15

Standard Gonadotropin-Suppressive Therapy in Japanese Girls with Idiopathic Central Precocious or Early Puberty Does Not Adversely Affect Body Composition

Toshihide Kubo
National Hospital Organization, Okayama Medical Center
Japan

1. Introduction

Estrogen deprivation, for instance after ovariectomy or natural menopause, is associated with significant bone loss in adult women. (Lindsay, 1995) Gonadotropin-releasing hormone agonist (GnRHa) inhibits hypothalamo-pituitary-gonadal hormone secretion and gradually reduces the estrogen level. (Wacharawsindhu et al., 2006) Consequently, decreases in bone mineral density, which are also observed after ovariectomy and natural menopause, have been observed during GnRHa therapy in women with endometriosis and men with benign prostatic hyperplasia. (Goldray et al., 1993) Moreover, women who were treated with this analog showed body composition changes, including a decrease in lean mass and an increase in fat mass, which resemble the body changes that occur during the menopause. (Revila et al., 1998)

Meanwhile, GnRHa has also been the treatment of choice for central precocious puberty (CPP) since the mid-1980s. (Crowley et al., 1981) Many of the previous studies on the auxological effects of GnRHa treatment on CPP have focused on assessing the patient's final height, whereas much less attention has been paid to changes in their weight and body composition. (Arrigo et al., 2004)

However, concern has been expressed that CPP might be associated with increases in body mass index (BMI) both at the initial presentation and during GnRHa treatment (Boot et al., 1998) and that individuals with the condition are prone to developing obesity. This concern is supported by adult cases that were treated with GnRHa, as described above.

On the other hand, it is well known that BMI and percentage body fat increase during puberty. Consequently, gonadotropin-suppressive therapy can theoretically halt the progression to obesity by inhibiting pubertal development.

Recently, there have been many reports about the changes in body composition that occur in children with CPP who are treated with GnRHa (Wacharsindhu et al., 2006, Arrigo et al., 2004, Boot et al., 1998, Feuillan et al.,1999, Palmert et al., 1999, Chiumello et al., 2000, van der Sluis et al., 2002, Paterson et al., 2004, Oosdijk et al., 1996, Traggiai et al., 2005, Herger et al., 1999, Pasuquino et al., 2008). Some reports have shown that obesity occurs at a high frequency among children with CPP (Arrigo et al., 2004, Feuillan et al., 1999, Palmert et al.,

1999, Chiumello et al., 2000, van der Sluis et al., 2002, Paterson et al., 2004). However, most of these reports studied populations in Western countries, and almost none investigated Asian children (Wacharsindhu et al., 2006). Furthermore, in these studies, GnRHa was administered at higher doses (Boot et al., 1998, Chiumello et al., 2000, van der Sluis et al., 2002) than are used in the standard gonadotropin-suppressive therapy protocol that is currently in operation in Japan. With some exceptions, all these reports showed that obesity is aggravated during GnRHa therapy (Wacharsindhu et al., 2006, Boot et al., 1998, Chiumello et al., 2000, van der Sluis et al., 2002, Paterson et al., 2004, Oosdijk et al., 1996, http://www.iotf.org/documents/iotfsocplan251006.pdf). Therefore, we assessed the effects of the standard gonadotropin-suppressive therapy protocol that is currently used in Japan on body composition in order to review the optimal dose of GnRHa.

The aims of the present study were to prospectively evaluate whether obesity occurs at a high frequency among Japanese children with CPP and to longitudinally evaluate the body composition of Japanese children with CPP before and during GnRHa therapy.

2. Subjects and methods

2.1 Patients

Eighteen patients participated in the study. At diagnosis, all of the patients had a history of increased growth velocity, breast development of Tanner stage 2 or more, and a bone age that was more than 1 yr above their chronological age. Ten girls had idiopathic central precocious puberty (ICPP), and 8 girls had idiopathic central early puberty (ICEP). The diagnosis of ICPP was made based upon the onset of breast development before the age of 7 yr and 6 mo, the generation of pubic hair before the age of 9 yr, or the onset of menses before the age of 10 yr and 6 mo, according to the diagnostic criteria currently used in Japan. ICEP was defined as the appearance of pubertal signs between 8 -10 yr of age. Furthermore, neither set of patients showed any evidence of hypothalamo-pituitary lesions on magnetic resonance imaging or additional conditions that might have affected their body mass index (BMI).

