Mirjana Doknić[1]

GROWTH HORMONE DEFICIENCY (GHD) AND THE IMPORTANCE OF GROWTH HORMONE REPLACEMENT IN TRANSITION FROM LATE ADOLESCENCE TO ADULTHOOD
Guidelines for patients with GHD in transition from pediatric to adult endocrinologist

Abstract: Transitional period (TP) is the time of several years in a person`s life after reaching of final body height, spanning from about the age of 16 to about the age of 26 years. In this period the person reaches a peak in muscle mass and bone mineral density. Growth hormone deficiency (GHD) in the TP leads to reduced bone mineral density and inadequate body composition with reduced muscle mass and increased abdominal fat mass. GHD in TP is also associated with impaired lipid profile, increased insulin resistance and risk for metabolic syndrome. GH replacement during TP has a favorable effect on bone density and quality, on body composition and on cardiovascular health, thus reducing future morbidity and mortality in adulthood. GH replacement is of particular importance for quality of life improvement in the young patients.

To facilitate and optimize the continuance of GH replacement in the TP for the patients treated with GH in childhood, we have comprised these guidelines aimed to improve the communication between pediatric and adult endocrinologists. A closer collaboration between these two services would ensure easier continuance of treatment and follow up for the patients with hypopituitarism in transition to adulthood. The goal of presenting these guidelines is to prevent the drop out of patients with GHD in TP from continuing GH replacement and other relevant hormonal replacement.

Key words: growth hormone deficiency, transitional period, guidelines

.

[1] Department for Neuroendocrinology, Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical centre of Serbia, Dr Subotića 13, 11000 Beograd, Serbia ; mirjanadoknic@gmail.com

Introduction

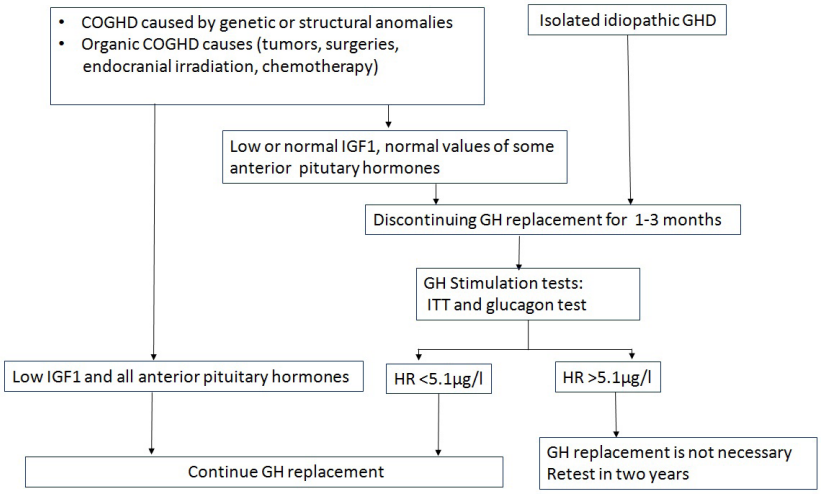
Transitional period (TP) in a person`s life represents the time from late adolescence until the reaching of full physical and psychosocial maturation into an adult person. This period lasts for several years after the termination of linear growth in height, spanning from the age of 16 to the age of 26 years.[1] Due to physical, metabolic, psychological and social specificities commonly related to the transition from late puberty to adulthood, in the young patients with growth hormone deficiency (GHD) a particular attention needs to be paid to the collaboration between pediatric endocrinologist and "adult" internist endocrinologist. In the patients treated for GHD in childhood, continuance of treatment needs to be reassessed.[2]

Reaching of sufficient body height is only a prerequisite for acquisition of normal body composition. In the past, GH replacement was discontinued when the patient stopped growing and reached the final body height. However, the TP is in fact the period when a peak in muscle mass and bone mineral density is yet to be reached. Development of bone is believed to continue as far as to the age of 30 years. GH deficit in TP results in failure to reach maximal bone mineral density potential and leads to inadequate body composition with reduced muscle mass and increased abdominal fat mass[3]. Lipid profile is also impaired leading to incrased risk of metabolic syndrome. Thus the second most important period of GH action, next to its crucial role in childhood, is in fact in the TP. GH replacement in TP has a favourable effect on bone, body composition and cardiovascular health, leading to reduction of future morbidity and mortality in adulthood[4]. An improvement of quality of life was documented during GH replacement in this psychosocialy voulneralble period of a person`s life.

