

The Side Effects of Gonadotropin Releasing Hormone Analog (Diphereline) in Treatment of Idiopathic Central Precocious Puberty

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Abstract- Treatment of central precocious puberty (CPP) is the administration of GnRH analogs. Metabolic syndrome comprised metabolic disturbances that confer increased risk of (CVD) diabetes mellitus (DM) and cardiovascular disease. This study is a longitudinal prospective study in pediatric endocrinology clinic. 30 non-obese children with idiopathic CPP were involved. Total body weight, height, blood pressure, BMI and waist circumference of the patients along with their triglyceride (TG), total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), fasting plasma sugar (FPS) were evaluated at the beginning and during 3 and 6 months GnRH analog therapy. All of the patients involved in this study were female with age 9.5 ± 1.02 years. Waist circumference, weight and BMI were 69.3 cm, 37.21 kg, and 19.13 kg/cm^2 before therapy and 72.25 cm, 40.11 kg, and 19.54 kg/m^2 6 months after therapy respectively. Mean systolic and diastolic blood pressure of the patients before therapy was 96.83 mmHg, 66mmHg and after 6 months therapy was 98.66 mmHg, 89.63 mmHg respectively. Mean TG, LDL, HDL and FPS were 90.06 mg/dl, 91.6 mg/dl, 43.7 mg/dl and 89.6 mg/dl before therapy and 96.4 mg/dl, 93.1 mg/dl, 44.7 mg/dl and 91.36 after 6 months therapy respectively. GnRH analog therapy doesn't cause metabolic syndrome after 3 and 6 month therapy but it may cause hyperlipidemia and central obesity.

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Introduction

Premature activation of the hypothalamic gonadotropin releasing hormone (GnRH) pulse generator, with the following pulsatile gonadotropin secretion leads to central precocious puberty (CPP). Its prevalence is approximated to be 1:5000 to 1:10000 and it is 5 to 10 times as common in girls as boys (1-6). In CPP, treatment is primarily indicated for two reasons. The first is the significant psychosocial stress on the affected child cause by the very early signs of puberty and normally wrong but frequent assumption by others that the child has early mental and emotional maturity in a corresponding manner. The second reason for treatment is the risk of decrease in adult height due to disproportionate increase in rate of skeletal age (2, 3). It has been estimated that height loss is 20 cm and 12 cm in boys and girls, respectively (7). Treatment involves the administration of GnRH analog where there is

extended inhibition of pituitary gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and through down-regulation of the pituitary GnRH receptors (2,3). Several preparations of GnRH analog are currently available. These include Leuprorelin, Goserelin and Diphereline. As with all new therapies, the long-term effects of GnRH analog therapy began to be discussed by researches, most were on final height and catch-up growth. Besides, there is some variable evidence about the promotion of bone metabolism and weight gain (8-20). Now, it is important to assess whether or this therapy aggravates the risk of metabolic syndrome or not. The metabolic syndrome consists of metabolic disturbances that confer increased risk of diabetes mellitus (DM) and cardiovascular disease (CVD). The main characteristics of the metabolic syndrome include central obesity, hypertriglyceridemia, low high density lipoprotein (HDL) cholesterol, hyperglycemia and hypertension (1). According to

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findings from the Third National Health and Nutrition Examination Survey, Fasting triglycerides >100 mg/dl, HDL cholesterol <50 mg/dl, fasting plasma glucose >110 mg/dl, waist circumference >75 percentile for age and sex and systolic Blood pressure >90 percentile for age sex and height is the criteria for metabolic syndrome in children (21,22).

In children, there is some investigation with variable results about the effect of GnRH analog on body fat distribution and bone metabolism of children (8,20,23), but as we search there is no data about effect of GnRH analog in metabolic syndrome in children using GnRH analog. Importance of metabolic syndrome in increasing risk of cardiovascular disease and diabetes mellitus and morbidities associated with obesity and lack of information about effect of GnRH analog on metabolic syndrome and its possible side effects in children encourage us to do this investigation.