The median age at the start of treatment was 8.3 yr (range: 6 to 11). All patients received leuprolide acetate (LUPRON DEPOT, Takeda, Osaka, Japan) at an initial dose of 30 μg/kg, which was administered subcutaneously every 4 weeks according to the standard gonadotropin-suppressive therapy currently used in Japan.

2.2 Methods

Standard anthropometric measurements were taken at the baseline and during the 2-year GnRHa treatment period. BMI was calculated as weight (kg)/height (m^2), compared with age- and sex-matched reference values, and expressed as a standard deviation score (SDS) according to the method of Inokuchi (Inokuchi, 2009). The percentage of overweight (POW) was calculated as 100 x (the measured weight – normal weight)/normal weight (%). Normal weight data were derived from the 1990 Ministry of Health and Welfare data (Yamazaki et al., 1994). A POW of ≥ 20% was considered to indicate obesity (Asayama et al., 2003). Pubertal development was determined according to the method of Tanner (Tanner & Whitehouse, 1976).

Pituitary-gonadal axis function was considered to be adequately suppressed during treatment if the concentrations of LH and E2 were maintained within the prepubertal normal ranges of our laboratory; i.e., if a) the basal serum LH level was below 0.5 mIU/ml and b) the basal serum E2 level was below 10 pg/ml. In the patients that demonstrated

incomplete suppression, the dose of leuprolide acetate was increased to 150 μg/kg. Bone age (BA) was assessed by one investigator using an x-ray of the left hand, according to the method of Greulich and Pyle (Greulich & Pyle, 1959).

2.3 Statistical analysis

For statistical purposes, the Wilcoxon test was used when appropriate in order to estimate the significance of differences between groups. The correlations between individual values were examined using Pearson's test. All values are given as the mean ± S.E. The significance threshold was set at $p < 0.05$.

3. Results

3.1 Prevalence of obesity

In our recent study of 18 girls with CPP or early puberty, five girls (27.8%) were diagnosed with obesity because their BMI values were higher than the 95th centile (Inokuchi, 2009) at the initiation of therapy. Moreover, the BMI standard deviation score (SDS) for chronological age (CA) was higher than zero in 14 (77.8%) patients, and the mean BMI SDS for CA was 1.07±0.32 at the baseline. Even when it was corrected for bone age (BA), the BMI SDS was still higher than zero in 9 (50.0%) patients, and the mean BMI SDS was 0.33±0.25 at the baseline. On the other hand, the POW was higher than 20% (indicating obesity) in 5 patients (27.8%) at the baseline.

3.2 BMI and POW during follow-up

The mean BMI was significantly increased after 1 year and increased further afterwards (Fig.1). BMI was higher than the 95th centile in 5 patients (27.8%) at the initiation of therapy, which was also true after 2 years treatment.