When a pediatric endocrinologist concludes that the patient has finalised growth in height, a GH axis reassesment by an adult endcrinologist should follow[5]. It is recommended that prior to retesting GH replacement should be discontinued for 1 to 3 months. One third of patients which have an isolated idiopathic GHD in childhood may recover their GH axis in TP. If the cause of GHD is structural (endocranial tumors, hypothalamic anomalies) or a confirmed genetic mutation (involving transcriptional factors for pituitary region development) then GHD is expected to persist (Figure 1). In such patients, there is usually a complete anterior pituitary hormonal deficiency (affecting ACTH, TSH, FSH/LH) and GH stimulation tests might be unnecessary in the presence of reduced IGF-1 which is sufficient for diagnosing GHD[2,5]. In other patients, along with IGF-1 assessment, retesting of GH axis with one or two GH stimulation tests is advised. In TP patients we use ITT (insulin tolerance test) and glucagon test. Peak response of GH < 5.1μg/l in these tests is indicative of GHD. Since TP patients are in the transition from childhood to adulthood, GH replacement doses should be targeted between the recommended doses for these two age groups. Replacement is initiated with lower daily doses (0.3 -0.5 mg/d GH) and the dose is further titratred

according to serum IGF-1 values and clinical response to treatment, but rarely exceeds 1.6mg/d. GH replacement dose is individaly determined for each patient, aiming for IGF-1 in mid normal age speciffic range[5,7]. Followup of GH replacement during TP should include 6-monthly visits for assessment of body weight and height, waist and hip circumference, blood pressure, fasting glucose, HbA1c and lipid profile, and annual visits to asses quality of life using a speciffic questionaire - AGHDA-QoL, and to asses thyroid status and serum cortisol level. Body compostion and bone mineral density assesment, by using DXA is necessary at baseline and then every 2 to 5 years[2].

Algorithm for retesting patients with growth hormone deficiency in the transitional period[6]



Guidelines for GHD patient transition from a pediatric endocrinologist to and internist endocrinologist

Mirjana Doknić[1,3], Tatjana Milenkovic[2], Vera Zdravkovic[3,4], Maja Jesic[3,4], Sladjana Todorovic[2], Katarina Mitrovic[2,4], Rade Vukovic[2]; Study Group for GH treatment in transitional period*

Treatment of patients with growth hormone deficiency (GHD) in the transitional period remains a challenge for both pediatric endocrinologists and "adult" internist endocrinologists. Collaboration between the two services is the key to success in treatment of this group of patients leading to their achievement of full psycho-physical maturity in adulthood.

A patient in transitional period lacks a clear understanding of what to expect from his future care at an adult endocrine service. He or she is usually intimidated for leaving the care of pediatric endocrinologist who treated him or her for years, and for needing to continue the treatment with a new and unfamiliar doctor. Thus the first visits to an adult endocrinologist are crucial to break these fears and close communication with the patient is essential for his or her future treatment. Based on 15 years of experience in the field of transition of patients with GHD in Serbia, we have devised the guidelines for leading both the patients and the caring endocrinologists – pediatricians and internists. The aim was to improve the collaboration between the pediatric and "adult" endocrinologists, and to reduce the fraction of patients who drop out from further follow up and treatment of hypopituitarism in transitional period. The guidelines were adapted from the algorithm for approach to patient in transition from a pediatric to adult care advised by *Endocrine Society* (*www.endocrinetransitions.org*).

Guidelines for transition of GHD patients from pediatric to adult endocrinologist care consist of 3 forms: 1) Information for the patients and his or her parents 2) Patient`s clinical data (provided by a pediatric endocrinologist and sent to the internist endocrinologist) 3) Patient`s clinical data after assessment by the adult endocrinologist (provided by the internist endocrinologist and returned to the pediatric endocrinologist who has referred the patient).

***Study Group for GH treatment in transitional period** (alphabetically):Bajkin Ivana[8,10], Bojić Vladimir[4], Vorgučin Ivana[9,10], Dautović Slavica[9,10], Đukić Aleksandar[11,13], Živić Saša[5,7], Katanić Dragan[9,10], Lešović Snežana[14], Marković Slavica[12, 13], Marinković Snežana[14], Medić Milica[8,10], Miljić Dragana[1,3], Pekić Sandra[1,3], Petakov Milan[1,3], Sajić Silvija[3,4], Soldatovic Ivan[4,15], Stanković Sandra[5], Stojanović Marko[1,3], Radenković Saša [6,7], Radojković Danijela [6,7], Cvetković Vesna[5], Šaranac Ljiljana [5,7]

