the serum levels of IGF-1 and IGFBP-3, the subjects were rearranged according to the Tanner staging of puberty for males and females as shown in Fig. 3, 4 and Table 2. In the same Tanner stage of puberty, the mean ages of females were younger than males with a significant difference in children within Tanner stages II, III, and V. The younger age of females than males in Tanner stage II clearly showed that females entered puberty at an earlier age than males. The concentrations of IGF-1 and IGFBP-3 gradually increased with Tanner stage of puberty and peaked at Tanner stage IV. In Tanner stage V, the levels of IGF-1 and IGFBP-3 decreased significantly from the peak concentrations in males, but were still high and not significantly different from the peak concentration in females. Comparing between sexes, the levels of IGF-1 and IGFBP-3 showed no difference, except for Tanner stage II in which the level of IGF-1 was significantly greater in males than females, and Tanner stage V in which the levels of IGF-1 and IGFBP-3 were significantly greater in females than males.

It is of note that the prepubertal concentration and the peak concentration of IGF-1 was approximately 5 times different in both sexes, whereas, that of IGFBP-3 was approximately only 1.5 times different. This observation suggested a lesser variation in the concentration of IGFBP-3 than IGF-1. In addition, the concentrations of IGF-1 and IGFBP-3 showed a linear correlation in both sexes as shown in Fig. 5 ($r = 0.7$; $p < 0.01$).

Effect of menstruation in females

To demonstrate the effect of menstruation, we then focused on 46 females within Tanner stage III and IV. We divided the subjects into 2 groups : those who were non-menstruating and those who already had menstruation. The mean ages, the concentrations of IGF-1 and IGFBP-3 were compared as shown in Table 3. The mean age, the concentrations of IGF-1 and IGFBP-3 were all significantly lower in non-menstruating females than the menstruated females ($p = 0.01$, 0.04, and 0.02, respectively). However, when age was adjusted, the difference between the groups was insignificant ($p = 0.07$ and 0.078 for IGF-1 and IGFBP-3, respectively).

Multiple regression analysis

Multiple regression analysis was applied to demonstrate what factors had effect on the concentrations of IGF-1 and IGFBP-3. The results showed that sex, age, and stage of puberty affected the concentration of IGF-1, whereas, only sex and age, but not stage of puberty, affected the concentration of IGFBP-3.

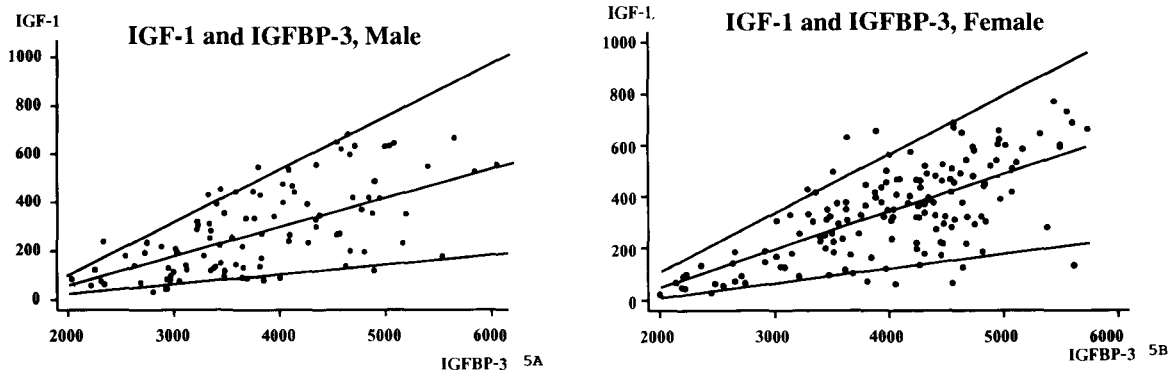

Fig. 5. The linear correlation of IGF-1 and IGFBP-3 in males (A) and females (B) ($r = 0.7$; $p < 0.01$* for both curves).

Table 3. Comparison between menstruating and non-menstruating Tanner stage III and IV females in age, serum IGF-1 and IGFBP-3 levels (mean ± standard deviation).

	N	Age	IGF-1	IGFBP-3
Non-menstruating	16	12.3 ± 0.9	337.8 ± 34.6	3812 ± 182
Menstruating	30	13.7 ± 0.5	450.7 ± 314	4408 ± 140
p value	-	0.01	0.04	0.02
p value when adjusted for age	-	-	0.07	0.078

DISCUSSION

Our results showed that the concentration of IGF-1 depended on age, sex, and stage of puberty, and the concentration of IGFBP-3 depended only on age and sex. The age-dependent IGF-1 and IGFBP-3 were clearly shown by the increasing level with age in both sexes. The sex-dependent was shown by the greater concentrations of IGF-1 and IGFBP-3 in females than males at almost all ages. Stage of puberty had an effect on the concentration of only IGF-1, but not the IGFBP-3, which could be explained by the smaller variation difference of IGFBP-3 than the IGF-1 levels.