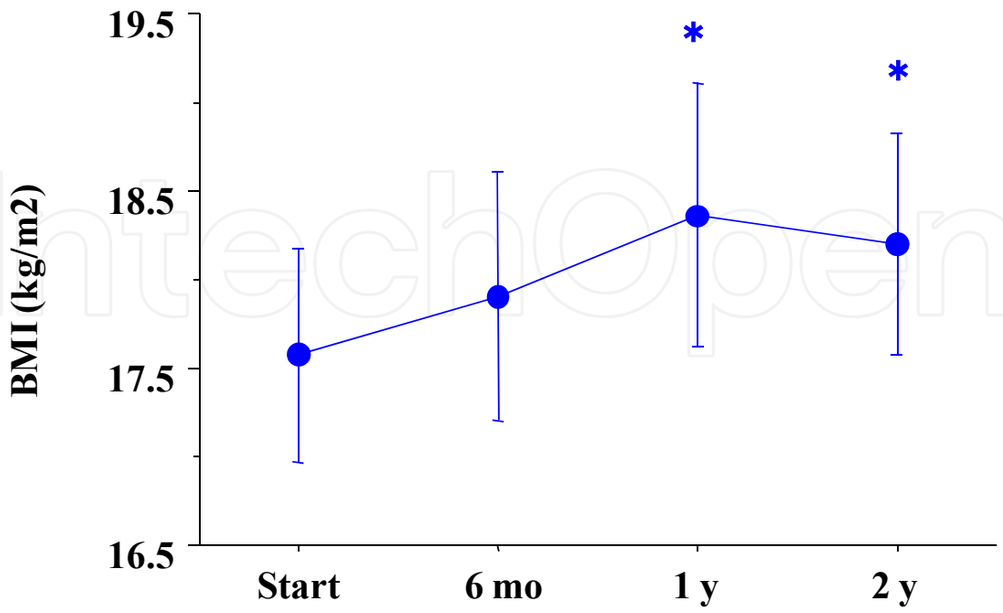


Fig. 1. Changes in BMI during GnRHa therapy

The BMI SDS for CA was higher than zero in 14 patients (77.8%) at the initiation of therapy, which was also the case for 13 individuals (72.2%) after 2 years treatment. Furthermore, 5 patients had BMI SDS of higher than 2 SD at the baseline, and 4 patients had BMI SDS of higher than 2 SD after 2 years treatment. The mean BMI SDS for CA was 1.07 ± 0.32 at the baseline and changed little during the therapy (Fig. 2).

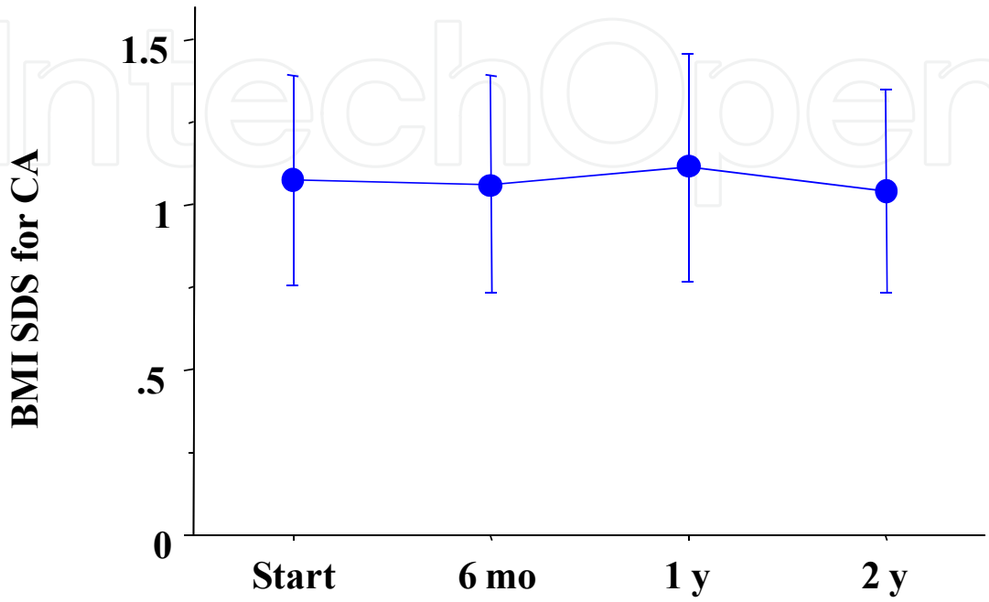


Fig. 2. Changes in the BMI SDS for CA during GnRHa therapy

On the other hand, the mean BMI SDS for BA was 0.33 ± 0.25 at the baseline and slightly but not significantly increased during the GnRHa therapy (Fig.3).