[1]Department for neuroendocrinology, Clinic for endocrinology, diabetes and metabolic diseases, Clinical Centre of Serbia; [2]Endcrinology department, Insittute for healthcare of mother and child "Dr Vukan Čupić"; [3]Medical Faculty, University of Belgrade [4]Tiršova University pediatric Clinic; [5]Department of endocrinology, Clinic for pediatric internal medicine, Clinical Centre Niš [6]Clinic for Endocrinology, Clinical Centre Niš; [7]Medical Faculty, University of Niš; [6]Clinic for endocrinology, diabetes and metabolic diseases, Clinical Centre of Vojvodina, Novi Sad; [9]Institute for health care of children and youth of Vojvodina – Department of Endocrinology, Clinical Center of Vojvodina, Novi Sad; [10]Medical Faculty, University of Novi Sad;[11]Center for Endocrinology, diabetes and metabolic diseases, Clinical Centre Kragujevac;[12]Pediatrics Clinic, Clinical Centre Kragujevac; [13]Faculty of medical sciences University of Kragujevac; [14]Special hospital for thyroid diseases and metabolic diseases "Zlatibor";[15]Institute for Medical statistics and informactics, Belgrade

1) Information for the patient and his or her parents

NAME AND CONTACT DETAILS OF THE INTERNIST ENDOCRINOLOGIST IN CHARGE**:

Institutional address:

Phone:

Mobile:

e-mail:

**Pediatric endocrinologist provides the contact of the internist to whome the patients in transition is referred.

1. The first appointment with an internist endocrinologist should be scheduled by mobile phone call or e-mail
2. Patient should attend the first meeting with an internist endocrinologist accompanied by his or her parents. All relevant medical records should be brought (discharge letters and pediatric visit notes, MR images). A referral letter for an outpatient visit to internist endocrinologist must be provided by a primary care physician. At this first appointment, the internist endocrinologist will explain the patient and the parents in detail about the reasons for continuing hormonal treatment, and about the risks of discontinuing this treatment. Internist endocrinologist is obliged to answer all relevant questions posed by the patient or the parents regarding the patient`s health condition and treatment. Short term and long term expectations from treatment should be discussed.
3. Hormonal and metabolic investigation is designed through a 3 to 5 day in-hospital stay at an adult endocrine department. A referral letter for in-patient stay must be provided by a primary care physician. During the hospital investigation the following is to be performed:

- Stimulation tests of pituitary reserve assessment (usually two tests)
- DXA- bone mineral density and body composition assessment
- Abdominal and neck ultrasound
- Chest X-ray and profile craniogram
- Hand X-ray (to assess the termination of linear growth)
- Quality of life assessment by questionnaire

If the patients can provide other accommodation in the vicinity of the referral center (Beograd, Niš, Novi Sad, Kragujevac), he needs not stay at the hospital department but must present for 3 to 5 consecutive days at the endocrine department

and be available for the investigation during the morning hours until 12h. In this way patient would be free of commitments in the afternoon until the next morning. This option is also based on the in-hospital referral letter from GP.

4. Patient is discharged with the next appointment scheduled usually within a month to evaluate the results of the performed tests.
5. Based on the test results, a decision is made on the future treatment of the patient. Most patients continue with the treatment initiated by the pediatric endocrinologist. GH replacement doses are much lower for the adults compared to children (0.3-1.0 mg daily). Some patients recover their pituitary function and do not need further hormonal replacement. These are most often patients with isolated GH deficiency.
6. If the replacement hormonal treatment is continuing, the visits to internist endocrinologist are usually scheduled for every 6 months. Stimulation tests are not repeated.
7. Six-monthly appointments are scheduled with the internist endocrinologist. Hormonal status will be analyzed (by a single morning blood sampling, in the patient`s city of residence or at the Endocrinology clinic, as arranged. Serum IGF-1 is analyzed to assess efficacy and safety of the current GH replacement dose.
8. Patient is introduced to the delegated departmental endocrine nurse in charge for his or her training for adequate GH self administration, and for further monitoring of correct self administration.
9. Patient and his or her parents must be familiar with the patient`s treatment, including doses and procedures in special circumstances (e.g. fever over 38C, vomiting, diarrhea, surgical procedures, infections, loss of consciousness, trauma). Patient`s family members must be educated on high dose hydrocortisone administration in such emergencies. They also must be familiar with the nearest ER location or other point of emergency first healthcare contact in order to avoid delay in reacting in the event of emergency.
10. If the patient receives hydrocortisone replacement, he or she needs to always carry an emergency identity card (provided by the internist endocrinologist), assuring that stress doses of i.v. hydrocortisone would be WITHOUT DELAY administered in the event of an emergency (infection, unconsciousness, surgery, trauma).