The age, sex, and stage of puberty-dependent IGF-1 and IGFBP-3 concentrations can be explained by the distinct pattern of growth and puberty between males and females. As already known, puberty, along with the peak growth velocity, occurs about 2 years earlier in females than males[10,13-15]. The increased concentrations of sex steroids during the time of puberty then augment the growth hormone secretion which result in increased production of IGF-1 and IGFBP-3[16-18]. Furthermore, the sex steroids may have a direct action on the production of IGF-1 and IGFBP-3. In our study, the influence of sex steroids on IGF-1 and IGFBP-3 concentrations was clearly demonstrated as the levels increased according to the stage of puberty. However, the significant effect of sex steroids was found only on the concentration of IGF-1, but not the IGFBP-3. The peak concentrations of IGF-1 and IGFBP-3 occurred at age 15 years in males and age 13 years in females, which were close to the mean ages of children in Tanner stage IV or mid-puberty in both sexes. When we compared the concentrations of IGF-1, as well as the IGFBP-3, between males and females in the same stage of puberty, we found a significant difference of IGF-1 only in subjects within Tanner stage II and stage V, and the difference of IGFBP-3 only in subjects within Tanner stage V. The signifi-

Table 4. Multiple regression analysis of factors affecing serum levels of IGF-1 and IGFBP-3.

Factors	p value for IGF-1	p value of IGFBP-3
Sex	0.001	0.001
Age	< 0.001	0.003
Puberty	< 0.001	0.339

cant lower level of IGF-1 in females than males in Tanner stage II is probably explained by the almost 2 years younger age of females, while females in other groups were only 1.2 to 1.4 years younger than males. For Tanner stage V, the significant greater concentrations of IGF-1 and IGFBP-3 in females is not exactly known. A possible explanation is the distinct type and pattern of sex steroid secretion. The sex steroids in females are estrogens and their secretions are cyclic related with menstruation. The sex steroids in males are androgens and their secretions are relatively more constant, have less fluctuation, and are not cyclic. Numerous studies have shown a higher growth hormone secretion in females than in males which was postulated to be a result of a greater stimulatory effect of estrogens on hypothalamic-pituitary axis or a decrease in the metabolic clearance rate of growth hormone in women[19,20]. However, the effect of menstrual cycle in females on the concentrations of IGF-1 and IGFBP-3 was insignificant when age was adjusted.

The concentrations of IGF-1 and IGFBP-3 in our study was approximately 50-100 ng/ml and 200-400 ng/ml, respectively, lower than those in the studies from Western countries[21,22]. As already known, the concentrations of IGF-1 and IGFBP-3 are affected by various factors such as nutritional status, exercise, and illness[1-4]. All these factors effect the amount of growth hormone secretion, as well as the IGF-1 and IGFBP-3 production. Hence, the lower concentration of IGF-1 and IGFBP-3 in our population than Caucasians is possibly explained by the difference in ethnic[23], socioeconomic status, nutritional intake (less protein, less dairy products), and social life-style (less activity, less exercise). The other important fact is a different measuring method. Our study used IRMA, whereas most of the Western studies used RIA[24]. However, this can not be the explanation since the IRMA method is a more sensitive method than RIA. Hence, the lower concentration measured by the IRMA method should be a much lower concentration than when measured by the RIA method.

In conclusion, we demonstrated the effect of age, sex, and stage of puberty on the serum concentration of IGF-1 and IGFBP-3. All these factors should be included when evaluating children with an abnormal growth pattern[25-27]. Furthermore, we emphasize to have the standard IGF-1 and IGFBP-3 concentrations of Thai children for evaluation of the growth hormone status in our own population.

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ระดับของ insulin-like growth factor-1 (IGF-1) และ insulin-like growth factor binding protein-3 (IGFBP-3) ในซีรั่มของเด็กและวัยรุ่นไทยปกติ : ความสัมพันธ์กับอายุ เพศ และระยะของการเข้าสู่วัยหนุ่มสาว

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ได้ทำการศึกษาระดับของ insulin-like growth factor-1 (IGF-1) และ insulin-like growth factor binding protein-3 (IGFBP-3) ในเด็กและวัยรุ่นไทยที่มีสุขภาพดี อายุ 5-20 ปี จำนวน 260 คน (ชาย 115 คน หญิง 145 คน) โดยแบ่งออกเป็น 12 กลุ่ม ตามเพศและอายุต่างๆ ผลการศึกษาพบว่าระดับ IGF-1 และ IGFBP-3 เพิ่มขึ้นตามอายุจนถึงระดับสูงสุดที่อายุ 13-15 ปีในเพศชาย และอายุ 11-13 ปีในเพศหญิง หลังจากนั้นระดับจะลดลงอย่างมีนัยสำคัญทางสถิติในเพศชาย ในขณะที่ระดับยังคงสูงในเพศหญิง ได้ทำการเปรียบเทียบระหว่างเพศพบว่าระดับ IGF-1 และ IGFBP-3 ในเพศหญิงสูงกว่าในเพศชายอย่างมีนัยสำคัญทางสถิติในทุกกลุ่มอายุ เมื่อทำการจัดกลุ่มใหม่โดยแบ่งตามระยะของการเข้าสู่วัยหนุ่มสาว พบว่าไม่มีความแตกต่างของระดับ IGF-1 และ IGFBP-3 ระหว่างเพศ ยกเว้นในกลุ่มที่มีการเปลี่ยนแปลงของการเข้าสู่วัยหนุ่มสาวระยะ Tanner stage 5 ที่ระดับ IGF-1 และ IGFBP-3 ในเพศหญิงสูงกว่าเพศชายอย่างมีนัยสำคัญทางสถิติ การวิเคราะห์โดยใช้ multiple regression พบว่า อายุ เพศ และระยะของการเข้าสู่วัยหนุ่มสาวมีผลต่อระดับ IGF-1 ในขณะที่อายุและเพศเท่านั้นที่มีผลต่อระดับ IGFBP-3

คำสำคัญ : การเจริญเติบโต, Insulin-lkie Growth Factor-1, IGF-1, Insulin-like Growth Factor Binding Protein-3, IGFBP-3, การเข้าสู่วัยหนุ่มสาว

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