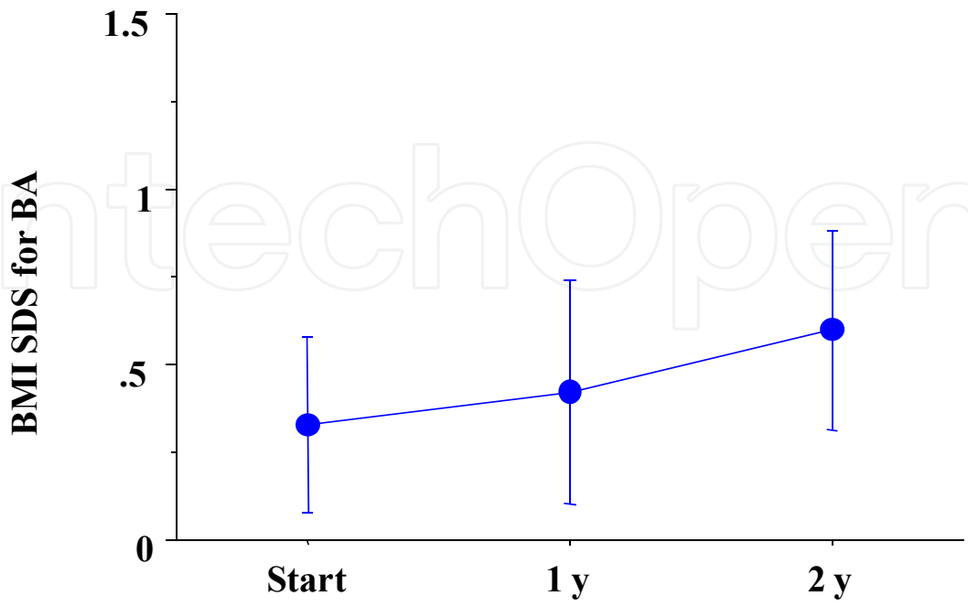


Fig. 3. Changes in the BMI SDS for BA during GnRHa therapy

In addition, the POW was higher than 20% (indicating obesity) in 5 patients (27.8%) at the baseline, which was also true after 2 yrs treatment. The mean POW was 8.2 ± 4.0% at the baseline and changed little during the GnRHa therapy (Fig. 4).

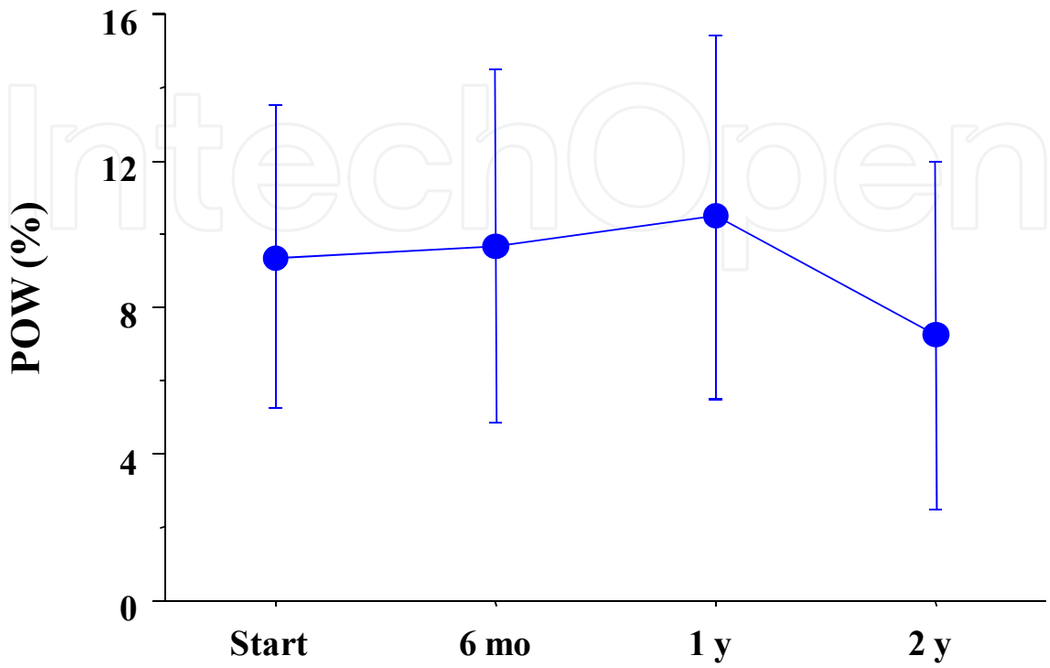


Fig. 4. Changes in POW during GnRHa therapy

3.3 Correlation between the BMI SDS at the start of treatment and that during treatment for CA and BA

Regression analysis showed that the BMI SDS for CA and BA at the start of treatment were positively correlated with those during treatment (Table 1, 2).