Patients and Methods

Patients

This prospective cross sectional study covers children with idiopathic central precocious puberty (ICPP) referred to endocrinology clinic during February 2010 to February 2011. The criteria for diagnosis of ICPP were *a)* onset of breast enlargement before the age of 8yr in girls (menarche before age 10 years) and onset of testicular enlargement before the age of 9 years in boys, *b)* a ratio of stimulated LH/FSH of more than 1, *c)* LH response to exogenous GnRH in pubertal range, *d)* no evidence of hypothalamus or pituitary lesions on Brain magnetic resonance imaging (MRI) and *e)* no history and clinical signs of organic causes of CPP (21). Children with personal history of DM, or who presented evidence of thyroid dysfunction, glucose intolerance, or late onset congenital adrenal hyperplasia, hyperlipidemia, hypertension and BMI >85th percentile for age and sex, and those receiving any other medication known to affect gonadal function or carbohydrate metabolism were also excluded from the study.

Methods

In all cases, history and physical examination including total body weight, height, blood pressure, body mass index (BMI) and waist circumference of patients evaluated at the beginning and during follow-up. Serum level of Triglyceride (TG), total cholesterol (TC), HDL, low density lipoprotein (LDL), and fasting plasma sugar (FPS) were also checked at the beginning

and during follow-up. Bone age and pelvic ultrasonography was also obtained in all patients. Total body weight, height, blood pressure and waist circumference of patients evaluated at the beginning and during follow-up. According to inclusion and exclusion criteria mentioned above all cases with bone age of less than 12 years were treated with GnRH analog (Diphereline) 80 mg/kg (max: 3.75 mg) intramuscular early four weeks were enrolled in this study.

It was better if we compared our data with control group but it is unethical, because no further treatment except Depherelin was approved for the treatment of precocious puberty. But our study was carried out during 6 months therapy, each patient before treatment was its control after treatment, by using repeated measure test.

Blood sampling were carried out using an intravenous cannula that was inserted into an antecubital vein. Blood was centrifuged (3000 x g at 10 min) within 30 min and plasma immediately stored at -20°C until analyses for FPS, TG, cholesterol (HDL, LDL).

Analyses

Glucose and lipids (TC, HDL, LDL, and TG) were checked on a Roche Modular Analytics (SWA) Module P (Roche Diagnostics). Glucose was established by enzymatic absorption photometry (Glu; Roche) with intra and inter assay coefficient of variation (CV) less than 2%, respectively. TC, LDL, HDL and TG were determined by enzymatic colorimetric analyses (CfAS TC/LDL/HDL plus, TG GPO-PAP; Roche). For all lipids the intra- and inter assay CVs was less than 3% respectively. Serum FSH and LH were measured by time-resolved immunofluorometric assays (Delfia; Perkin Elmer, Boston, MA) with detection limits of 0.06 and 0.05 IU/l for FSH and LH respectively. Intra- and inter assay C.V. in both gonadotropin assays was less than 5%. The detection limit of Estradiol determined by RIA (Pantex, Santa, Monica, CA) were 18 pmol/liter. Intra assay and inter assay CVs of 7.5 and 12.3%, respectively. Bone age was evaluated by the computer-based bone age analyzer Bonexpert. A research bionutritionist performed anthropomorphic measurements. Fasting subjects were weighed a hospital gown and no shoes. Body weight was measured to the nearest 0.1 kg using a digital platform scale (Blue Bell Biomedical Model 500; SR Instruments, Toawanda, NY). Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. Waist circumference was also measured to the nearest 0.1 cm when the subjects were in supine post and during expiration at the level of Iliac crest. Body mass index

(BMI) was calculated as weight (kg) divided by height square (m²).

Statistics

Statistical analyses were performed using SPSS 11.5 (SPSS, InG, Chicago, IL) at Department of Biostatistics, Shiraz University of Medical Science. Repeated measurement design with multiple comparisons was used for data analysis.

Ethics

This study was in accordance with the ethical principles of the Helsinki II declaration. The study protocol was approved by the local ethics committee in Department of Medical Ethics, Shiraz University of Medical Sciences. All children and parents gave their informed written consent.

Results

The main results of the study are summarized in Table 1. In this study 30 patients with ICPP were enrolled. All of them were female. None of our patients was overweight (BMI>85%) at the beginning of the therapy. Their age were 9.5(1.02) years. Nine girls (26.6%) had family history of hypertension, 12 girls (40%) had family history of DM and 13 girls (43%) had family history of hyperlipidemia in their second and third degree relatives. None of the patients fulfilled the criteria of metabolic syndrome, but trend of changes in each criteria of metabolic syndrome during Depherelin therapy were observed by using repeated measure test.

Waist circumference of patients was 69.3 cm, 70.46 cm and 72.25 cm before, 3 month and 6 month after

therapy respectively. Mean weight of patients before after 3 and 6 month therapy were 37.21 kg, 38.26 kg and 40.11 kg with rising of 2.9 kg during 6 months. Mean height of children before, after 3 and 6 month follow up were 139.7 cm, 141.58 cm and 143.38 cm with rising of about 3.68 during 6 months. Mean BMI were 19.13 kg/m², 19.18 kg/m² and 19.54 kg/m², before, 3 month and 6 months after therapy. Mean diastolic blood pressure of patients were 66 mmHg, 65.6 mmHg and 66.16 mmHg before, 3 month and 6 month after therapy respectively. Mean systolic blood pressure of patients before, after 3 and 6 months therapy was 96.83 mmHg, 96.6 mmHg and 98.66 mmHg.

Mean TG levels are 90.06 mg/dl, 92.63 mg/dl and 96.4 mg/l before treatment, after 3 months and after 6 months respectively. Mean LDL levels before, after 3 month and after 6 months therapy were 91.6 mg/dl, 90.13 mg/dl and 93.1 mg/dl. Mean HDL levels before, after 3 and 6 month therapy was 43.7 mg/dl, 44.35 mg/dl and 44.73 mg/dl respectively. Mean FPS levels before, after 3 month and 6 month therapy were 89.6 mg/dl 89.63 mg/dl and 91.36 respectively.

In physical examination of patients there was no sign of Insulin resistance such as acanthoses Nigerians.

Discussion

The aim of this prospective study was to evaluate whether metabolic syndrome occurs at a high rate in ICPP during the treatment with GnRH analog. As we stated earlier central obesity is one of the main features of the metabolic syndrome. Different reports were found in the literature about BMI and obesity in children with ICPP using GnRH analogs (6,10,13,23-25).

Table 1. Results of TG, LDL, HDL, FPS, waist circumference, weight, height, systolic and diastolic blood pressure and BMI before, 3 month & 6 month after GnRH analog therapy in patients with ICPP and *P*-value of changes during this period. Data mentioned as mean (SD).

Time	Before treatment	3 months of therapy	6 months after therapy	<i>P</i> -value of changes after 6 month therapy
TG (mg/dl)	90.06(23.15)	92.63(19.89)	96.4(23.03)	0.002
LDL (mg/dl)	91.6(19.14)	90.13(17.38)	93.1(16.61)	0.009
HDL (mg/dl)	43.7(8.36)	44.36(8.13)	44.73(7.35)	0.231
Waist circumference (cm)	69.3(5.51)	70.46(5.99)	72.25(6.33)	0.000
FPS (mg/dl)	89.6(8.86)	89.63(6.88)	91.36(6.52)	0.164
Weight (kg)	37.21(6.71)	38.26(7.14)	40.11(7.41)	0.000
Height (cm)	139.7(6.11)	141.58(6.14)	143.38(6.07)	0.000
Systolic blood pressure (mmHg)	96.83(7.00)	96.6(6.20)	98.66(7.420)	0.104
Diastolic blood pressure (mmHg)	66(6.21)	65.6(5.68)	66.16(5.20)	0.670
Body mass index (kg/m ²)	19.13(2.52)	19.18(2.64)	19.54(2.84)	0.006

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Arrigo *et al.*, in 2004, (15) reported a large series of patients with CPP who had reduced BMI values during therapy with GnRH analog. In the study, 23.8% of the girls were obese before they initiated drug administration. Their patients were obese at the beginning of their study compare to our, and the authors did not mention the diet or exercise habit of those cases. Heger *et al.* reported that obesity in CPP does not seem to be either exacerbated or caused during the treatment (8). Although some individuals may experience noticeable increases and decreases during the period of therapy, Palmert *et al.* declared that BMI did not change significantly during treatment (20). Van der Sluis *et al.* claimed that despite there was an initial exacerbation of fattiness, which follows GnRH analog therapy onset, no long-term negative effects were detectable (8). Pasquino *et al.* stated that BMI increased during and after the treatment, but it was not significant (25). Recently, Carel *et al.* published the consensus about the use of GnRH in children (13). That conference did not support common concerns about the use of GnRH analog, such as promotion of weight gain. Tascilar, In 2011, *et al.* reported slight increase in BMI and moderate increase in total body fat percentage (23). The differences between all these studies can be attributed to different pretreatment body weight of cases selected in the previous studies and post-treatment follow-up duration. None of our patients was overweight or obese just before the therapy began. Our study declared that BMI, waist circumference, body weight and were raised 6 month after therapy with GnRH analog therapy with *P*-values of less than 0.05 (Table 1) not after 3 months therapy (*P*>0.05). Our study also showed the more the pretreatment BMI is the more weight gain after therapy is (*P*<0.05). The maximum weight gain of our cases was seen at sixth months of therapy. In addition our data showed that rise in waist circumference of the patients is more than rise in BMI (*P*<0.05). So it means that GnRH analog therapy may cause central obesity, not symmetrical rise in fat composition of the whole body.

In other aspects of metabolic syndrome in children using GnRH analog there is lack of data; however some investigation were done on adults with prostatic cancer using GnRH analog (26). In 2008 Smith *et al.* showed that serum TG of patients with prostatic cancer was raised after using GnRH analog (26). Our study showed that level of serum TG was raised after 6 months therapy with *P*-value 0.004, but level of HDL cholesterol did not change after GnRH analog therapy. It means that our study revealed that hypertriglyceridemia was a side

effect of GnRH treatment. HDL levels were not decreased following GnRH therapy in our study which is against classical risk factors which are associated with metabolic syndrome. Also serum level of LDL cholesterol was raised after 6 month therapy (*P*=0.001).

Our study showed that FPS was not elevated after 3 and 6 month therapy with GnRH analog (*P*>0.05) and it is against definition of metabolic syndrome as well. It means that our patients did not show insulin resistance after using GnRH analogs. Also blood pressure did not change in the course of GnRH therapy however in metabolic syndrome hypertension is one of diagnostic criteria. In conclusion, our study showed GnRH analogs increase body weight, BMI and waist circumference after 6 months and not 3 months after therapy. The more the pretreatment BMI is the more weight gain after therapy is. Our study also showed that GnRH analogs caused central obesity not symmetrical rise in fat composition of the whole body. Our investigation revealed that GnRH analog therapy causes hypertriglyceridemia, but there is no change in HDL level. Systolic and diastolic hypertension was not observed in our patients and also FPS was normal during GnRH analog therapy and no insulin resistance was seen according to physical examination and laboratory data. None of observed effects fulfilled all criteria of metabolic syndrome. Our study also showed that GnRH analogs caused elevated LDL level. Our result showed that GnRH analog therapy did not cause metabolic syndrome after 6 month therapy, however further case-control study with long term follow-up can investigate long term side effects of GnRH analogs.

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