2) Patient`s clinical data on GHD during childhood

(provided by the pediatrician endocrinologist and sent to the internist endocrinologist)

PATIENT`S FULL NAME_____

PATIENT`S DATE OF BIRTH _____

DATE OF DIAGNOSIS OF HYPOPITUITARISM _____

AGE OF DIAGNOSIS OF HYPOPITUITARISM _____

Present condition: _____

_____

Etiology of hormonal deficiency: Congenital □ Genetic analysis Yes □ No □
Tumors □

Tumors of H/H region or brain, trauma: Craiopharyngeoma □ Meduloblastoma □
Germinoma □ Pituitary adenoma □
Astrocytoma □ Perinatal trauma □
Rathke`s cyst □ TBI □
PNET □ Vascular lessions □
Other brain tumors □

Endocranial tumor treatment: Surgery □ Date:
Radiotherapy □ Date (start and end date):
Chemotherapy □ Date:

Number of impaired hormonal axes: Isolated GH deficiency □ FSH/LH deficiency □
ACTH deficiency □ ADH deficiency □
TSH deficiency □

HORMONAL REPLACEMENT (provide current doses prior to the referral to internist endocrinologist):

Growth hormone: When was replacement initiated? _____ Dose:
When was replacement discontinued? _____

Hydrocortisone: When was replacement initiated? _____ Dose::

L-Thyroxine: When was replacement initiated? _____ Dose:

Sex steroids: When was replacement initiated? _____ Dose::
ADH: When was replacement initiated?_____ Dose:

Pituitary reserve tests: test date, type of test, **GH peak value, cortisol peak value**:

Comorbidites: Yes □ No □

Sellar region or endocranial MRI: Date of imaging: MR finding:

Hand radiography: (bone age determined prior to referral to internist endocrinologist**)**:

Date: Finding:

Date: Signed by referring pediatrician endocrinologist:

3) Patient`s clinical data – <u>after the evaluation</u> by the internist endocrinologist

(provided by the internist endocrinologist and returned to pediatrician who referred the patient)

After 3 months since the investigation in the referral endocrinology department, internist endocrinologist informs the pediatric endocrinologist of the following:

Was the patient validly evaluated? Yes □ No □

1. Has GH deficiency and other anterior pituitary hormones deficiency been confirmed?
Yes □ No □

2. Was an initial or control sellar region MRI performed and what are the findings?
Yes □ No □

_____

3. Was DXA (bone densitometry and body composition) performed and what are the results?
Yes □ No □

_____

4. Did the patient psychologically take well the transition from a pediatrician to an adult endocrinologist?
Yes □ No □

5. Did the patient find a job or continue with his or her education?
Yes □ No □

_____

6. What is the emotional status of the patient and motivation for reproduction?

_____

Date: Signed by the internist endocrinologist

References:

1. Clayton PE, Cuneo RC, Juul A, Monson JP, Shalet SM, Tauber M. Consensus steatement on the management of the GH treated adolescent in the transistion to adult care. Eur J Endocrinol, 152:165-170, 2005.
2. Molitch M, Clemmons D, Malozovski S, Merriam G, Shalet S, Vance M L, for The Endocrine Society's Clinical Guidelines Subcommittee, Clinical Practice Guideline – Evaluation and treatment of adult growth hormone deficiency: An endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab, 96: 1578-1609, 2011.
3. Cook D.M. , Rose S.R. A review of guidelines for use of growth hormone in pediatric and transition patients. Pituitary, 15: 301-310, 2012.
4. Inzaghi E, Cianfarani S. The Challenge of Growth Hormone Deficiency Diagnosis and Treatment during the Transition from Puberty into Adulthood.Front Endocrinol (Lausanne), 20; 4:34, 2013
5. Petakov M, Doknić M: Ispitivanje i lečenje osoba sa nedostatkom hormona rasta u period tranzicije I odraslom dobu. Glavni urednik Damjanović S.Endokrinološka sekcija SLD, 2016.
6. Radovick S, DiVall S. Approach to the growth hormone-deficient child during transition to adulthood.J Clin Endocrinol Metab. 92:1195-200, 2007.
7. Ahmid M, Perry CG, Ahmed SF, Shaikh MG. Growth hormone deficiency during young adulthood and the benefits of growth hormone replacement.Endocr Connect. 5:R1-R11, 2016.