	r
After 6 months of therapy	0.963
After 1 year of therapy	0.971
After 2 years of therapy	0.975

Table 1. Relationship among BMI SDS for CA during therapy

	r
After 1 year or therapy	0.947
After 2 years of therapy	0.926

Table 2. Relationship among BMI SDS for BA during therapy

4. Discussion

Many reports have shown that obesity occurs at a high frequency among children with CPP. (Arrigo et al., 2004, Boot et al., 1998, Feuillan et al., 1999, Palmert et al., 1999, Chiumello et al., 2000, van der Sluis et al., 2002, Paterson et al., 2004) Feuillan et al. reported that the mean BMI of 18 girls with precocious puberty due to hypothalamic hamartoma (HH) and 32 with ICPP was higher than normal before GnRHa treatment (Feuillan et al., 1999), and Arrigo et al. reported that 23.6% of the 101 girls with ICPP that they studied were obese before the start of therapy. (Arrigo et al., 2004) Our results confirm that obesity is a common problem in children with CPP in Japan. Indeed, in this study, a quarter of our patients were found to be obese according to both BMI and POW before the start of therapy. Moreover, the BMI SDS for CA and BA were higher than zero in more than half of the patients at the baseline. Since the prevalence of obesity in girls in later childhood is 14.3% in Japan (http://www.iotf.org/documents/iotfsocplan251006.pdf), the above figure indicates that the prevalence of obesity in children with CPP is unusually high.

Although several reports have stated that obesity is a common problem in girls with CPP, as mentioned above, the reason why so many girls with CPP have an increased BMI is unclear. A decrease in lean body mass and an increase in fat mass leads to obesity. Chiumello et al. suggested that girls with CPP undergo a shortened period of prepubertal lean mass development and so possess an insufficient lean body mass, leading to obesity. (Chiumello et al., 2000) Recently, Arrigo et al. hypothesized that the pre-treatment increase in BMI is caused pubertal hormonal changes and secondary changes in body fat rather than CPP itself, as in their series they found that the suppression of pituitary-gonadal axis function was accompanied by a significant decrease in excess weight (Arrigo et al., 2004). However, our results showed that the suppression of the pituitary-gonadal axis did not bring about a significant change in excess weight, as described below. Furthermore, as for the number of patients whose BMI SDS for CA was higher than zero, it decreased from 14 (77.8%) to 9 (50%) after correcting for BA, and the mean BMI SDS for CA (1.07±0.32) also decreased to 0.33±0.25 after correcting for BA at the start of treatment. Moreover, Oostdijk et al. reported that the BMI SDS for CA of CPP patients was higher than that of the reference population, whereas their BMI SDS for bone age (BA) was normal at the start of treatment. (Oosdijk et al., 1996) Taken together, the BMI of children with CPP might be appropriate for the onset of adolescence, even though they are indicated to be overweight by BMI calculations. Therefore, it is reasonable to suggest that the pre-treatment overweightness observed in CPP girls is due to pubertal hormonal changes and secondary changes in body fat, rather than being a cause of their CPP.

As for the progression of baseline overweightness in CPP patients, the available data in the literature are very inconsistent; however, many reports have suggested that obesity progresses in this group (Wacharsindhu et al., 2006, Boot et al., 1998, Chiumello et al., 2000, van der Sluis et al., 2002, Paterson et al., 2004, Oosdijk et al., 1996, Traggiai et al., 2005). Oostdijk et al. treated 31 girls with CPP with triptorelin for a mean period of 3.4 years. (Oosdijk et al., 1996) The mean BMI SDS for CA at the start of treatment was higher than that of the reference population, and it did not change significantly during treatment. However, the mean BMI SDS for BA at the start of treatment was normal and increased during treatment. Boot et al. treated 32 girls and 2 boys with CPP or early puberty with leuprolide-acetate for 2 years. (Boot et al., 1998) Their lean tissue mass SDS decreased significantly during treatment, whereas their fat mass SDS and percentage body fat SDS

increased. In addition, their mean BMI SDS was higher than zero at the baseline and increased during treatment. Chiumello et al. treated 14 girls and 2 boys with CPP with leuprolide and triptorelin for at least 1 year. (Chiumello et al., 2000) They concluded that fat mass is increased by GnRHa therapy and that this could lead to obesity; therefore, they suggested that CPP patients undergo a shortened period of pubertal lean mass development and that while the progression of puberty in these patients is associated with increases in fat and lean mass, only the latter is blocked by the "menopausal effect" or the GnRHa therapy itself. van der Sluis et al., who belong to the same group as Boot, reported 47 patients (36 girls and 11 boys) with CPP or early puberty who received leuprolide-acetate for a mean period of 2.7 years. (van der Sluis et al., 2002) In this cohort, BMI SDS increased significantly during treatment, whereas lean body mass decreased significantly during treatment, and percentage body fat increased. Paterson et al. reported 46 girls with CPP or early puberty who received goserelin for a mean period of 1.6 years. (Paterson et al., 2004) In this group, there was a marked increase in BMI following treatment. On average, the girls were fatter than the general population before treatment (BMI SDS: 0.93) and were significantly fatter (BMI SDS: 1.2) than the general population after the completion of therapy. Before treatment, 19 (41%) girls were overweight (BMI > 85th centile), 13 (28%) of whom were obese (BMI > 95th centile), which rose to 27 (59%) overweight patients, of whom 18 (39%) were obese, after the completion of therapy. Wacharasindhu et al. treated 10 Thai girls with CPP for a period of 1 year and reported that their percentage fat values increased significantly. (Wacharsindhu et al., 2006) So far, this is the only report in an Oriental population.

In contrast, some authors have reported no change throughout the observation period. (Palmert et al., 1999, Herger et al., 1999, Pasuquino et al., 2008) For example, Heger et al. treated 50 girls with CPP with depot triptorelin for a mean period of 4.4 years and reported that their BMI SDS values at pretreatment, at the end of treatment, and at final height were not significantly different. (Herger et al., 1999) Palmert et al. treated 96 girls and 14 boys with CPP with deslorelin or histrelin for 36 months. (Palmert et al., 1999) Among the girls, multiple regression analysis indicated that the BMI SDS for CA at the pretherapy visit was the greatest predictor of the BMI SDS for CA at the end of treatment. They concluded that the administration of GnRHa did not influence the progression of adolescent CPP patients toward obesity. Pasquino et al. reported 87 girls with CPP who received depot triptorelin for a mean period of 4.2 years. (Pasuquino et al., 2008) Their BMI increased markedly during treatment, but their BMI SDS for CA did not change significantly. In addition, 14.3% of the girls were overweight and 9.1 % were obese at the start of therapy, and both categories contained 11.7% of patients at the discontinuation of treatment. Although the patients' overall BMI increased, they remained in the same BMI centile and had the same BMI SDS throughout the treatment period. Regression analysis showed that the BMI SDS for CA at the end of treatment was positively correlated with the BMI SDS for CA at the start of treatment. As a result, they concluded that GnRHa treatment did not result in a significant BMI increase.

On the other hand, Arrigo et al. reported 101 girls with CPP who received decapeptyl depot for over 2 years. (Arrigo et al., 2004) As described above, a quarter of the girls were classified as obese at the start of therapy, and only 4% of them were still obese at the end of therapy. BMI SDS did not increase in any of the patients during the therapy period. In fact, both the mean BMI SDS and obesity prevalence significantly decreased during the treatment period. This is the only report to state that BMI and the prevalence of obesity decreased during GnRHa therapy.

In our study, although on the whole BMI increased, the SDS for both CA and BA remained the same throughout the treatment period. Moreover, POW also changed little during the therapeutic period, as reported by Chiumello (who described it as relative body weight) (Chiumello et al., 2000). It should be noted that we used a small amount of GnRHa in relation to body weight in accordance with the standard treatment protocol used in Japan, as described above (we used 2.5mg or less) and were able to control CPP. In the reports from Western countries in which the same leuprolide acetate drug was used, a dose of 3.75mg was used from the first stage onwards, and all showed a significant increase in BMI during treatment (Boot et al., 1998, Chiumello et al., 2000, van der Sluis et al., 2002). The doses used in other reports were also larger than the dose that is usually administered in Japan.

In this study, regression analysis showed that the BMI SDS for both CA and BA during treatment were positively correlated with those observed at the start of treatment, as reported by Pasquino et al. (Pasuquino et al., 2008) and Palmert (Palmert et al., 1999). Therefore, we consider that the initial BMI SDS is a predictor of BMI SDS at subsequent visits.

Taken together, the administration of GnRHa according to the standard Japanese protocol does not seem to influence the progression of children with CPP towards obesity. One possible reason for this is the suitability of the standard gonadotropin-suppressive therapy administered to girls with CPP in Japan, although racial differences might also be relevant.

5. Conclusion

In conclusion, the standard gonadotropin-suppressive therapy protocol used to treat girls with ICCP or ICEP in Japan does not adversely affect body composition, at least when administered for up to 2 years.

6. References

Arrigo T., De Luca F., Antoniazzi F., Galluzzi F., Segni M., Rosano M., Messnia MF., & Lombardo F. (2004). Reduction of baseline body mass index under gonadotropin-suppressive therapy in girls with idiopathic precocious puberty. European Journal of Endocrinology Vol.150, pp. 533-537

Asayama K., Ozeki T., Sugihara S., et al. (2003). Criteria for medical intervention in obese children: a new definition of 'obesity disease' in Japanese children. Pediatr Int. Vol.45, pp. 642-646

Boot AM., de Muinck Keizer-Schrama SMPF., Pols HAP., Krenning EP., & Drop SLS. (1998). Bone mineral density and body composition before and during treatment with gonadotropin-releaseing hormone agonist in children with central precocious and early puberty. J Clin Endocrinol Metab Vol.83, No.2, pp. 370-373

Chiumello G., Brambilla P., Guarneri M.P, Russo G., Manzoni P., & Sgaramella P. (2000). Precious puberty and body composition: Effects of GnRH analog treatment. J Ped Endocrinol Metab V13: 791-794

Crowley WF., Comite F., Vale W, Rivier J., Loriauz DL., & Cutler GB. (1981). Therapeutic use of pituitary desensitization with a long-acting LHRH agonist: a potential new treatment for idiopathic precocious puberty. J Clin Endocrinol MetabVol.52, pp. 370-372

Feuillan PP., Jones JV., Barnes K., Oerter-Klein K., & Cutler Jr GB. (1999). Reproductive axis after discontinuation of gonadotropin-releasing hormone analog treatment of girls

with precocious puberty: Long term follow-up comparing girls with hypothalamic hamartoma to those with idiopathic precocious puberty. J Clin Endocrinol Metab Vol.84, No.1, pp. 44-49

Goldray D., Weisman Y., Laccard N., Merdler C., Chen J., & Matzkin H. (1993). Decreased bone density in elderly men treated with the gonadotropin-relseasing hormone agonist decapeptyl(D-Trp6-GnRH). J Clin Endocrinol Metab Vol.76, pp. 288-90

Greulich WW., & Pyle SI. (1959). Radiographic atlas of skeletal development of the hand and wrist. 2nd ed. Stanford; USA

Heger S., Partsch C-J., & Sippell WG. (1999). Long-term outcome after gonadotropin-releasing hormone agonist treatment of central precocious puberty: Final height, body proportions, body composition, bone mineral density, and reproductive function. J Clin Endocrinol Metab Vol.84, No.12, pp. 4583-4590

http://www.iotf.org/documents/iotfsocplan251006.pdf

Inokuchi M. (2009).Obesity in Japanese children The Keio Journal of the Keio Medical Society Vol.85, No.2, pp. T53-T85 (in Japanese)

Lindsay, R. (1995). Estrogen deficiency. In: Osteoporosis, etiology, diagnosis, and management, 2nd ed. Riggs BL, Melton LJ, (Ed.), 133-160, Philadelphia, USA

Oostdijk W., Rikken B., Schrerude S., Otten B., Odink R., Rouwe C., et al. (1996). Final height in central precocious puberty after long term treatment with a slow release GnRH agonist. Arch Dis Child Vol.75, pp. 292-297

Palmert MR, Mansfield MJ., Crowley Jr WF., Crigler Jr JF., Crawford JD., & Boepple PA. (1999). Is obesity an outcome of gonadotropin-releasing hormone agonist administration? Analysis of growth and body composition in 110 patients with central precocious puberty. J Clin Endocrinol Metab Vol.84, No.12, pp. 480-4488

Pasquino AM., Pucarelli I., Accardo F., Demiraj V., Segni M., & di Nardo R. (2008). Long-term observation of 87 girls with idiopathic central precocious puberty treated with gonadotropin-releasing hormone analogs: Impact on adult height, body mass index, bone mineral content, and reproductive function. J Clin Endocrinol Metab Vol.93, No.1, pp. 190-195

Paterson WF., McNeill E, Young D., & Donaldson MDC. (2004). Auxological outcome and time menarche following long-acting goserelin therapy in girls with central precocious or early puberty. Clinical Endocrinology Vol.61, pp. 626-634

Revila R., Revilla M., Villa LF., Cortes ., Arribas J., & Rico H. (1998). Changes in body composition in women treated with gonadotropin-releasing hormone agonist. Maturitas pp. 3163-68

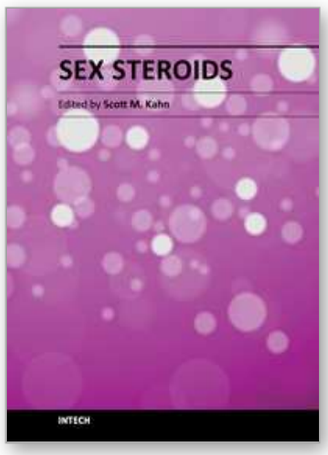
Tanner JM., & Whitehouse R. (1976). Longitudinal standards for height, weight-height, weight-height, weight-velocity and stages of puberty. Arch Dis Child. Vol.51, pp. 170-179

Traggiai C., Perucchin PP., Zerbini K., Gastaldi R., De Biasio P., & Lorini R. (2005). Outcome after depot gonadotropin-releasing hormone agonist treatment for central precocious puberty: effects on body mass index and final height. European Journal of Endocrinology Vol.153, pp. 463-464

Wacharasindhu, S., Petwijit, T., Aroonparkmongkol S., Srivuthana S,. & Kingpetch K. (2006). Bone mineral density and body composition in Thai precocious puberty girls treated with GnRH agonist. J Med Assoc Thai Vol.89, No.8, pp.1194-1198

van der Sluis IM., Boot AM., Krenning EP., Drop SLS., & de Muinck Keizer-Schrama SMPF. (2002). Longitudinal follow-up of bone density and body composition in children with precocious or early puberty before, during and after cessation of GnRH agonist therapy. J Clin Endocrinol Metab 2Vol.87, No.2, pp. 506-512

Yamazaki K., Matsuoka H., Kawanobe S., Hujita Y., & Murata M. (1994). Evaluation of standard body weight by sex, age, and height. On the basis of 1990 school year data. J Jpn. Pediatr. Soc. Vol.98, pp. 96-102(in Japanese)



Sex Steroids

Edited by Dr. Scott M. Kahn

ISBN 978-953-307-857-1

Hard cover, 330 pages

Publisher InTech

Published online 27, January, 2012

Published in print edition January, 2012

This book, entitled "Sex Steroids", features a valuable collection of reviews and research articles written by experts in signal transduction, cellular biology, diseases and disorders. "Sex Steroids" is comprised of four sections, "The Biology of Sex Steroids", "Sex Steroids, Memory, and the Brain", "Sex Steroids and the Immune Response", and "Therapy"; individual chapters address a broad range of recognized and predicted functions and applications of sex steroids. "Sex Steroids" is intended to provide seasoned veterans as well as newcomers to this area of research with informative, resourceful, and provocative insights. Readers of "Sex Steroids" should emerge with an appreciation and understanding of the multitude and complexity of biologic processes attributed to these important hormones, and possible future directions of research in this fascinating and ever evolving field.

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen