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STUDY OF ADHERENCE TO RECOMBINANT GROWTH HORMONE TREATMENT OF CHILDREN WITH A GH DEFICIENCY: CONTRIBUTIONS TO TREATMENT CONTROL AND ECONOMIC IMPACT

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
SD	Standard Deviation
GABA	Gamma - Aminobutyric acid
GH	Growth Hormone
GHD	Growth Hormone deficiency
GHRH	Growth Hormone releasing hormone
IGF-BP	Insulin-Like Growth Factor - binding protein
IGF-1	Insulin-Like Growth Factor - 1
IGF-2	Insulin-Like Growth Factor - 2
IGFBP-3	Insulin-Like Growth Factor - binding protein -3
O2	Oxygen
WHO	World Health Organization
P3	3rd Percentile
PTH	Parathyroid Hormone
r-GH	Recombinant – Human Growth Hormone
CNS	Central Nervous System
SNS	Spanish National Health System
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid Stimulating Hormone
GR	Growth rate

ABSTRACT AND KEY WORDS

STUDY OF ADHERENCE TO RECOMBINANT GROWTH HORMONE (GH) TREATMENT IN CHILDREN WITH GH DEFICIENCY: CONSIDERATIONS FOR A BETTER MANAGEMENT AND ECONOMIC IMPACT.

BACKGROUND AND OBJECTIVES

The treatment for children with growth hormone deficiency has significantly developed since its first uses from human cadavers (1958), until the arrival of recombinant human growth hormone (1985). This biotechnological advance has allowed an expansion in its uses due to a greater availability, as well as a greater biological safety of this hormone and significant refinements regarding dosage and administration frequency, achieving significant results in the final growth of these children. However, the existence of non-responder phenotypes, as well as the more common lack of therapeutic compliance, can pose severe limitations regarding effectiveness, with the corresponding economic impact for Health Systems, which may be mitigated by innovations in administration devices.

METHODOLOGY

Bibliographic search in PubMed with the following limits: articles in English and Spanish published until 31/07/2013, in humans of paediatric age. Once the articles related to the aim of this study were selected, the variables considered important for an economic approach in this type of treatment were classified. The economic analysis carried out was based on a cost-minimization model.

RESULTS

There are currently two main methods on the market to administer GH in children: an electronic device and pens (disposable or reusable). For the economic analysis, the variables which appear to be most important in establishing this type of treatment are: size of the population to be treated, distribution by weight, age, and sex, treatment period, therapeutic regime (mg hormone/kg weight of child/day), adherence to treatment, volume of GH vials on the market, amount wasted according to method of administration used and price of hormone. Adherence to treatment is one of the most important practical aspects to consider in this type of treatment, which is long term and has a complex administration. Administration by electronic devices allows a notable improvement in the better usage of GH, reducing the amount that may be wasted with other forms of administration.

CONCLUSIONS

Adherence to treatment is one of the most important practical aspects to take into account in treatments such as this one, of prolonged duration and complex

administration. Administration of growth hormone using an electronic device allows complete use of the total vial content. At the same time, it registers information regarding therapeutic compliance which allows: a) aiding in the optimal adjustment of treatment regime by the specialist; b) identification of patients with a non-responder phenotype.

KEY WORDS

Growth hormone, adherence, short stature, growth hormone deficiency, waste, economic analysis.

INAHTA STRUCTURED ABSTRACT

Title: STUDY OF ADHERENCE TO RECOMBINANT GROWTH HORMONE (GH) TREATMENT IN CHILDREN WITH GH DEFICIENCY: CONSIDERATIONS FOR A BETTER MANAGEMENT AND ECONOMIC IMPACT.

Authors: María del Sol Granados; Zuleika Saz-Parkinson; José M. Amate. **Agency:** AETS (Agencia de Evaluación de Tecnologías Sanitarias) (Spanish Health Technology Assessment Agency). **Contact:** Amate Blanco, JM. **Date:** October, 2013. **Pages:** 69. **References:** 71. **Price:** Free (on-line). **Language:** Spanish. **English abstract:** Yes. **ISBN:** Online Identification number for Official Publications: 725-14-017-3. **MeSH Keywords**: Growth hormone, adherence, short stature, growth hormone deficiency, waste, economic analysis.

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Cost/economic analysis: Yes. **Expert opinion:** No.

Content of report/Main findings: There are currently two main methods on the market to administer GH in children: an electronic device and pens (disposable or reusable). For the economic analysis, the variables which appear to be most important in establishing this type of treatment are: size of the population to be treated, distribution by weight, age, and sex, treatment period, therapeutic regime (mg hormone/kg weight of child/day), adherence to treatment, volume of GH vials on the market, amount wasted according to method of administration used and price of hormone. Adherence to treatment is one of the most important practical aspects to consider in this type of treatment, long term and complex administration. Administration by electronic devices allows a notable improvement in the better usage of GH, reducing the amount that may be wasted with other forms of administration.

Recommendations/Conclusions: Administration of growth hormone using an Electronic device allows complete use of the total vial content. At the same time, it

registers information regarding therapeutic compliance which allows: a) aiding in the optimal adjustment of treatment regime by specialist; b) identification of patients with a non-responder phenotype.

Peer review process: No.

Keywords: Growth hormone, adherence, short stature, growth hormone deficiency, waste, economic analysis.

BACKGROUND

ASSESSMENT OF NORMAL GROWTH

Growth is a complex biological process, product of the interaction between multiple endogenous factors (genetic, hormonal, metabolic, receptivity of target tissues) and exogenous factors (nutrition, physical activity and psychosocial influences), through which living creatures, at the same time as increasing their size, they physiologically mature and progressively acquire a complete functional capacity. The growth process, although it does not occur in a uniform manner, takes place according to an organism´s nutrition. The improvement of social, economic, health and cultural conditions in developed countries has allowed an adequate food intake of a larger proportion of people, which has thus extended the possibility not only of evolutionary increasing the adult size of privileged populations, but also achieving it earlier, with puberty progressively starting before (See Annex b, graphs 1;2;3;) (1).

Height is factor of social acceptance which aids in the modelling of an individual´s self-esteem. The physical appearance provided by an adequate height, contributes to improving our own self-concept, generating feelings of wellbeing. Short stature can many times lead to poor social integration of the individual, also producing feelings of inferiority. Untreated children are at a greater risk of becoming shyer and presenting problems related to establishing interpersonal relationships, and some can present anxiety and poor school performance (2).

Height is one of the most sensitive indicators of a child´s health status, his or her nutrition and their genetic background. For this reason, a significant deviation from normal parameters can be a first manifestation of an underlying congenital or acquired condition, which is why it is necessary to have a correct understanding of the growth process and different disorders which can affect it (2).

The average height of the population has considerably increased thanks to the improvement of diet and health conditions, as well as medical advances of the last decades (see Graph 1). Many people with short stature currently benefit from new hormone therapies, which allow them to now reach an adequate height, not previously possible (1).

It is important to mention that, in addition to the size of a child, their rate of growth must be assessed (See Annex a, Figures 1 and 2). This is a more sensitive parameter, as it allows detection of changes in the growth curve, which usually precede changes in absolute size. In order to be reliable, growth rate must be established in periods no shorter than 6 months (2), paying special attention to significant deviations from the growth curve (2).

Growth in terms of height is a continuous process, but it is not linear. We can distinguish three post-natal growth phases, each with different characteristics: (See Annex a, Figure 3).

a. Breastfeeding period: characterized by a rapid growth during the first two years of life with an increase in size of 35 to 40 cm.

b. Childhood: characterized by a relatively constant rate of growth around 5 to 7 cm per year.
c. Puberty: characterized by a growth spurt between 8 and 12 cm per year depending on the sex of the adolescent.

In the first evaluation of the growth of a patient, three main parameters must be considered: anthropometry, growth curve and family size (2).

The most frequently used instrument in anthropometry is the anthropometer which must have a solid structure, preferably located in a fixed location, and with a scale including cm and mm. The ideal instrument to measure children over the age of 3 in a standing position is the stadiometer, and an infantometer for children under that age in a supine position. In patients who seek doctor´s advice on short stature, it is preferable to carry out several measurements (at least three) during each measurement session and by the same observer, which allows a more precise determination of the real size of a patient. Anthropometry must include the body proportions, as several growth disorders are characterized by disharmonic growth. The following measurements are taken: head size, proximal and distal segments, and arm span. The distal segment is the distance between the pubic symphysis and the floor; the proximal segment is the difference between the height and the distal segment. The arm span is measured with arms completely extended and 90º abduction. Short stature is classified as harmonic or disharmonic, depending on the characteristics of the body proportions. In addition, a careful examination by segments needs to be carried out in search of signs of gammopathy or bone dysplasia. The degree of pubertal development must be examined in order to determine if there is delayed puberty, which produces short stature as compared with their peers by age and sex. Together with this physical examination, the physician should enquire about the medical history, signs and symptoms indicative of chronic diseases such as heart diseases, cystic fibrosis, kidney or respiratory disorders, tumours, malabsorption due to Celiac´s disease or inflammatory bowel disorders, metabolic diseases, malnutrition, psychosocial deprivation, some of which can be oligosymptomatic and may be expressed only by short stature. In addition, the patient´s daily habits should be recorded, including food ingestion, sport activity, hours of sleep and medicine or drug consumption such as alcohol, tobacco or marihuana (adolescents) (2).

GROWTH PHYSIOLOGY

Growth is a biological process in which, as well as an increase in body weight, there is a progressive morphologic and functional maturing of the individual. Therefore, it is a quantitative process, with respect to the increase in number and cell size and extracellular substances, but it is also a qualitative process as it entails a progressive specialization of all the organisms´ systems (3).

GROWTH FACTORS

They can be classified into four different types (3):

- Determinant factors.
- Permissive factors.

- Regulatory factors.
- Achieving factors.

a) *Determinant Factors:* They are the genetic ones, those responsible for maximum growth potential. They are determined by the parents´ size and by the rhythm of growth throughout the different sequential stages of life. Height is determined in a polygenic way which is why chromosome disorders are almost always associated with undergrowth, on many occasions presenting prenatally. We find many genes which are important for determining growth and development on the sexual chromosomes, which explains the differences in maturing and final size between both sexes. Thus, girls mature before boys, but the final height achieved is lower. The genes which regulate size in the sexual chromosomes have been found to be located in the short arm of chromosome X and the long arm of chromosome Y.

b) *Permissive Factors:* These are the ones which make it possible to achieve a genetically determined growth. We can distinguish two different types (3):
   a. *Nutrition-metabolic factors:* In order to achieve a normal growth, the nutrients and oxygen provided to the organism must be sufficient, and the absorption – digestion functions, as well as the organism´s metabolism, needs to be adequate. It is well recognized that the difference in size between people from different countries, and the secular speed of the growth rate, are largely due to improvement in nutrition among the population. "Socio-economic" malnutrition is still the main cause of a high percentage of cases of undergrowth.(3) On the other hand, in obesity there is a transient acceleration of the growth rate, reaching a size above the mean and an increase in the insulin growth factor (IGF-I) is observed, although the final size achieved is that which is genetically expected (3).
   b. *Environmental factors:* The environmental surrounding of the subject is included here, such as the socio-economic status, lifestyle, climate, rural or urban setting, and in particular the family setting (number of children, emotional relationships, etc.). The lack of emotional support cannot be forgotten when evaluating the possible causes of short stature, even more so taking into account that it can lead to severe undergrowth (2).

c) *Regulatory factors:* They coordinate the determinant and permissive factors so growth can take place. There are two different groups (3):
   a. *Hormonal factors:* The hormones which are most involved in growth, in addition to growth hormone (GH), are IGFs, thyroid hormones, cortisol, sexual steroids, either from the gonads or adrenal glands, vitamin D and its metabolites, and insulin, as well as all hypothalamic factors that regulate synthesis and secretion of the aforementioned compounds. Thyroid hormones, particularly in their active form (T3), play an important role in synthesis and secretion of GH and they mediate in IGF-I´s action on the chondrocyte. At the level of cartilage growth, they have an effect on mineralization and, therefore, on bone maturation, although they do not affect cell proliferation. Their main action lies in their importance in neurological development. Androgens increase secretion of GH during puberty, and at the level of cartilage growth, they stimulate cell proliferation and synthesis of the extracellular matrix. They also stimulate muscle and

bone growth. The greater size of males is due in part to the action of these hormones, and the increase in the rate of growth during puberty is due to the increase in gonad production. The small growth spurt which occurs in both sexes around the age of 7-8, adrenarche, is also caused by androgens of suprarenal origin. Estrogens stimulate synthesis of GH at the hypothalamic-pituitary gland level. At the level of cartilage growth, at small doses, they stimulate synthesis of the extracellular matrix and its mineralization, but at high doses they produce its calcification, worsening the final height.

Insulin has a very similar structure to IGF type growth factors. With regards to growth, it plays a critical role during the prenatal period. Later, its importance lies in facilitating the uptake of nutrients by the cell. Cortisol, at physiological levels, favours growth, but at high levels it inhibits it by decreasing the synthesis of GH, IGF´s and collagen, and promoting protein catabolism. Vitamin D, parathyroid hormone (PTH) and osteocalcin play an important role in bone metabolism (3).

b. *Autocrine and paracrine factors:* They are peptide factors which act by stimulating or inhibiting cell proliferation and growth at a local level. If the action takes place on the same cell that has synthesized them, it is referred to as autocrine control, whereas if it occurs on nearby cells, it is paracrine control. In both cases, the action mechanism is due to interaction with cell membrane receptors, which induce physical-chemical changes in the cell. IGFs or somatomedins are included in this group, and their synthesis depends on age, GH and nutrition state (3).

d) *Achieving factors:* They are represented by the "target" organs on which the rest of the growth factors act. The most important one is bone, and within the bone, the growth cartilage (3).

PREDICTION OF ADULT SIZE

It allows an orientation of the therapeutic actions to be taken when faced with a patient of short stature, in addition to controlling response to treatment. It is possible to establish a *target height* for patients, which is defined as the average of the parents' height + 6.5 cm if it is a boy or – 6.5 cm if it is a girl (+ 5 cm SD). With these three main parameters: anthropometry, growth curve and family sizes, it is possible to guide the study of a patient with short stature (2).

Height prediction, according to the child´s growth percentile, is useful in children with a normal height and with not much difference between their chronological age and their bone age. It is more valuable after the age of 6 (3).

Bayley – Pinneau´s method uses tables that indicate the percentage of final height achieved according to bone age (3) (See Annex C, images 1 and 2). It can be used in children over the age of 6. *Roche, Wainer y Thissen* use correlation coefficients for different ages between height, weight, average size of parents and bone age (3). *Tanner – Whitehouse* take into account the current age, bone age, chronological age and final size (3).

CONCEPT OF SHORT STATURE

Size, during the overall growth process of an individual, is a continuous variable, with values around a mean following a normal distribution. For this reason, it is impossible to have an exact and static line to distinguish between normal and short stature. We can define short stature when the child is below the 3rd percentile (p3) or less than 2.5 standard deviations (SD) (1) away with respect to the growth curve according to his age, sex, size, ethnic origin and genetic potential (having established the size of parents, brothers and sisters and, if possible, grand-parents) (2). In general, there are national curves for many countries, but international patterns can be followed, such as the curves from the National Center for Health Statistics, when there are no national curves. In Spain, the reference growth curves and tables are those by Fundación Faustino Orbegozo Eizaguirre of Bilbao.(4) These growth curves were created after a Project which began in 1978 with the objective of obtaining standards in order to carry out a follow-up of a particular individual and assess if his/her pattern or rhythm of growth was within or beyond the "normal" variation limits, and thus make available patterns or reference curves which allow the main anthropometric parameters to be compared with those from other populations (4) (See Annex b, graph 4). In general, it is worth studying those patients whose size is below the 3rd percentile, or whose growth rate has significantly deteriorated, even before they are 2.5 SD below the mean.

In order to progress in the concept of short stature, the growth rate (GR) of the particular patient, measured on an annual basis, must be compared to adequate standards. A GR below -1 SD (around 25th percentile) can be considered pathologic, if it remains like this for two to three years. Although in terms of GR it can be considered normal to have + 2 SD, a child who is continuously achieving a GR below –1 SD, for an indefinite period of time, will most likely end up with short stature (1).

CLASSIFICATION OF SHORT STATURE

It is important to distinguish between short stature considered a "normal variant", which represent 80 to 85 percent of all cases (constitutional delay of growth and puberty and short family statures) and pathological short stature presenting pre or post-natally (2) (See Annex d, table 1).

Normal Variants

The two most frequent causes of short stature are normal growth variants. These include short family stature and constitutional delay of development. In the first case, there is usually a family history of short stature. The decrease in growth rate is usually observed in the first 2 or 3 years of life and reflects the change from the intrauterine growth canal to the infant growth canal. Blood tests do not show any altered growth factors. There is usually a history of delayed puberty in family members, and short stature is frequent. On medical examination, short stature is noticeable for the age of the child (can be below P3), late appearance of signs of puberty and an adequate growth rate (>4 cm per year). Bone age is usually delayed in about one year or sometimes more (3). In the constitutional delay of short stature, a halt in growth

and bone maturation is observed. However, this delay is characterised by an agreement between the age by height, bone age, and genital development.

Short family stature appears frequently associated with constitutional delays. It is defined by short stature in one or both parents, with normal size and weight at birth, an adequate growth rate and normal puberty, and a bone age which is compatible with their chronological age. If growth factors are normal, final size will be short, but within the range of the genetic size (3).

In some cases, undergrowth is linked to ethnic factors, therefore it would be considered to be one of the normal variants (3).

Pathologic short stature

A first classification tries to distinguish between those children with short stature and normal proportion of body segments, and those with short stature and disproportionate body size. It is also necessary to assess if undergrowth is of pre or postnatal origin (3) (See Annex d, table 2).

Primary growth disorders

Primary growth disorders encompass a variety of pathologies that affect growth from a very early stage of life, so they usually make their clinical appearance around birth (prenatal origin). Several bone dysplasias, such as achondroplasia and osteogenesis imperfecta, are included here and are characterized by disharmonic short stature. It is usually a clinical diagnosis and is confirmed by a radiologic study. There is a long list of bone dysplasias, metabolic diseases and genetic diseases which can affect growth. Delayed intrauterine growth is a primary growth disorder which can affect between 5 – 10% of live births, depending on the country (2) Regarding disorders of post-natal origin, we can classify them as undergrowth of psychosocial origin, nutritional origin, chronic diseases, skeletal diseases, endocrine diseases and those of iatrogenic origin (2).

Secondary growth disorders

There are numerous systemic diseases which can delay growth. Most of these have a serious clinical presentation and are usually chronic. Among these, we can mention some digestive symptoms, such as malabsorption syndrome due to Celiac´s disease or inflammatory bowel disorders such as regional ileitis. Other presentations affect renal function, such as renal tubular acidosis or renal failure. Haematological disorders, such as serious anaemia or leukaemia, or cancer processes, particularly those located in the Central Nervous System (CNS), can also affect growth (3).

Endocrine alterations

The most frequent endocrine pathologies leading to serious growth delays are: alterations of the somatotroph axis, which are a group of diseases that lead to a reduction in growth rate and final height. The seriousness of the disease depends on its aetiology and the magnitude of hormone deficiency. Congenital GH deficiency syndrome should be explored when a patient shows deterioration in his/her growth, particularly after the age of 6 months, with hypoglycaemic episodes during the breastfeeding period, harmonic short stature, delayed bone age, prominent forehead,

low nasal bridge, and micropenis in males. When it is an acquired deficiency, the most important sign observed is a decrease in growth rate. Hypothyroidism is a relatively frequent disease in adolescence, generally secondary to an autoimmune thyroiditis. This disease can delay growth and bone age, although in some cases it may not be too symptomatic. If there is a suspicion of hypothyroidism, T4 and TSH in serum and anti-thyroid autoantibodies should be measured, and, if necessary, a thyroid ultrasound should be carried out. If it is proven to be this type of disease, hormone replacement should be begun. Hypocortisolism is a relatively infrequent disease in paediatrics; generally it is secondary to chronic administration of exogenous corticoids and its prognosis depends on the basal disease and length of treatment period. If there is no history of corticoid treatment in a patient who is not growing, has centripetal obesity, pink stretch marks, acne, hirsutism, hypertension, moon face, menstrual or psychological disorders, ecchymosis and hyperpigmentation, then endogenous hypercortisolism can be suspected, caused by a pituitary or adrenal disorder (2).

Treatment of undergrowth can be successful only if an early diagnosis of the specific disease causing it can be made. When faced with children with a short family stature or delayed constitutional growth and development, the general paediatrician can make a prognosis of final height and periodically control growth. An adequate nutrition and healthy lifestyle is recommended. Patients with significant slowdown in their growth should be sent to a medical specialist for a complete study with the aim of determining the appropriate diagnosis and therapy for each case (2).

GROWTH HORMONE DEFICIENCY (GHD)

The importance of carrying out a correct diagnosis in children with short stature due to growth hormone deficiency lies in the need to come to a diagnosis as soon as possible with the aim of beginning a hormone replacement therapy at an early stage.

GHD can be defined as a combination of auxological, clinical, biochemical and metabolic anomalies caused due to a lack of or insufficient GH.

GHD can be complete or partial. Deficiencies are more frequent in clinical practice and usually present in an isolated way, without any other clinical symptoms, making the diagnosis very complex. Once it is diagnosed, treatment should begin as soon as possible for three reasons (1):

1. Avoid the deterioration and progressive distancing from the standards of reference which cause an impact not only on size, but also on the psychological state and self-esteem.
2. Avoid known negative metabolic effects, such as a poor bone mineralisation, excessive accumulation of adipose tissue at the expense of lean body mass or an increase in plasma lipids, as well as other effects still not completely understood, such as increase in apoptosis, cell differentiation, etc.
3. Achieve the best size possible at the start of puberty.

If children affected by the following 5 diseases: GHD, Turner´s syndrome, chronic renal failure, Prader-Willi Syndrome and idiopathic short stature, are not treated, they could reach an adult size 12-36 cm less than the rest of children (5, 6). Among children

who do not receive treatment with GH, males reach a height between 134 – 146 cm and 128 – 134 cm for females (5, 6).

Epidemiology of growth hormone deficiency: incidence and prevalence

It is difficult to obtain a precise figure for incidence and prevalence of GHD due to its difficult diagnosis. On the other hand, it is difficult to estimate how many of the children belonging to the lowest 3% of sizes should be prescribed GH for GHD.

The "UK Child Growth Foundation" has estimated that, in England and Wales, GHD of unknown origin occurs in 1 of every 3800 births, but it is difficult to obtain reliable data (5). Data from a Belgian study indicate a general prevalence of GHD of 1 for every 5600 children (5). According to another study carried out in Belgium, it is estimated that in 41% of patients with GHD, the cause is unknown, in 20% of cases it is congenital and it is acquired in 35% of cases (7).

The prevalence of GHD published in the literature, at the current moment on a world level, varies between 1/3480 to 1/30,000 children (7).

A Danish study based on 1823 patients who began their treatment in the period 1980 – 1999, calculated a rate of incidence of GHD appearance in children of 2.58 per 100,000 inhabitants (with a 95% confidence interval of 2.3 to 2.88) for men and 1.70 (95% confidence interval of 1.48 to 1.96) for women, being the difference between both sexes statistically significant ($p<0.001$) (5) (See Annex b, Graphs 5-7). Other sources suggest that this disorder is twice or three times more common in men than in women (9, 10).

Studies in the United States (11) estimate an incidence in children with GHD of 1 for every 3500 live births. Only 20% of these children have organic GHD. Organic causes include tumours in the central nervous system, radiation, infections and traumatic brain injury. The remaining 80% do not have an identifiable cause for receiving an idiopathic GHD diagnosis (11).

In Spain there are no specific data on patients diagnosed with short stature due to growth hormone deficiency. Only the Advisory Committees of each Autonomous Community involved in authorising use of growth hormone have this data as, in Spain, growth hormone is authorised as a drug for Hospital Diagnosis covered by the National Health System. The Expert Committees were created in the different Autonomous Communities and in the INSALUD to supervise, monitor and control the use of GH (13). Within our review, we were only able to find data from the Autonomous Community of Valencia and Cataluña (12, 13) (See Annex d, Tables 3-6).

In the report on activities of the Advisory Committee of Cataluña on therapeutic use of growth hormone and related substances (12), there were a total of 2864 patients, 2660 children and 204 adults, receiving treatment with GH on the 1st January 2010. A total of 899 new cases were authorized during 2009, representing an incidence of 54.43 treatments per 100,000 children between 0 and 20 years of age, and a prevalence of 172.9 treatments per 100,000 children aged 0 to 20. Treatment incidence has increased from 44.43 to 58.43 as has prevalence from 149.93 in 2008 to 172.9 in 2009 (12) (See Annex b, graphs 8 and 9).

Grau Rubio (13) and his collaborators carried out a study, using the data from the Health Council of the Autonomous Community of Valencia to evaluate the consumption of growth hormone in this Community during the period from 2003 to 2007. The number of patients treated during this period has risen from 346 in 2003 to 520 in 2007.

Physiology of growth hormone

Growth hormone or somatotrophin is a polypeptide of 191 amino acids with a molecular weight of 22,000 KDa produced in the anterior pituitary gland. The gene which regulates the secretion of GH from the pituitary gland is located in the long arm of chromosome 17 and the presence of a pituitary transcription factor, protein Pit-1 which also controls activation of the prolactin gene and the beta fraction of TSH, is necessary for its expression. Therefore, a deficiency produces a multiple pituitary failure. Production and release of GH from the anterior pituitary lobe is regulated by two pituitary neurohormones: GHRH produced in the arcuate nucleus of the hypothalamus which stimulates the release of growth hormone, and somatostatin which is produced in the paraventricular nucleus and is involved in inhibiting the release of the hormone. From the intermediate lobe through to the portal system, they reach the posterior pituitary lobe and act on the somatotrophin cells. Other neurotransmitters and neuropeptides are known to modulate the secretion of GH, either by directly acting on the pituitary gland or indirectly through the GHRH and somatostatin. In this way, it is known that the cholinergic systems, GABA and dopamine, stimulate GHRH production (2).

GH is secreted in a pulsatile manner; during the day there are small peaks, and it is during the 3rd and 4th phase of sleep that the greatest amount of secretion is produced. The greatest peaks and those of greatest amplitude are produced during puberty. Certain factors such as the sleep-wake cycle, stress, nutritional state, age, and sex affect this pulsatile GH secretion. Once it is released, GH circulates joined to a high affinity transporter protein. GH is present in plasma even during the foetal stage, and it increases significantly during puberty (3).

GH acts in two ways, on the one hand directly through the growth cartilage, and on the other through several peptide growth factors (IGFs). In chondrocytes, it stimulates cell multiplication and induces IGF synthesis. There are two growth factors IGF-I e IGF-2 and up to six transporter proteins (IGF-BP), though IGF-BP1 and IGF-BP3 are the two most studied. They are peptides of 230 – 290 amino acids, very rich in cysteine. IGF1 is produced in most tissues (with highest production in the liver) and is found in plasma, urine, lymph and spinal fluid. Growth factors circulate joined to transporter proteins, and only a small proportion (0.1%) is found in a free form. The concentration of IGF-1 increases with age, reaching a maximum peak in puberty and decreasing slightly thereafter. These levels are regulated by GH itself and by the state of nutrition, being elevated in obesity and lower in malnutrition. It acts through receptors in chondrocytes, stimulating cell proliferation and matrix synthesis (3).

During childhood, the main action of GH is growth stimulation. It also acts on the metabolism of carbohydrates, proteins and lipids. In protein metabolism, it acts as an anabolic agent, increasing the synthesis of nucleic acids and proteins. It has a diabetogenic action on carbohydrates, creating a reduced sensitivity to insulin. In lipid metabolism, it stimulates lipolysis. At a cell level it also acts on muscle tissue, increasing the number and size of cells (3).

As has been said, the present study focuses on the application of GH therapy in children with GH deficiency, but it must be pointed out that this hormone figures in the 2013 list of prohibitions of the World Anti-doping Code[1] so, although remote, the

[1] Resolution of 10th December 2012, from the Presidency of the Sports Council, which approves a list of substances and methods prohibited in sports. BOE Nr. 306, on 21st December 2012.

possibility exists that there may be an illicit diversion of the drug correctly prescribed to a patient, towards non-qualified users, of the fitness world or other similar physical activities.

Aetiology of GH deficiency

When there is a change in synthesis, secretion or peripheral action and mediators (IGF) of growth hormone, the result is undergrowth. According to the level where the disorder occurs, there are different groups of GH deficiency (3):

1. Idiopathic deficiency:

In most cases, the reason for GH deficiency is unknown. The true incidence is unknown, but it could represent up to 80 percent of all GH deficiencies (3). Many of these cases respond to administration of Growth Hormone Releasing Factor (GHRF) which suggests that it is a growth hormone deficiency secondary to lack of hypothalamic GHRF. It is more frequent in males and is sometimes associated with a defect in other pituitary hormones. Endocrine manifestations can be either panhypopituitarism or an isolated hormone deficiency, being the most common GH deficiency followed by gonadotrophin deficiency (3).

2. Genetic deficiency:

Within the GH defects of unknown origin, three different types, with a hereditary basis, have been identified in their isolated form: The most frequent is Type 1, which has an autosomal recessive inheritance. It is divided into type 1A (complete GH deficiency) and is accompanied, after GH administration, with elevated anti GH antibodies which prevent the action of exogenous GH, and type 1B (partial GH deficiency) which responds to exogenous GH administration. Type II GH deficiency has an autosomal dominant inheritance. Type III is X-linked recessive inheritance. Hormone deficiency is only partial and patients respond to treatment with GH (2).

3. Deficiency secondary to injuries in hypothalamus – pituitary gland:

There is an increasing detection of cases in this group. Currently they make up 25 to 35 percent of all GH deficiencies. They can be:

a. Congenital
   i. CNS Anomalies.
   ii. Connatal infections.
   iii. Malformation syndromes.

b. Acquired
   i. Tumours: The most frequent is the craniopharyngioma which affects the hypothalamus-pituitary function and the most common hormone defect is a growth hormone deficiency (3).
   ii. Histiocytosis: infiltration of the hypothalamus-pituitary area by antigen presenting cells generally leads to delayed growth due to GH deficiency (3).
   iii. Central nervous system infections, such as meningitis and encephalitis, can leave, as a side effect, changes in the hypothalamus – pituitary functions (3).

iv. Cranial or total body radiotherapy: It is used in treating leukaemia and tumours such as optic glioma, meduloblastoma, and retinoblastoma: they constitute an important cause of GHD. In the case of children with brain tumours who receive radiotherapy, the frequency of GHD as a side effect is 100% at 5 years (2). The risk is directly proportional to the amount of radiation received and inversely proportional to the age of the child. This GHD is of hypothalamic origin and its clinical effects appear within 6 to 24 months (3).

v. Traumatic brain injury: The origin of the GHD is hypothalamic and can appear many years after the trauma (3).

4. Changes in the mechanism of action of GH (3):
   a. Defects in GH structure.
   b. Receptor defects: Laron.
   c. Post-receptor defects.
   d. Peripheral resistance of IGF.
5. Changes in GH secretion (3):
   a. GH neurosecretory dysfunction.
   b. Reversible decrease in GH secretion.

Clinical expression of growth hormone deficiency

The most evident clinical expression which leads patients to seek medical advice is delayed growth. These children are generally more than 2 SD below the size for their age. The rate of growth is also slower, although the size at birth is normal in most cases as GH is not essential for intrauterine growth (2).

Patients with primary GH deficiency present some unique phenotypical characteristics; thus it is frequent on exploration to find obesity, primarily in the trunk, with thin extremities; the face has a peculiar aspect with a bulging forehead, sunken nasal root, and "baby-doll" facial appearance. Hands and feet are small, nails grow slowly, skin is fine and they have a high-pitched voice. They have delayed development of teeth and in the closure of the fontanelle. Bone maturation is very retarded. They generally do not have mental retardation. Other symptoms depend on patient´s age: thus in new-borns there are frequent hypoglycaemia episodes and up to 50 percent present jaundice. In males, a micropenis is observed as well as cryptorchidism and in girls there is hyperplasia of the clitoris and labia minora. In older children a delayed onset of puberty is common. In those cases of GHD secondary to organic hypothalamus –pituitary lesions, the clinical expression is similar to that previously mentioned except that they are children with normal growth for some time and then begin to present changes with respect to the structural lesion. After, other symptoms derived from deficiencies in other pituitary hormones begin to appear. Weakness, asthenia, constipation, intolerance to cold and bradycardia are symptoms of low thyroid function (3).

Growth hormone deficiency diagnosis

a. Upon suspicion of growth hormone deficiency, with clinical manifestations of short stature and typical phenotype, in presence of an altered growth pattern,

specific tests for GH determination, under basal conditions or after a stimulus can allow detection of the disorder (1-3).

b. Anamnesis: It is important to ask about height and puberty development of parents and other family members, as well as the presence or not of hereditary diseases. The date of birth, height and weight at birth, diseases during pregnancy and childbirth, post-natal diseases, appearance of teeth, feeding, moment undergrowth was noticed (1-3).

c. Physical examination: Complete weight and size examination, measurement of body segments, puberty development, nutrition state, and search of phenotypical features (1-3).

d. Complementary tests:
   - Blood count and blood and urine chemistry, urine culture, stool tests, gliadin antibodies, etc. (to rule out chronic diseases) (1-3).
   - IGF-1: If GHD is suspected, IGF-1 and IGFBP-3 levels must be measured and a study of GH secretion should be carried out. Values of IGF-1 or IGFBP-3 which are more than 2 SD below the normal range suggest a serious disorder of the GH axis, if other causes have been ruled out (malnutrition, liver diseases, hypothyroidism) (1-3).
   - Radiological examination: An X-ray of the left hand wrist can assess bone age. In situations of GH deficiency there is a delayed development of over two years with respect to chronological age (See images 1 and 2 of the Annex). A lateral skull x-ray is useful to see the volume of the sella turcica and presence of calcifications. The most sensitive technique to detect lesions in the hypothalamus - pituitary area is a nuclear magnetic resonance of the sellar region (1-3).
   - Hormone study: the study of thyroid hormones, gonadotrophins and sexual steroids is useful if there is a suspicion puberty disorders, phosphocalcium metabolism, adrenal hormones, etc. Studies of GH and other growth factors should also be carried out (1-3).
   - Special studies: Karyotype, biopsy of jejunum, etc. (2).

e. Specific tests: Carry out basal determinations as well as after stimulation with GH. Basal determination of GH is not very useful except when it is very high (above 10 ng/ml) which can rule out a pituitary origin of undergrowth. In normal children, values are frequently low (< 5 ng/ml)(3):
   a. Dynamic test: a fasting sample, under resting conditions, must be collected and then the appropriate stimulation must be performed: physiological stimuli, such as exercise and sleep, or pharmacological stimulation with insulin, arginine, glucagon, clonidine, L – Dopa. A complete GH deficiency is diagnosed if the response to two pharmacological tests is below 5 ng/ml.
   b. Propanolol test – exercise: 10 mg of propanolol are administered to children with a weight under 20 kg and 20 mg are given to children over that weight. Two hours after propanolol administration, children exercise for 20 minutes. Two GH determinations are carried out, one under basal conditions and another after stimulation. Stimulation test with insulin: 0,1U/kg of rapid action insulin is administered intravenously, followed by GH administration after 30, 60, 90 and 120 minutes.

c. 24 hours or overnight GH secretion: This test provides a more exact quantification of GH secretion. In order to carry it out, samples are taken every 20 or 30 minutes and the number of peaks are assessed which, under normal conditions, are usually 6 or 8, the amplitude of peaks and the overall GH secretion which, in normal subjects, should be over 3.5 ng/ml. This test allows diagnosis of patients with neurosecretory GH deficiency.

d. Plasma IGF-1 and IGFBP-3 are very useful as an initial guide and, although by themselves they do not have a diagnostic value, when a patient presents normal or high values, it is very unlikely that the patient has GHD (1-3).

Growth hormone deficiency treatment

Treatment for isolated, idiopathic or hereditary GH deficiency is based on administration of growth hormone.

Growth hormone, dose and administration routes

Growth hormone (GH) is a biosynthetic drug, obtained through genetic engineering, with an identical sequence to human growth hormone (191 amino acids). This hormone has been available since 1985, a short period after the use of growth hormone obtained from human cadavers was stopped (1956), due to its association with the transmission of Creutzfeld – Jacob´s disease (11). At the beginning, GH was exclusively used to treat growth hormone deficiency (GHD) in children. Later, research was carried out on use of GH for other disorders associated with delayed growth, and its use spread to other clinical conditions. In the United States, GH has been approved for use in renal failure in children (1997), short stature related to Turner´s syndrome (1998), short stature for gestational age with no increase in growth (2001) and for Noonan´s syndrome (2007). Growth hormone was approved for GH deficiency in adults in 1997 (11).

In Spain, GH is prescribed by a paediatric endocrinologist and authorised by the Advisory Committee on Growth Hormone Use in each Autonomous Community.

GH is prescribed in milligrams (mg) or in international units (IU) according to the weight or body Surface area (3IU=1mg) and is self-administered (or administered by parents) at home, as a subcutaneous injection normally 6 to 7 times a week. The injection spot must be changed to avoid plaques of cutaneous atrophy which can negatively affect hormone absorption. Usually, injections are administered at night (between 9 and 10pm) in order to resemble natural GH fluctuations. The dose used varies according to authorized guidelines in each country. In the US, the recommended dose is between 0.025 and 0.05 mg/kg/day; the dose in Europe (and Spain) is between 0.025 and 0.035 mg/kg/day; and in Japan, the common daily dose is 0.025 mg/kg/day or below (14, 15). Experts believe GH treatment should generally not begin before the age of 4 (6). Until very recently, treatment continued until the end of the growth spurt, after puberty, just when the rate of growth is below 3 cm/year and bone age is above 15 years of age for boys and 13 for girls, but with the approval of GH use in treating adults, treatment could continue until growth has completed. During GH treatment, it is necessary to have a series of peptide controls which are repeated every 6 months (2, 16).

The rate of growth (GR) is the most important parameter to monitor. In the case of a bad response, poor compliance or incorrect diagnosis must be ruled out (1). IGF-1 and IGF-BP3 must be annually monitored to assess therapeutic compliance

and for long term safety purposes, assuring levels are within normal range (below + 2 SD according to age and sex) (1). The predictive factors of a good response are delayed bone age at the beginning of treatment and GR in the first year of treatment.

The response to treatment is greater in younger children than in adolescents, in complete deficiency as opposed to partial deficiencies, and in obese patients compared to thin patients. If the indication for hormone replacement is correct, the rate of growth increases with respect to the rate before treatment. During the first year of treatment, the response is usually striking and patients grow between 10 and 12 cm, after it decreases but remains at a similar rate to the normal rate for his/her age. Response is assessed every 6 months by calculating rate of growth and bone maturation. When response is insufficient or it decreases unexpectedly, diagnosis should be rethought and other causes for the delay in growth should be explored such as: poor treatment compliance or presence of an intercurrent illness which stimulates hormone catabolism (1).

Criteria for a rational use of growth hormone (17)

Approved indications

1. Classic growth hormone deficiency.
2. Turner´s Syndrome.
3. Chronic renal failure, in children in pre-puberty period.
4. Prader – Willi Syndrome.
5. Retarded intrauterine growth.
6. Growth deficiency due to an altered SHOX gene.

The patient must meet all auxologic and analytical criteria filling out the protocol for GH use and the growth curves according to the Spanish integrated auxologic standards (2008).

Auxologic Criteria

1. Short stature: less than – 2 SD or below 1 SD of average parent height and, where appropriate, an adult height predicted to be less than genetic height in more than 1 SD.
2. Decreased growth rate: below 10th percentile for corresponding bone age, maintained for a minimum of 6 months.
3. Delayed bone maturation: in over a year as compared to chronological age, except in the exceptional case of association to central precocious puberty secondary to radiotherapy.
4. Newborn: In the case of clinical manifestation of GHD during a neonatal stage (hypoglucaemia), it is not necessary to meet auxologic criteria.

Adherence or compliance problems

To achieve desirable results in long term treatments, such as treatment for growth hormone deficiency in children, an adequate therapeutic compliance is required. The main cause of failure in growth hormone treatment is lack of compliance or adherence and non-persistence with prescribed regime.

Perhaps it is useful to explain some definitions at this point:

Compliance: It is defined as the measure of how patients´ behaviour coincides with clinical prescription or medical advice, or more specifically, the measure of how patients take the medication according to the regime prescribed by health professionals (18). It can also be defined as how patients follow established doctor´s orders in a certain framework (number of days medication is supplied in an observation period). The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has defined therapeutic compliance as the degree to which a patient acts according to dose, dose regime and prescribed period.

Adherence: In the year 2003, the World Health Organization (WHO)(22), defined the term adherence as "the extent to which a person's behaviour - taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider."

However, the clinical treatment results are affected not only by how patients take their medication but for how long they do so, which is why the term persistence is also used.

Persistence: It is defined as the amount of time a patient continues his prescribed therapy. It is also quantified as the percentage of patients who continue following their prescribed therapy after a specific period of time based on prescription and refills (18).

The main difference between adherence and compliance is that adherence requires a patient´s consent with the recommendations received and expresses an active collaboration health professional-patient in decision making which affects his own health. On the other hand, the term compliance implies a submission or obedience to an order, inherent to a paternalistic health professional-patient relationship. This lack of patient participation in the definition may explain the disuse of the term compliance in favour of adherence, but in clinical practice, both terms are used interchangeably. For this reason, in the last few years, the term persistence has gained acceptance in order to define the time a patient continues with his treatment, that is, the amount of time that passes from the start of treatment until its interruption. The benefits of a continuous long-term treatment consistent in administration of GH therapy to children with growth disorders have been deeply studied. The availability of r-GH has benefited children with regards to centimetres gained, when the diagnosis is carried out early and appropriately, as they reach an adult height within the normal range (+ 2 SD). Some studies have shown that many children with growth hormone deficiency do not reach the desired height as adults or their genetic height (+ 0.5 SD). Although most failures are attributed to a late or erroneous GHD diagnosis, in a large proportion of patients growth is suboptimal due to problems in compliance and persistence (18).

The range of compliance in general, in long-term treatment, varies between 50% and 54% (18). These data have been obtained by the NCGS (National Cooperative Growth Study), which started in 1985 recruiting approximately 20 000 children to register results obtained with GH therapy. All children whose data was entered into the database showed a reduction in persistence in each age group. Among children who began GH therapy in 1997, only 44% remained in the NCGS database after four years. Among those who began treatment in 2001, the persistence range after 4 years was reduced even more to 20%. The reasons for discontinuation are reported to NCGS

for about 55% of all patients with about half the reasons reported as completion of the planned course (closure of epiphyses, height within the normal range or satisfaction of patients with height achieved), therefore one can speculate that at least quarter of patients who begin GH therapy discontinue it before completion of growth. Recent estimates by pharmacy specialists indicate that there is a constant reduction in persistence within the first 11 months of treatment with GH, and compliance in children is on average 67% (18).

OBJECTIVES AND HYPOTHESIS

OBJECTIVES

1. Identify key factors that strongly affect growth hormone treatment adherence in paediatric patients with a diagnosis of growth hormone deficiency.
2. Carry out an approach to an economic assessment of growth hormone treatment in children diagnosed with growth hormone deficiency, taking into account the variables which affect this treatment.
3. Determine clinical and management impact derived from self-administration of GH in Spanish paediatric population suffering from growth hormone deficiency using an electronic device that registers administration and therapeutic adherence parameters.

HYPOTHESIS

Improvement in control of GH treatment adherence in a paediatric population could lead to health and economic benefits.

Justification

The possibility of administering biosynthetic growth hormone to certain short stature groups has not only improved their physical conditions, but also their quality of life and psychological wellbeing. It is fairly common in the social and family surroundings of children of short stature to use inadequate educational patterns. Short stature is a multidimensional problem which requires interdisciplinary medical, psychological, educational and social care for its correct treatment. In GH deficiency we commonly find emotional, neuropsychological, school and family problems which require psychological guidance and intervention as a crucial element to optimize the attention and treatment received by these patients (20).

Early administration of growth hormone in pituitary deficiency not only improves the physical appearance of an individual, but also improves the synaptic activity in neural networks and circuits, particularly in the cerebral cortex, helping to improve the cognitive and adaptive functions of the subject, especially during the schooling period.

Patients with growth hormone deficiency, particularly those treated at an early age, respond well to this treatment and can achieve a normal height during childhood and normal or almost normal height in the adult age, but "drugs will not work if they are not taken" (22, 23). As GH deficiency is not a life-threatening disorder, adherence to treatment can be problematic. Once diagnosis is confirmed, hormone replacement is recommended for a long period of time, exacerbating adherence problems. It has been observed that the duration of a treatment is inversely related to its adherence in chronic diseases. In addition, treatment adherence can, at some times, be compromised by the low motivation of the doctor who does not adequately explain treatment

benefits or the fact that its results are not immediate (7). The need for daily subcutaneous injections can further aggravate treatment adherence as injectable therapies are perceived as painful and difficult to administer. In order to achieve a good degree of adherence, an effective and efficient planning of treatment is necessary. For this reason, it is very important for devices used for treatment administration be easy to use (8).

The World Health Organization considers the lack of adherence to be a serious problem and proclaims setting up adequate strategies to solve this issue, as it has important clinical as well as economic consequences. Low adherence attenuates optimal clinical benefits and, therefore, reduces the general effectiveness of health systems.

When analysing clinical and economic consequences of lack of adherence it is necessary to take into account: the difficulty in measuring it, the different methods used and the lack of a reference "gold standard", so comparisons must be made with caution (24). Regarding clinical consequences, there is a clear and direct relationship between lack of compliance and achievement of worse results in health. The difference between efficacy and effectiveness of a treatment are ever more evident in situations of non- compliance with therapy. The clinical impact of lack of adherence depends on the interrelationship between three factors: the type of non-compliance, the disease treated and the properties of the drug prescribed. With regards to the type of non-compliance, two situations are possible: treatment does not begin or treatment is interrupted once it is started, which will have different consequences depending on the disease being treated.

On the other hand, assessment of the economic consequences derived from non-compliance is hindered by methodological type problems, due to the difficulty in establishing a consensus on its definition and assessment. However, it is clear that lack of adherence directly affects the increase in costs of treatment (24).

For over three decades, researchers and doctors have tried to understand and improve patient adherence to their treatment regime in chronic diseases, including prophylactic treatments or those for disease management.

The aim of this research study is to study adherence to growth hormone treatment in paediatric patients, the factors that affect it and how it can be improved.

METHODS

LITERATURE REVIEW

Search strategy

A literature review was conducted in PubMed (US National Library of Medicine) with the following limits: articles published in English or Spanish until 31st July 2013, in humans and in paediatric patients (0-18 years of age). The following key words were used: "Growth Hormone", deficiency, treatment, adherence, compliance, "treatment adherence", and "treatment compliance", and were combined in an advanced search.

The reference lists of the articles were reviewed and contacts with experts and pharmaceutical companies were contacted to try and find published or unpublished clinical trials.

Selection Criteria

Articles included in the search were: general review articles on growth hormone deficiency in children of short stature; treatment with growth hormone; compliance and persistence in patients receiving hormone; factors affecting treatment compliance; controlled multicentre clinical trials which include compliance with growth hormone treatment in children (0-18 years of age); controlled clinical trials with results on final height achieved after treatment.

Review Methods

In our search strategy, after combining the previously mentioned key words, we only selected those articles providing relevant information to complete this research study.

Titles, abstracts and key words of all registries were examined by two reviewers (ZS y MG) and those articles that did not meet inclusion criteria were excluded. As the results obtained were limited and several of our questions remained unanswered, we completed the Medline Search with a manual search.

The exclusion criteria included: Studies that had not been carried out in humans or carried out in adults, studies where participants did not have short stature due to growth hormone deficiency, studies in which GH was not administered, studies in which growth was not one of the results measured.

Other references

For the introduction of this work, other bibliographic sources were checked, such as books, publications of the Spanish Society of Paediatric Endocrinology (SEEP), and we also attended the 2011 Spanish National Congress on Paediatrics in order to update our knowledge on this topic.

Selection of articles

Publications were selected if they met the following inclusion criteria:

1. Target population: Children between the ages of 0 – 18 years of age with growth hormone deficiency (Idiopathic Growth Hormone Deficiency).
2. Factors that affect compliance, adherence and/or persistence of recombinant growth hormone treatment, including the device used. AND/OR:
3. Assessment of final results after GH administration: cm gained, rate of growth or changes in height with standard deviation.

Data gathering and analysis

Two reviewers assessed whether articles met the inclusion criteria. A reviewer extracted the data and this was verified by the second reviewer. The primary results were: final height achieved in children after recombinant growth hormone treatment and adherence to treatment. Secondary results included the variables considered to be important to carry out the economic approach.

Data extraction and processing

Data was extracted from each selected article according to a form created by the reviewer´s themselves in order to obtain the data necessary to achieve the objectives outlined above.

1. General Information: authors, reference, country, year of publication and, where appropriate, study design.
2. Intervention: Dose, administration route, administration regime, types of devices for hormone administration.
3. Participants: Total number, number of groups being compared, age, sex, inclusion and exclusion criteria.
4. Variables: The following were identified from the articles selected:
   a. Factors which affect adherence to growth hormone treatment.
   b. Data from published articles useful for carrying out the economic model: Height of child at the beginning of treatment and results obtained after it, focusing mainly on: centimetres gained, rate of growth, changes in height measured by a standard deviation score, final or close to final adult height.

Synthesis of data

We carried out a qualitative review of the chosen articles, and later carried out a descriptive summary of the results obtained, identifying the variables of interest in order to respond to the objectives set out.

ECONOMIC MODEL

Assumptions of the model

1. For the age distribution of the infant population treated, the data published in March 2010 by the "Consell Assessor sobre la utilització terapèutica de l'hormona de creixement i substàncies relacionades", in table 9 of its activity

report for the year 2009 was used (See Annex d, table 4) (12). For this model, only ages between 4 and 18 were considered, assuming that for the age groups (three years), in the previously mentioned table, the proportion of children in each specific age was considered to be the same (For example: in the 4-6 age group, there are 102 children with idiopathic GH deficiency which is equivalent to 34 children aged 4, 34 children aged 5 and 34 children aged 6).

2. Only idiopathic growth hormone diagnosis was considered, and the remaining indications for which GH is provided were excluded.
3. The sex distribution used was that provided by Grimberg´s data (54% males and 46% females) (9).
4. The tables published by Fundación Faustino Orbegozo Eizaguirre were used for the distribution by weight and age: (4).
5. The treatment period considered in the economic assessment was one year, and the population treated was established at 1000 children between the ages of 4 and 18.
6. Calculations were performed using a uniform therapeutic regime for the entire year of 0.035 mg/kg weight and day, regardless of weight variations and changes that can occur during the therapeutic regime after regular medical check-ups.
7. Regarding compliance with dose administration, a threshold was established at 75% of the prescribed dose. This means that, if the amount remaining in a vial is above that threshold, a complete administration of the next dose will be assumed whereas, if the amount left in a vial is less than 75% of a dose, than it is assumed that the following dose has not been administered.
8. A compliance of 100% is assumed which, in the future, could be adjusted once the real compliance for each patient is checked.

Calculations

1. a daily dose distribution (mg/day) is calculated for each child according to their weight, in order to determine the percentage of the total population that needs each dose.
2. The cost of the annual dose is calculated by multiplying the dose (mg/day) by the percentage of total population under treatment that needs that particular dose and the number of days (365.25) in a year (which is the length of time established for the treatment) and by the cost of the drug being evaluated (the Laboratory Sale Price, which is the maximum industry price of drugs).
3. As the daily dose each child needs is based on his/her weight, the mg of growth hormone wasted per vial depends on the content of the vial being used and the patient´s dose, assuming that if after the last complete dose there is less than 75% of another dose left in the vial, it will be wasted, while if the amount remaining in the vial is more than 75% of a dose, we assume a complete dose has been administered.
4. On the other hand, the cost of doses wasted is calculated, multiplying the mg of hormone wasted (according to what was discussed in point 7 above) by the cost of growth hormone being used, according to Laboratory Sale Price (17.5€/mg in this case).

5. The total cost for a 12 month treatment is, therefore, the cost of complete vials used by each child of a certain age and weight as well as the cost of mg of hormone wasted.

RESULTS

TYPES OF DEVICES FOR ADMINISTERING GROWTH HORMONE

The European Paediatric Endocrinology Society and the Society for Research on Growth Hormone recommend that GH replacement therapy should be carried out for an extended period, and should begin at the time of diagnosis. GH therapy faces the challenge of achieving an adequate compliance due to the following: the use of growth hormone takes place mainly in children; it is a chronic treatment; often the treatment benefits are not immediate; and treatment requires daily subcutaneous injections. For these reasons, in order to assure treatment adherence, convenient methods are required which should be easy to learn to use, and well accepted by patients and/or their families, as usually it is them who administer treatment taking into account that the patients receiving treatment are children (21).

The development of devices for self-administration of drugs has allowed the daily therapeutic management to be a lot easier and thus lead to improved compliance. Towards the end of 1980, pens started to be used for hormone administration, and towards the end of 1990, needless devices were already available. Years later, an important technological innovation took place. In 2007 an automatic device for hormone administration was put on the market. This device is easy to use for children, the date and dose of each injection is recorded, and it allows control of treatment compliance or, where appropriate, a patient with a non-responder phenotype can be identified. There are very few publications or studies which evaluate factors that affect the choice of a device and, therefore, its effect on treatment compliance, which is very low in this group of patients (25).

The devices available for growth hormone administration have evolved through the years, from conventional needles and syringes, which are directly related to the lack of adherence, to more friendly devices such as pre-charged pens and electronic devices (26).

The following devices for r-GH administration are currently on the market:

1. PEN TYPE INJECTION DEVICE: Its appearance is similar to a pen. It has a cartridge for growth hormone inside. The advantages of this system are that the doses are predetermined and the devices can be attractive for children.
2. SELF-INJECTION DEVICES: These devices completely hide the syringe and needle so they are not visible. With a simple button, the needle is introduced into the skin and the growth hormone is injected. This procedure is quick and is not painful.
3. HYPOGUARD INJECTION SYSTEM: This device uses an enclosed insulin syringe. They are very useful for those parents who find it difficult to give their small children injections.
4. NEEDLESS INJECTION SYSTEM: In this device, GH is introduced through the skin using a high pressure air injector. Therefore, this system does not use a needle. This can sometimes produce slight pain or leave a small mark on the skin.

5. ELECTRONIC DEVICE: This device, together with reminder alarms and other customizable elements, has software which allows an automatic adjustment of the daily dose through an algorithm which calculates and adjusts the load of each cartridge to the dose prescribed by the doctor with a minimum variation. Dose information appears on the digital screen showing: the amount injected; the amount of GH remaining in the cartridge and the number of doses administered. Therefore, it has no wastage and allows the true compliance with treatment regime to be monitored, thus allowing non-responder children to be distinguished from non-adherent children, and avoiding superfluous expense to the health system and inconvenience and unnecessary risks to non-responder patients.
6. CONVENTIONAL SYRINGE AND NEEDLE SYSTEM: In its early stages, r-GH was administered with a syringe and an insulin needle. Needles can have different lengths and gauges. The short needle, measuring 8mm and with a diameter 31G, is the one recommended for children and adolescents. This way of administering growth hormone is subjectively associated with pain and, if the technique is not adequate, a small amount of blood can appear in the injection site.

Types of devices:

Product	Device	Vial	Size of vials
Genotonorm	Pen	Double chamber	5.3 mg; 12 mg
Genotonorm	Precharged pen	Single doses	0.2-2 mg
Humatrope	Precharged pen	Powder and solvent	6mg; 12 mg; 24 mg
Norditropin SimpleXx	Pen	Injectable solution	5mg; 10 mg; 15 mg
Omnitrope	Syringe and pen	Injectable solution	3.3 mg; 5 mg; 6.7 mg
Nutropin AQ	Syringe and pen	Injectable solution	10 mg
Zomacton	Jeringa	Powder and solvent	4 mg
Saizen *	Electronic device	Powder and solvent	1.33 mg; 8 mg

** In the present study, it was assumed that administration of Saizen was carried out with the electronic device Easypod®.*

With regards to adherence to treatment in paediatric patients, in the publications found, compliance was assessed in an indirect way using directed questionnaires. Very few studies have examined GH treatment regimes, and the methods used to measure adherence are very varied. In general, in the articles included in our project to identify the dependent variables for our assessment of adherence to r-GH treatment, the following aspects were evaluated: start date of treatment; who trained them in their administration; number of units in the bottle, frequency of dose administration, number of doses missed, importance of treatment, description of administration device, who administers the hormone. Environmental factors and the emotional state of patients are also evaluated. The following factors were associated with non-compliance: patient age, presence of pain, doses forgotten, adverse effects, being outside home, presence of concomitant disease, need to take "holidays from doses", participate in an important event, underestimation of treatment and results obtained, poor doctor-patient relationship, length of treatment, accessibility and ease of use of the administration devices, design aspects of the device, and socio-economic influence. The lack of adherence leads to worse final treatment results.

FACTORS WHICH AFFECT NON-ADHERENCE TO TREATMENT

During this bibliographic review we have identified key factors which directly affect treatment adherence. In the following paragraphs we describe, in a general way, each of these. After their identification, we suggest strategies to improve the lack of compliance with therapy:

1. ***Factors related with the patient:*** Age (children are a special population), their social and cultural surroundings, the level of education of child and parents, personality and self-esteem of child and the degree of responsibility to face their medical problem. These factors affect treatment results. Some patients do not follow treatment because they feel they have not been treated correctly or the drug is not effective, or because they do not completely understand the medical explanations regarding their medical treatment. Other times the cause is simple forgetfulness, or difficulties in obtaining medication.
2. ***Factors related to medication:***
   a. Adverse effects: The interruption of treatment due to the appearance of adverse effects is one of the most common causes associated with non-compliance. These can be causes of therapeutic abandonment or they can appear when medical recommendations are not properly followed.
   b. Characteristics of the active principle: pharmacokinetics, pharmacodynamics, pharmaceutical form and administration route. Treatment is frequently abandoned if the expected result is not observed in the short term.
   c. Complexity of therapeutic regime. Therefore, simplification of treatment increases patient adherence (technological innovation), and thus the probability of obtaining positive results.
   d. Cost.
3. ***Factors related to the disease:*** In general, it is more likely for chronic diseases to have adherence problems.
4. ***Factors related to the medical professional:*** lack of time in medical consultations, poor doctor-patient communication, uninformative explanation of disease and consequences if therapy is discontinued, and inadequacy of technique used for teaching how medication is administered.

Factors which affect the lack of therapeutic adherence: synopsis

FACTORS THAT INFLUENCE LACK OF COMPLIANCE WITH TREATMENT	
Patient	Age (Children are a special population) Cultural and Social Setting Educational level Personality
Drug	Adverse effects Pharmacokinetic and pharmacodynamic characteristics of active principle. Pharmaceutical form, administration route and convenience of administration Complex therapeutic regime Cost
Disease	Chronic
Health Professional	Lack of time Inadequate doctor-patient communication Inadequate training in administration technique / method of taking drug Inadequate explanation of disease Inadequate explanation of consequences of lack of compliance

STUDIES THAT TRY TO MEASURE TREATMENT COMPLIANCE WITH GROWTH HORMONE

There are very few clinical studies that measure adherence to treatment with GH in children. In our search strategy, only one review related treatment adherence to the number of centimetres gained and the type of device used (27).

Few researchers have studied the reasons for lack of adherence to growth hormone therapy and strategies that could help reach 100% treatment compliance. Perhaps it is due to the complication of carrying out studies to measure treatment adherence, as the direct way to measure levels of medication or its metabolites in blood is expensive and inconvenient for patients. It is for this reason that most studies use indirect measures to assess compliance, such as questionnaires directed at children or their parents.

Next, a short description of the articles, according to their year of publication, found in the medical literature related to the topic of this report, is presented in order to show the evolution of research on GH treatment adherence.

Gacz and Hasszu (29), between the years 1973 and 1988, studied the effects of the educational level of parents on compliance with GH therapy in 78 GHD patients. Treatment was administered 2 or 3 times per week and patients were subjected to a medical check-up every 3 months. Researchers observed that patients whose parents had a greater educational level showed greater compliance with therapy. In addition, diagnosis of these children was made significantly earlier ($p<0.001$). This study concludes that socio-economic family factors are very important in the early diagnosis of a child with GHD and, as a result, in final height achieved. In addition, it was also observed that the group made up of girls were less compliant than the group with

boys, which perhaps reflects the importance that parents give to the height of their children depending on their sex.

Lieberman et al (30) studied 96 paediatric children (59 boys and 37 girls), 15 of them with GHD and all of them with a daily GH therapy prescription for 12 to 66 months. Its main objective was to assess the degree of satisfaction with therapy prescribed using a 53 item questionnaire. The areas evaluated were: emotional state of child, physical self-perception, perception about treatment prescribed and their medical problem, their relationship with their school mates and their family, satisfaction with their access to treatment, satisfaction with their medical-patient relationship and with results achieved. Despite the fact that a final height was not established, the degree of satisfaction and compliance with therapy in this sample was high.

In another work, Smith, (31) who also tried to study the factors which affect treatment adherence, developed a 22 item questionnaire which he tested with 188 patients who had received at least 1 year of treatment with r – GH. On the one hand, he assessed the degree of understanding that patients had about the therapy they had been prescribed. For this purpose, he designed questions to find out if patients knew the amount of milligrams they were administering on a daily basis and found that less than 20% of these patients were able to identify the correct amount in each vial of r-GH they were using. Only 40.4 % of patients showed that they had adequately understood their treatment; 29.3 % showed a limited understanding and the rest (30.3%) did not have a clear understanding of the amount of treatment they were receiving. In addition, he observed that among patients, there was quite a high degree of confusion regarding the daily doses required for injection. On the other hand, he observed that several mistakes were made when dissolving and mixing the hormone and this was the factor that most affected lack of adherence. Compliance was evaluated through questions that tried to find out the number of doses missed and the difficulties patients faced during the injection. 48% of patients were classified as good compliers (skipping less than 5 doses since their last visit to the doctor), 32% were classified as intermediate compliers (skipping less than 10 doses since their last visit) and 18% were non-compliers (skipping more than 30 doses)($p=<0.001$).

López- Siguero et al (32) carried out an observational study for 1.5 years analysing the psycho-social environment of 90 children (over the age of 8) on GH therapy from the Hospital of Málaga, to try to explain the factors that affect final results achieved after GH treatment. He observed that the degree of knowledge patients have about their disease and their understanding of the consequences of a lack of good adherence to therapy are important factors that determine the degree of compliance and acceptance of therapy. Out of the 88 valid questionnaires, 28 children had attended a workshop that was organized to explain growth problems and, specifically, GH treatment. The objective of the questionnaire was to evaluate acceptance and knowledge the child had regarding his therapy, considering 3 aspects: 6 questions were general, 8 questions were related to the knowledge the child had of his/her GH therapy and 7 questions focused on their degree of acceptance. The results obtained were compared between the two groups of children, those who had attended the workshop and those who had not. Those who had attended the workshop showed a greater degree of acceptance and compliance with therapy ($p=<0,001$). In general, it was observed that children showed a lack of knowledge regarding hormone administration. Approximately 40% of these children do not know the amount of

milligrams they have to administer, 85% do not know how many milligrams are in each vial, 68% do not pay attention to the brand of the hormone they use and 80% do not know how much solvent to add to the mixture. Finally, 50% of patients had no idea when they would complete the prescribed treatment. The results obtained were very similar to those observed by Smith.

The multicentre study of Oyarzábal et al (33), also evaluates factors that affect treatment adherence. A 28 item questionnaire, based on Smith´s and adapting it to the objectives of his study was applied to 473 Spanish paediatric patients (mean age 12.6, 246 boys) who had been receiving GH therapy for an average of 3 years. The questionnaire gathers data on compliance, dose calendar, type of device used, type of training received. Compliance was classified into four categories according to the percentage of doses missed and was classified as "excellent" if there was 0% doses missed, "good" <5%, "favourable" if 5 – 10% doses were missed and "poor" if more than 10% doses were missed. The degree of compliance was excellent in 74% patients, good in 20.1%, favourable in 3.4% patients and poor in 2.5%. Compliance was better in patients who self-administered their injection ($p<0.001$), in those who had received training by hospital personnel ($p<0.01$) and in those who used precharged pens ($p<0.05$). The socio-economic status and gender were not associated with therapeutic compliance. Regarding the type of device used, no significant differences were observed. However, in those patients using conventional syringes, compliance was worse than those using any of the other devices, while those using automatic pens had a better compliance than those using any of the other devices evaluated ($p<0.05$).

The objective of the article published by Wickramasuriya et al (25) was to evaluate factors which determine the reasons for patient choice of device for GH administration and the attributes which can affect compliance with therapy. 125 patients with pathological short stature were evaluated. These patients were offered the opportunity to freely choose a hormone administration device: 65 children, average age of 9.05, chose a device with a needle, 57 children, average age of 9.3, chose a needle-free device, and only 3 chose the conventional syringe. There was no significant difference between the ages of the children who chose a needle-free device and those who chose a device with a needle. Among male patients, it was observed that the appearance of the device was an important factor in their choice as blue devices were more popular among them (59.4%). However, dark blue devices were more popular among girls (40.8% of them chose this colour). If only light blue colour devices are considered, 66% of boys chose them ($p=0.056$). The following factors, in decreasing order of frequency, affect the choice of a device: ease of use, needle-free device, colour of device, noise-free device when administering hormone, presence or not of a needle-protection, automatic needle insertion, size and general appearance of device.

Haverkamp et al (34) described the following factors to be associated with low adherence to growth hormone treatment in children: age (adolescents have a lower adherence than younger patients due to the feeling of autonomy of adolescents and their need to be independent of their parents, disease chronicity, emotional and psychological problems, day to day social problems and inconveniences of the technique for hormone administration, as well as the ease of use of the device, duration of treatment, lack of understanding of the disease and consequences of non-adherence. Therefore, to face this challenge, the most important factors are medical advice and education both of patient and family. Haverkamp recognises that low

treatment adherence can be improved if it is detected early by a professional, so the child can be motivated to follow his prescribed treatment. Therefore, it is very important to provide individual attention to each patient so their behaviour towards their therapy can be improved. In addition, in this study, the need for economic studies to quantify the cost of lack of adherence to GH treatment is suggested so the financial benefits of a good adherence to therapy can be proven.

Rosenfeld y Bakker (18) also identify factors which affect GH therapy compliance, obtaining similar results to the previous study, regarding the fact that the group of adolescent patients is the one showing mostly a poor adherence to treatment (between 44% and 77%). They relate this lack of adherence to their unwillingness to assume responsibility for their prescribed treatment. Rosenfeld (4) carried out a study with the main aim of understanding cultural and intellectual beliefs surrounding growth hormone deficiency to try to identify specific problems for disease management. Most patients refer that they lack enough information regarding the disease and consequences of poor treatment compliance. The main reasons they state for abandoning therapy are that it is an uncomfortable treatment, the period of time between medical visits, every 3 to 4 months, is too long, and patients relate therapy to pain which leads to poor compliance. These results suggest that endocrinology specialists and the nursing teams must develop better tools and resources to monitor compliance and identify barriers involved in persistence and compliance with treatment.(4) A study was carried out to evaluate adherence and therapeutic compliance in different population groups in March 2006. The study included 882 patients diagnosed with GHD, Turner´s Syndrome and idiopathic short stature who had received therapy for at least 2 years. Patients were classified into three groups. Group 1 corresponds to paediatric patients between the ages of 4-12, Group 2 corresponds to adolescent patients between the ages of 13 and 17 and Group 3 corresponds to adults over the age of 18. Three subgroups were identified in each group: subgroup A was made up of highly compliant patients; subgroup b included patients who were occasionally compliant and subgroup c were non-compliant and sceptical patients. To evaluate compliance, a questionnaire was given to detect the reasons for lack of adherence. The study included questions focusing on determining the number of GH doses missed during the worst month (month with the maximum number of doses missed). They were asked to indicate: reasons for missed doses, their experience during the following periods: screening period, pre-diagnosis period, and period while diagnostic procedures were being carried out. They were also asked about the quality of the training received and the preparation of the hormone for its administration and injection, duration of medical visits and quality of doctor-patient relationship, degree of participation and patient´s knowledge about everything related to his/her treatment, beliefs about the benefits of GH therapy and the importance of compliance, satisfaction with initial results, cost of treatment and coverage, duration of therapy and patient´s demographic characteristics (age, education and monthly income).

The main reasons provided in the questionnaires for missed doses are: forgetfulness in taking doses, forget to renew prescription or recharge, experience of adverse effects, impossibility to pay treatment (would not be applicable in the Spanish National Health System), patient was away from home, dose coincided with an important event and patient feels a need to take “holidays” or have a rest from treatment.

This study concludes that the doctor must emphasise to his patients the importance of treatment adherence and that results obtained in final height of child depends on this. The medical professional must ensure that both children and their parents understand this and must provide advice and adequate training in the technique for hormone administration.

Kapoor (35) carried out a cross-sectional study to measure the concordance between therapy duration and doses missed. He gathered information from 75 paediatric patients, mean age of 12.3, with GHD who had been receiving therapy (0.08mg/kg/day doses) for a year. Questionnaires were sent to the general practitioner who prescribed GH. The questionnaire asked about total doses prescribed (number of vials and cartridges) which were specified in each prescription for three specific 12 month periods, using data registered in the last twelve months of the medical history of these patients. The questionnaire was sent to 66 GP´s and 58 answered. The devices used in this study were: automatic injection devices (n=38), manual pens (n=33), and needle-free devices (n=4).

Concordance was objectively assessed using total GH registered in the medical history compared to the amount prescribed by doctor in a 12 month period. 39% of all patients missed more than one dose a week and 23% missed more than two doses a week. This study concludes that a low concordance is associated with long-term treatments (over a year) and a reduced growth rate.

Norgren et al (28) observed that the main factors associated with lack of adherence are: underestimation of the consequences of missing doses, discomfort in applying injection and difficulty in using administration devices, lack of satisfaction with treatment results, poor doctor-patient relationship, poor patient motivation, inadequate training in self-injection technique and a length of treatment over 2 years. Factors which were positively associated with adherence were socioeconomic factors, where children of parents who had greater income presented better adherence (28).

The study of Fuchs et al (21) compares the pen NorditropinFlex Pro (precharged pen) with NovoFine (32G needles) regarding acceptance and ease of use. To evaluate acceptance of the device, 70 patients on GH treatment for over one year, with a median age of 14, 67% of them males and with no significant demographic differences, filled out a 21 item questionnaire. Out of the patients interviewed, 64% preferred the precharged pen. The use of the pen was reliable when the prescribed dose was administered. This means that the ease of use of the injectable pen could increase the number of patients using it, due to the advantages offered by this device compared to others, and this could have a positive effect on improving growth hormone treatment. The results from this study show that ease of use is an important factor in choosing an administration device for GH.

The article by Pfutzner et al (26) aims to evaluate the ease of use of GH administration devices, the intuitiveness in its use, and the preference for precharged pens to improve compliance with GH therapy. In this study, 56 patients (62.5% boys, mean age of 13.6 and 44 with GHD) were included and different devices on the market were evaluated (Norditropin FlexPro, NovoNordisk, A/S, Easypod and Genotropin). In this study, the time spent for hormone administration was measured in two groups, one which had been trained and one which had not received any training. In both groups the time spent for hormone administration was shorter when a precharged pen (FlexPro) was used than when any other device was used. This

device was considered a lot easier to use, it had greater precision in the doses, its use was more intuitive than the other devices evaluated and its use could improve adherence to GH treatment.

Bozzola (36) carried out a multi-centre observational study which lasted 3 months, where 824 children, with a mean age of 11, were included. The aim was, on the one hand to evaluate adherence to treatment using an electronic device for administration of r – GH and, on the other, device acceptance by patients. Two groups were made: one which had already received hormone treatment (223 children) and another group which had not received any previous treatment (601 children). Adherence was measured with data registered in the electronic device. Device acceptance was evaluated with a questionnaire which focused on questions regarding the number of doses missed in a month, ease of use of device, convenience in its use and their opinion about continuing to use the device in the future. 92% of these children showed good adherence to treatment and, on average, missed only 2 doses a month.

Lastly, Kappelgaard (68) carried out a non-controlled multinational study with 50 paediatric patients comparing ease of use and preference of patients for 2 devices, FlexPro Penmate and NordiFlex PenMate. Both systems hide the needle on injection which appears to reduce the perception of pain (69, 70). The difference is that FlexPro appears to be simpler to use and has an injection system which signals when the correct dose has been injected. Each participant received a one hour session to explain the use of both devices and then they were asked to fill out a questionnaire with 47 questions regarding the use and functionality of the devices, ease of use, preference for devices, evaluation of the potential impact in future treatment and, finally, the opinion of the moderator regarding the way in which each system had been used by each participant. 80% of patients preferred FlexPro, mainly because learning how to use it had been easier, as well as the fact that it was easier to mount and dismount the needle and inject the dose.

See Annex d, Table 7: Important aspects to consider in adherence to treatment with growth hormone, and assessment area by author.

RESULTS OBTAINED IN GROWTH AFTER GROWTH HORMONE THERAPY

Primary results used to evaluate the effectiveness of growth hormone treatment

1. **Height**: Measure of the height of the human body from feet until the cranial vault (cm).
2. **Height by standard deviation score**: Height relative to the size of other children the same age.
3. **Final height** (cm or Standard Deviation Score-SDS): height achieved after end of growth (in cm or in relation to adult rules).
4. **Growth rate** (GR): Change in size over a certain period of time (cm/year).
5. **Growth rate with standard deviation score**: GR compared to children of the same age.
6. **Bone age**: A measure of skeletal maturity.
7. **Psychology**: Measure to indicate if treatment has psychological effects. Evaluate how quality of life (QoL) of these children is affected by their disease.

Scientific evidence must be used to determine the effectiveness of growth hormone treatment. However, while carrying out this study we faced the limitation that in published articles, all variables which need to be considered to evaluate the efficacy of a treatment as observed in the growth table (Annex d, Table 8) were not measured. The results obtained show differences regarding the population treated and the doses used. On average, we can conclude that patients treated with growth hormone can reach an average population size, increasing their height by 40 to 50 cm (38). As we can see in Table 8, there is great variation in results obtained in growth after using r – GH. For this reason, it has not been possible to carry out economic calculations on a cost by centimetre gained basis.

See Annex d, Table 8: Table comparing effectiveness in the use of growth hormone r-GH, by author.

Results of the economic model

The following are the variables we consider necessary to take into account for an economic approach:

- Size of the population to be treated (patients diagnosed with GHD).
- Treatment period (12 months).
- Age (4 – 18 years of age).
- Distribution by age of population treated.
- Distribution by sex (54% males).
- Distribution of weight by age.
- Therapeutic dose.
- Volume of vials on the market.
- Price of vials (17.5 €/mg).
- % adherence (in our model we consider 100%).

Economic evaluation approach

In Table A we can observe the distribution by age, sex and weight. In the first column, we have specified the age of our population to be between 4 and 18; in the following column we specify the population affected by GHD, as a percentage over the total, according to age, using the "Informe d´activitats: Any 2009" as a reference12); in the following column, we observe that males are preferentially affected by this disorder (9) (calculations are made per 1000 children) and in the last column we observe the weight which corresponds to a certain age, having used the P3 data from the growth tables and curves used in Spain, Orbegozo (4). A quick view shows that the population most affected by GHD is that between the ages of 10 and 12, showing 13.8% of cases, followed by those between 7 and 9, 8.56%, and least affected are those between 16 and 17, representing 0.44%.

In Table B we have added the different presentations of growth hormone, size of vial, and cost per milligram which is 17.5€/mg for each brand. There are seven different pharmaceutical companies that have innovated in the area of growth hormone administration.

Table A: Distribution of the population by age, sex and weight

		Male	Female	Weight (kg)	
	POPULATION	54%	46%		
Age (years)	Percentage of total population	1000 children 4-18 years of age		Male	Female
4	5.06%	27	23	13.00	8.88
5	5.06%	27	23	13.55	9.25
6	5.06%	27	23	14.14	10.27
7	8.09%	44	37	14.75	11.86
8	8.09%	44	37	15.64	13.92
9	8.09%	44	37	16.99	16.36
10	12.46%	67	57	18.94	19.07
11	12.46%	67	57	21.51	21.96
12	12.46%	67	57	24.69	24.94
13	7.30%	39	34	28.37	27.90
14	7.30%	39	34	32.40	30.76
15	7.30%	39	34	36.52	33.41
16	0.42%	2	2	40.43	35.77
17	0.42%	2	2	43.75	37.73
18	0.42%	2	2	46.03	39.21
	100.00%	540	460		

Table B: Different presentations of growth hormone

Product	*Content of vial (mg)*	*Cost per mg*
ELECTRONIC DEVICE		
Saizen with Easypod (Merck Serono)	8	17.5 €
PRECHARGED PEN		
NutropinAq with NutropinAq Pen (Ipsen)	10	17.5 €
Humatrope with Humatrope Pen (Lilly)	6	17.5 €
Genotropin with Genotropin Pen (Pfizer)	5.3	17.5 €
Omnitrope with Omnitrope Pen (Sandoz)	5	17.5 €
Norditropin/SimpleXx with NordiPen (Novo Nordisk)	15	17.5 €
SYRINGE		
Zomacton (Ferring)	4	17.5 €

In Table C we see the cost per treatment period with growth hormone, in accordance with the measures taken in the Royal Decree-Law 16/2012 where a Laboratory Sale Price of 17.5€/mg has been established for all presentations, and the wastage cost varies depending on the device used. The average treatment cost of all devices is 4.446.000€. If we add the wastage, this means an additional 174.000€, on average (varying the wastage between 2.11% and 7.53% of the total hormone cost, which can be seen in Graph A). Therefore, the average total cost of the pens is 4.620.000€. All costs are calculated for one thousand children with GH deficiency treated for a year.

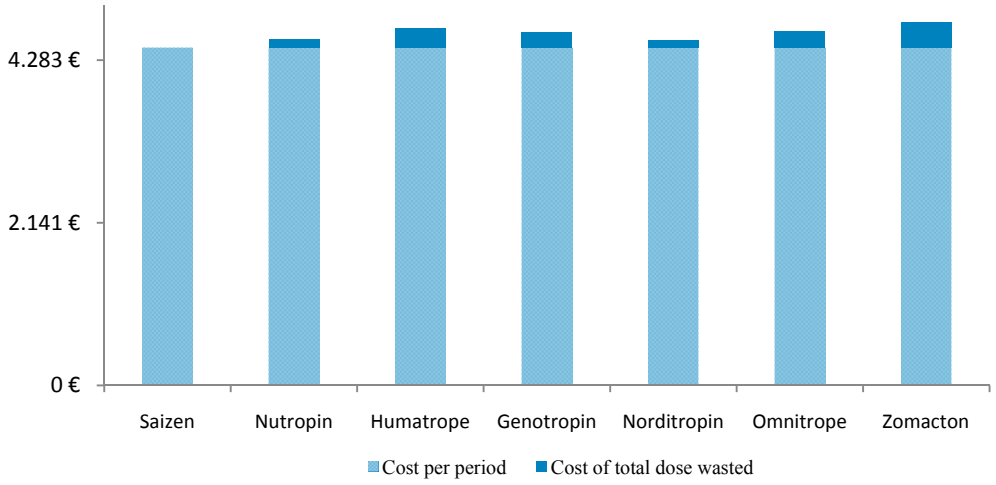
With this data we can conclude that, as healthcare decision makers, it is not enough to only consider the isolated cost per treatment period, but the wastage for each treatment vial must be included and a global analysis of the product must be carried out.

The electronic device, due to the characteristics described, offers zero wastage thanks to its dose adjustment and allows monitoring of effective compliance to treatment prescribed. This allows non-responder children to be distinguished from non-adherent children, thus avoiding unnecessary costs to the healthcare system and discomfort and unnecessary risks to non-responder patients, overall improving health results.

Table C: Device used, cost per period, cost per doses wasted and total cost

Device	*Cost per period*	*Cost of wasted doses*	*Total*
Electronic device (Saizen)	4,446,000 €	0 €	4,446,000 €
Pen (Nutropin)	4,446,000 €	108,000 €	4,554,000 €
Pen (Humatrope)	4,446,000 €	258,000 €	4,704,000 €
Pen (Genotropin)	4,446,000 €	208,000 €	4,654,000 €
Pen (Norditropin)	4,446,000 €	94,000 €	4,540,000 €
Pen (Omnitrope)	4,446,000 €	217,000 €	4,663,000 €
Syringe (Zomacton)	4,446,000 €	335,000 €	4,781,000 €

Graph A: Comparison of cost per vial and cost of wastage per vial depending on device used



DISCUSSION

Short stature is a frequent cause of medical consultation. In the United States it is the reason 1-5% of patients are sent to paediatric hospitals (1). Parents of "small" children seek medical advice because they are concerned that their child is the smallest in the class. Here is where the challenge of the doctor begins in order to try to identify the probable aetiology. The doctor will have to explain to the parents that in order to carry out a pathological short stature diagnosis, there is no unanimous definition but it is instead an arbitrary process. The parameter size, during the overall growth process of the individual is a continuous variable, with values around a mean, following a normal distribution. For this reason, it is impossible to place a clear dividing line between normal and short stature. Therefore, the doctor will focus on analysing the size of a specific child. A comparison, using adequate standards for that child with regards to sex, age and corresponding ethnical population he belongs to, as well as the relationship with the family genetic potential, will be carried out. If, despite this, he is below -2.5 SD of the individuals of his age, sex and ethnic background, then he can be classified as suffering from pathologic short stature. There are important aspects to consider during the diagnostic process of short stature such as: improvement in health and nutritional conditions, as well as the constant migration phenomenon between countries which has resulted in a change of size by geographical area through the years. Therefore, the use of universal tables for children over the age of 5 is not recommended, but instead specific National growth tables are recommended to adequately identify the average size of the population studied. In Spain, the most common graphs currently used by paediatricians are the longitudinal graphs by Orbegozo (4). When a child is below the established average, a careful medical evaluation needs to be carried out in each case. The rate of growth needs to be established, a complete medical history needs to be carried out, an exhaustive physical exploration as well as specific laboratory and diagnostic tests need to be done in order to come up with a final diagnosis and begin an adequate treatment.

Since 1985, the treatment for pathologic short stature is recombinant human growth hormone. In Europe it is authorized in six indications: classic growth hormone deficiency, Turner´s syndrome, chronic renal failure, Prader-Willi Syndrome, retarded intrauterine growth and growth deficiency due to alteration in SHOX gene. In Spain, the criteria for use of hormone are evaluated and authorized by the Advisory Committees on Growth Hormone.

The present study focused on Idiopathic Growth Hormone Deficit (GHD) as the cause of pathologic short stature, as it is the most prevalent indication among those which are authorised, despite its low incidence. The lack of reliable data on incidence and prevalence of this pathology in Spain leads to important limitations so in order to carry out an economic evaluation it is necessary to transfer data from other countries to the Spanish population.

The only studies which can give us an approximate figure of the number of patients with GHD in Spain are those generated by the Committees of Growth Hormone of the Autonomous Communities of Valencia and Cataluña. However, even

adjusting the populations of both Communities, the differences in results do not allow an acceptably precise calculation at the national level.

Despite the important role treatment compliance plays on treatment efficacy, there are few studies that analyse the factors which have a direct influence on the process and, even more so, we have found no articles that directly relate adherence with centimetres gained, final height achieved, rate of growth or type of device used, although on this latter aspect there are a few secondary approaches.

With our initial search strategy, we only found 15 articles meeting inclusion criteria which studied factors associated with GH treatment adherence in children. However, most of these studies were based on questionnaires directed towards patients or their parents. The absence of other types of comparison, together with the difference in perspectives and questionnaires between studies, leads to vague results where sometimes the concept of adherence can overlap with those of satisfaction, ease of administration and "eagerness to please the doctor".

The study of variables that can contribute to improve adherence to therapy has increased since the introduction of new devices for hormone administration. Thus, the influence of a greater educational level of parents has been identified as a factor that can allow an increase in awareness of the consequences of lack of therapy compliance and therefore lead to better results in the final height of patients. As has been described in the results, other authors consider the psychological environment of the child to be a critical factor to determine treatment adherence, observing that the age group that misses most doses are adolescents. Perhaps this is because they are in a transition stage where they fear being stigmatised by their school mates if they find out they have to have a daily injection, as well as the fact they do not like being controlled by their parents and this can be a way of showing their defiance.

In these cases, the importance of the doctor-patient relationship is even greater, and the actors involved must be made aware of the consequences, in clinical terms, of their lack of compliance to therapy, their knowledge of their expectations as patients must be improved as well as their degree of satisfaction with chronic therapy. This same doctor-patient relationship also helps improve the patient´s understanding of the therapy prescribed, which also contributes to improving adherence to treatment.

Overall, although with different preferences, all authors agree that a good doctor-patient relationship where the health professional takes the necessary time to provide a complete explanation regarding the disease (GHD) and its consequences to affected children and their parents, a good patient motivation, good training on the hormone administration technique by health personnel, a good family environment and high socio-economic level, helps to achieve a high adherence to r-GH therapy.

On the other hand and, as has been pointed out previously, in the last few years there has been a lot of attention paid to the technology used in hormone administration, as it is believed that the type of device used can be an important factor affecting treatment adherence. However, in none of the studies reviewed was there a complete association between the device used and the final size reached as a function of proven treatment adherence.

Each study has evaluated different variables related to final size, with different therapeutic regimes and obtaining, not surprisingly, different results. As mentioned previously, studies which compare devices are not complete, as only some devices are included, and the result variables did not properly address adherence but factors

surrounding it such as: administration speed, and ease of use or preference, which are only indirectly related to adherence. It is necessary to mention the lack of rigour in these comparisons, both due to the fact that each device has appeared progressively in time as well as the fact that many studies are promoted by the manufacturing companies, leading to bias in the distinctive variables which are selected and the choice of the most advantageous comparators.

Initially, the administration device available was a conventional syringe and needle. Later, in order to aid in its use and administration route, other precharged syringes, manual injection pens, self-injectors, needle-free injectors and hidden needle injectors were introduced into the market. Finally, an electronic device has been developed, with different positive attributes which could aid in improving treatment adherence as it has been observed that it is reliable, it decreases the feeling of pain during the injection, and it is safe and easy to use. This device is designed to control doses administered and therefore know how much hormone is left in the cartridge. The doctor and health professionals can objectively monitor if patients are adhering to their treatment or whether they are non-responders, which will help them reassess the dose administered as well as the diagnosis established. In this way, we can avoid costs to the SNS as well as adverse effects to patients that will not bring any clinical benefit to them.

The results of our economic approach allow us to calculate a treatment cost for a thousand children for one year of 4.446.000 € for the electronic device, with no wastage, compared with pens and syringes which amount to 4.540.000€ and 4.781.000€, respectively, with a cost of hormone wasted between 94.000€ and 335.000€. Therefore, according to our model, the cost of drug wasted depending on the type of administration device varies between 2.11% and 7.53% of the pharmaceutical cost of the hormone prescribed.

We must emphasize that, as was indicated in the Methods section, due to a lack of specific adherence data for each device, our economic model has assumed an adherence of 100% for all devices in our calculations. However, we are aware that this hypothetical adherence is very far from the true value which, according to recent estimates by Rosenfeld, adherence is around 67% (18). Taking this into account, and due to the adjustment of doses and thus on amount of hormone dispensed, based on true adherence, we could estimate that with devices such as Easypod, (if adherence could reach 80%), dispensation could be 20% less which, added to the savings in the amount of hormone used, could reach a total savings between 22% and 27% of the total cost of GH prescribed.

As there is a lack of reliable data published in the medical literature, it would be instructive to carry out an economic evaluation for each Autonomous Community, taking into account the specific data of children treated with GH in that Community as well as their response. A way in which this research could be supplemented is by providing the GH Advisory Committees with the adherence percentage of each of the children in their area and evaluating the results obtained. With all this information, there could be an objective assessment of the relevance of the treatment and thus improve the clinical management of the disorder with a reduction in costs for the SNS as well as avoidance of discomfort and unnecessary risks due to a poor therapeutic response or non-compliance with therapy.

At the same time, we believe it would be very convenient for new devices that develop for hormone administration in these types of treatment, to include mechanisms capable of registering data on patient size, making it easy to know the cm gained as a function of the amount of hormone truly administered.

CONCLUSIONS

The lack of therapeutic adherence is a complex process which is affected by multiple interrelated factors, and associated both with the patient as well as with the drug and the health professional, the consequences of which are two-fold: health results and healthcare costs. There is no ideal general strategy to help in treatment compliance so in each type of treatment, the interventions in line with the key factors associated with lack of adherence must be adopted.

The strategies proposed to improve adherence to growth hormone treatment in children with hormone deficiency are directed towards the following interventions: doctor-patient relationship where the health professional takes the necessary time to provide a complete explanation regarding the disease (GHD) and its consequences to affected children and their parents, a good patient motivation, adequate training on the hormone administration technique by health personnel, a good family environment that, together with the cultural level of the parents, have been unanimously identified as key factors.

On technical grounds, there is an increasing importance of administration devices for drugs which aim to make it easier and more convenient, though in this respect, the literature reviewed does not appear to offer such clear results with regards to adherence as it does on variables indirectly related to it such as patient preference and ease of use.

Together with the difficulties in knowing the effective adherence for each particular patient, there are difficulties in identifying their ability to respond, which use complex and expensive analyses. As a result there are uncertainties with regards to whether a poor response is due to lack of treatment adherence or a non-responder phenotype of patient.

The economic impact of lack of adherence or lack of response is highlighted in this case with the high price of the drug, which is increased by the quantities which remain in the vials and are wasted with most presentations, as doses are adjusted to the weight of the patient.

The economic model presented in this study has allowed a quantification of the savings due to the better use of the drug in the different presentations, which reaches a maximum in the case of administering GH with Easypod ®, which amounts to a savings between 2.11% and 7.53% as compared with other devices.

This savings could be quantified even further if we had specific data on treatment adherence for each of the different devices. As this information is lacking, we can only consider the general information obtained from the publications reviewed which provide a savings estimates for this device between 22% and 27% of the total cost of GH prescribed, as mentioned previously.

In addition, an administration system which allows the exact doses administered to be known in an easy way, would clear these uncertainties and would help in the

adoption of corrective measures if there was a loss of adherence, or cancellation of treatment in the case of non-responder patients, thus avoiding futile therapies.

At the same time, we believe it would be very convenient for new devices that develop for hormone administration in these types of treatment, to include mechanisms capable of registering data on patient size, making it easy to know the cm gained as a function of the amount of hormone truly administered.

The present review confirms the need to systematically address the study of adherence for the different presentations on the market which, until now, did not allow precise quantifications but only indirect estimates.

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ANNEXES

ANNEX A. FIGURES

Figure 1: Different stages in growth rate

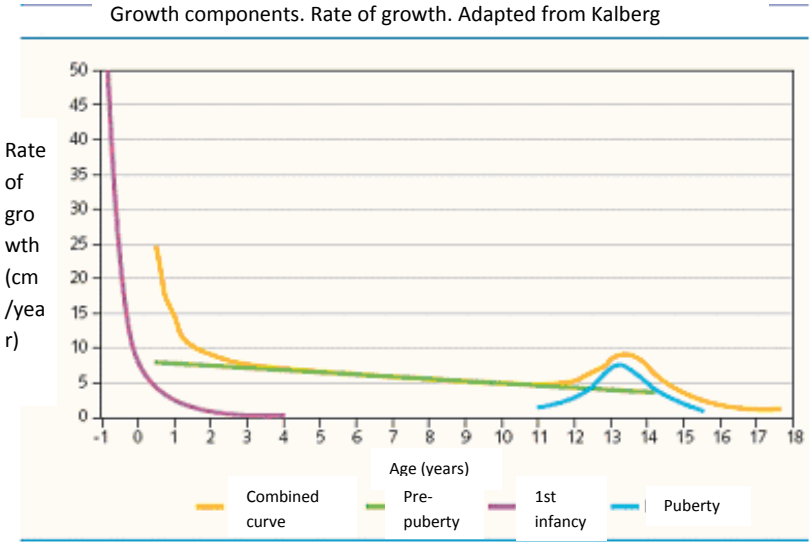


Figure 2: Growth according to age

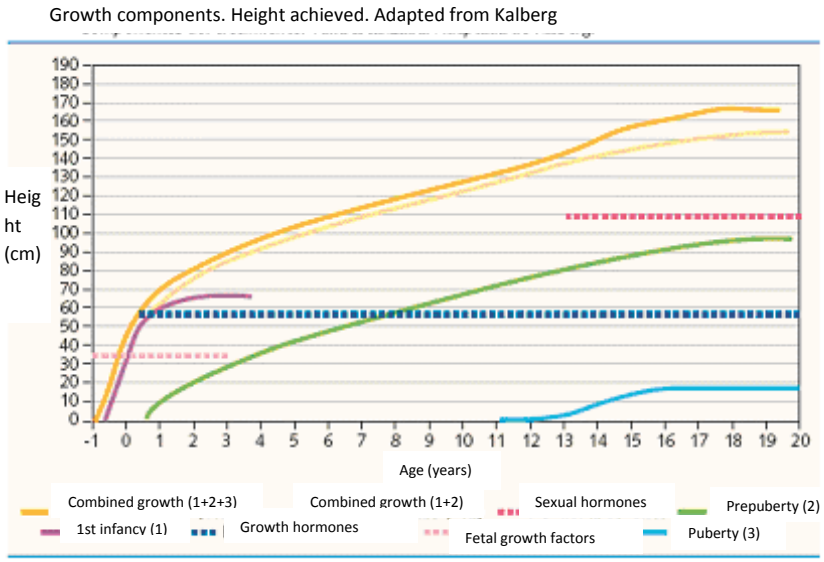
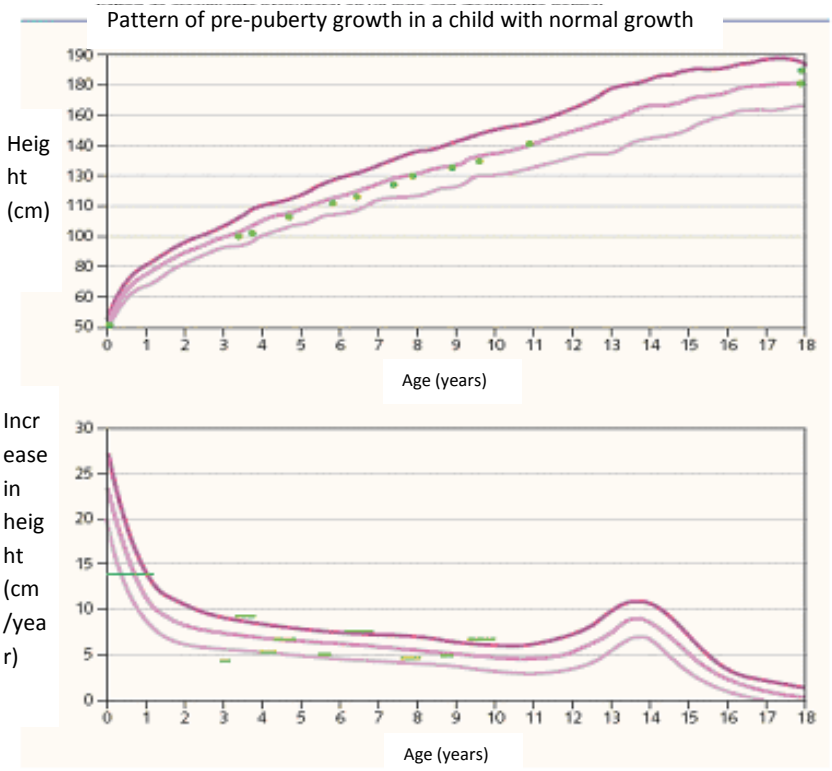
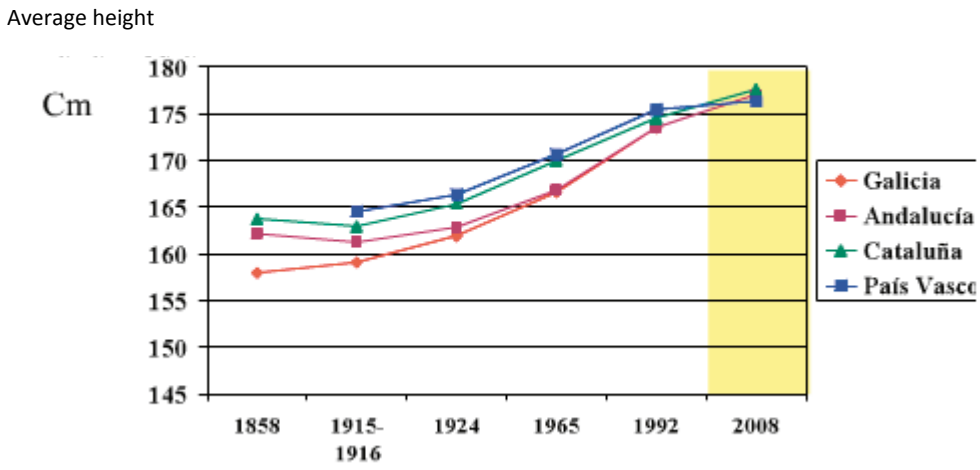


Figure 3: Comparison of growth curves (top graph) and increase in size (lower graph) in a child with normal growth



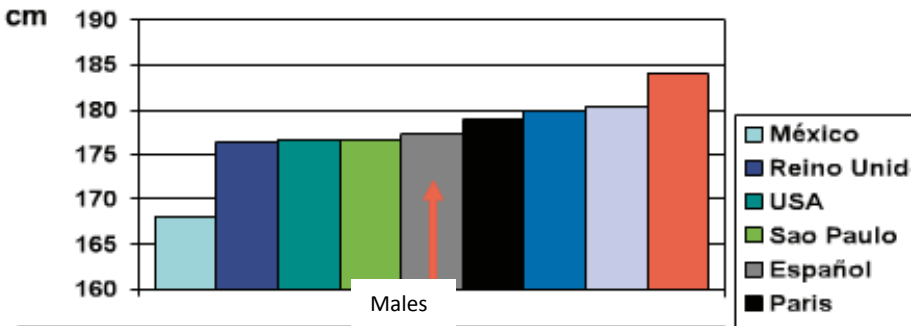
ANNEX B. GRAPHS

Graph 1: Average Size Development in Spain in the period from 1858 - 2008



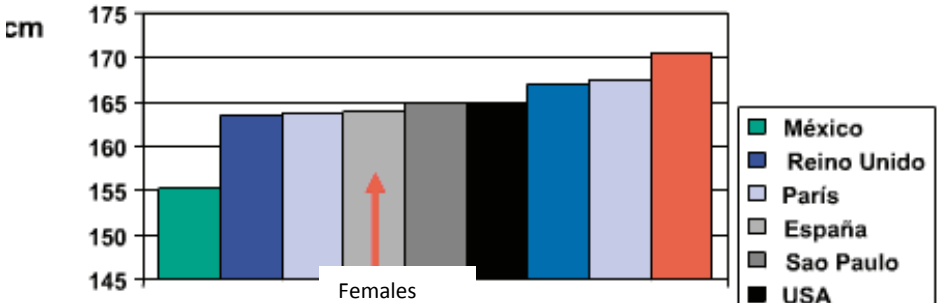
Fuentes: M. González Portilla (Ed.) "Los orígenes de una metrópoli industrial: La ría de Bilbao"; Fundación BBVA. Bilbao 2001.
A. Carrascosa, JM. Fernández, JP. López Siguero (Eds.): «Estudio Transversal Español». Pfizer. Barcelona 2008.

Graph 2: Comparison of average size of males in Spain to other countries



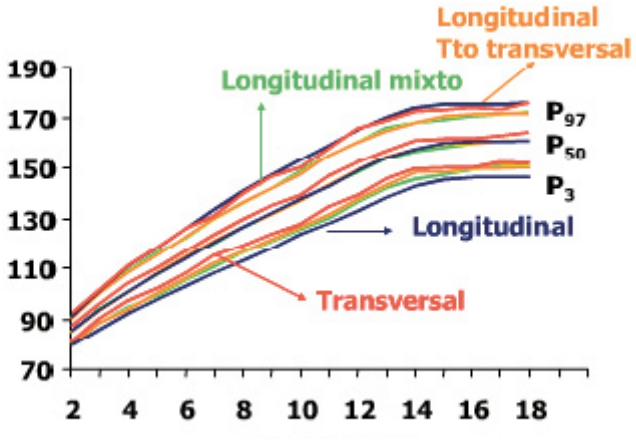
México	168
Reino Unido	176,4
USA	176,7
Sao Paulo	176,7
Español	177,3
Paris	178,9
Alemania	179,9
Suecia	180,4
Holanda	184

Graph 3: Comparison of average size of women in Spain to other countries

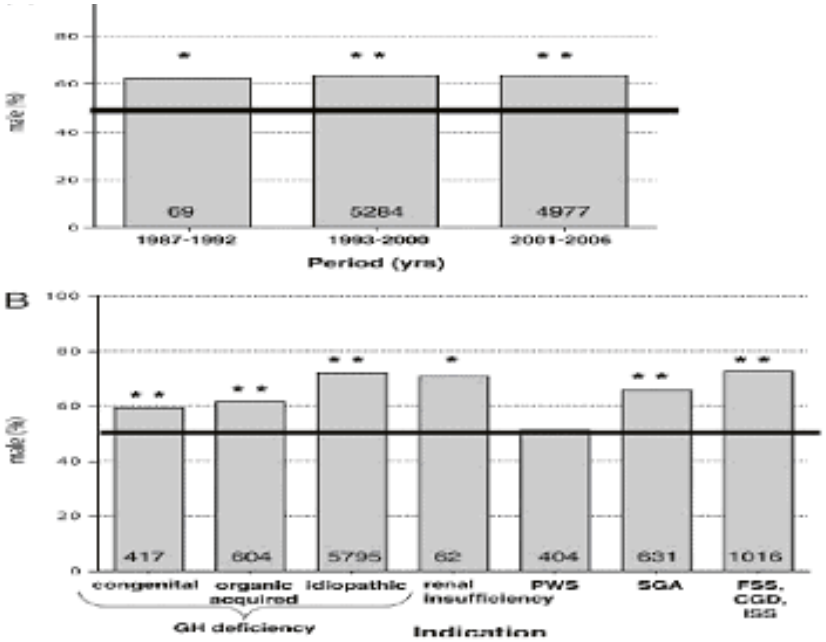


México	155,3
Reino Unido	163,6
París	163,7
España	163,9
Sao Paulo	164,9
USA	164,9
Alemania	167
Suecia	167,5
Holanda	170,6

Graph 4: Longitudinal and cross-sectional growth studies by Orbegozo Bilbao

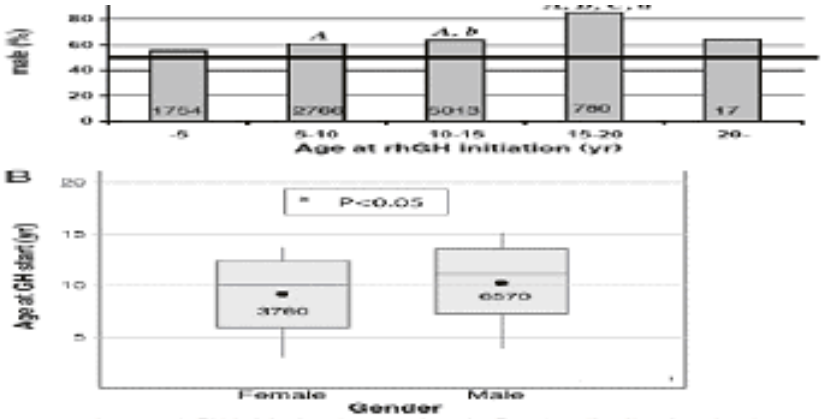


Graph 5: Comparative graphs of children suffering from GHD



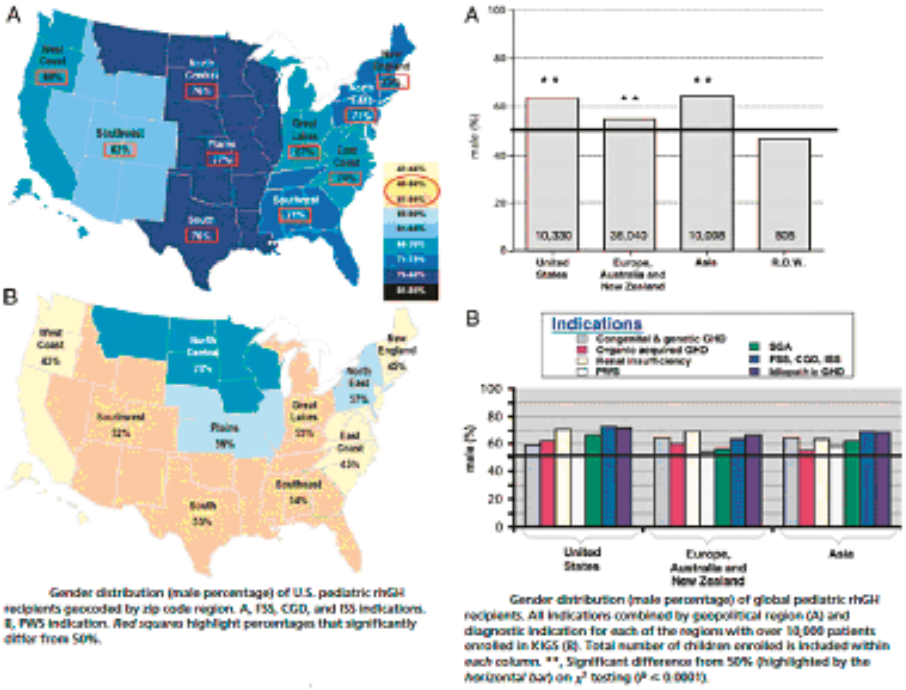
Gender distribution (male percentage) of U.S. pediatric rhGH recipients. A, All indications combined by time period as defined by the sequence of FDA-approved indications. B, All time periods combined by diagnostic indication. For *both panels*, the total number of children is included within *each column*. Fifty percent is highlighted by the *horizontal bar*. Difference from 50%, by χ^2 testing, is indicated. *$P < 0.05$.

Graph 6: Age Comparison of GHD appearance



Age at rhGH initiation by gender. A, Gender distribution (male percentage) of U.S. pediatric rhGH recipients per 5-yr strata of age. B, Box plots of the mean, median, and range of age at initiation of rhGH therapy for girls and boys. For *both panels*, the total number of children is included within *each column or box*. In *panel A*, significant differences are indicated with *lowercase letters* for $P < 0.05$ and *uppercase letters* for $P < 0.0005$: *a*, compared with less than 5 yr; *b*, compared with 5–10 yr; *c*, compared with 10–15 yr; and *d*, compared with 20+ yr. After applying the Bonferroni adjustment to account for multiplicity of testing, comparisons indicated by capital letters remained statistically significant at $P < 0.05$.

Graph 7: Distribution by sex of GHD, Grimberg (9)

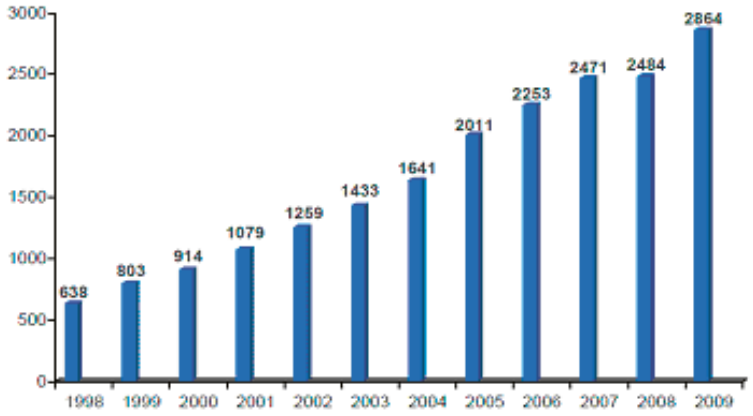


Gender distribution (male percentage) of U.S. pediatric rhGH recipients geocoded by zip code region. A, ISS, CGD, and ISS indications. B, PWS indication. Red squares highlight percentages that significantly differ from 50%.

Gender distribution (male percentage) of global pediatric rhGH recipients. All indications combined by geopolitical region (A) and diagnostic indication for each of the regions with over 10,000 patients enrolled in KIGS (B). Total number of children enrolled is included within each column. **, Significant difference from 50% (highlighted by the horizontal bar) on χ^2 testing ($P < 0.0001$).

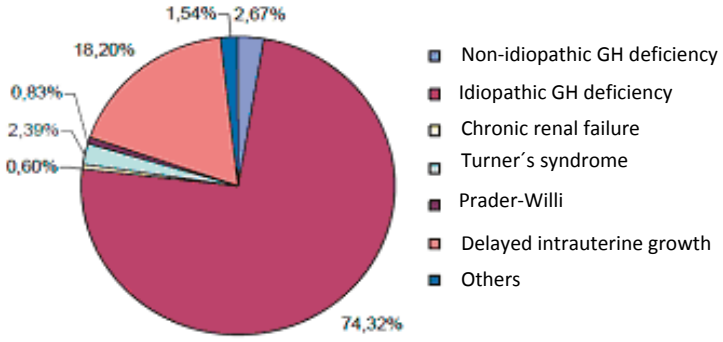
Graph 8: Annual increase of number of GH cases treated in Cataluña

Annual evolution of all patients treated with GH



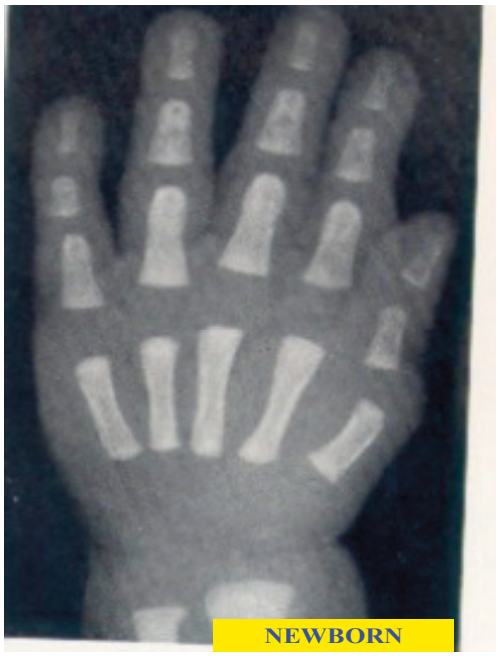
Graph 9: Distribution of cases of children treated with r-GH, according to their illness, during the year 2009

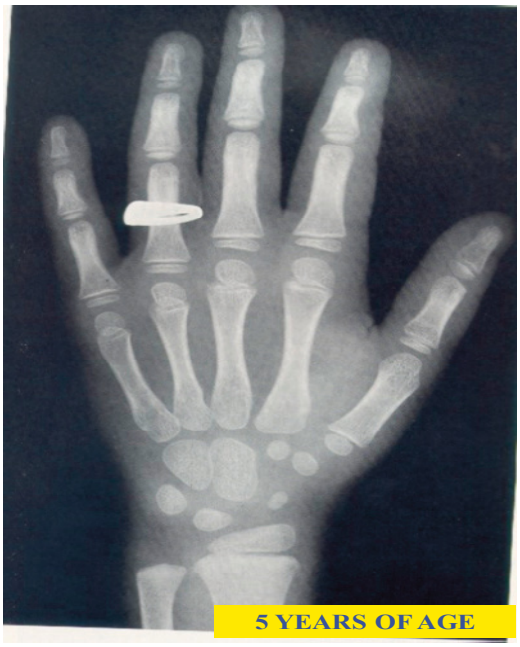
Distribution of cases. Children. 2009



ANNEX C. IMAGES

Image 1: Bone Age for Girls at 0 months, 5 years of age and 17 years of age





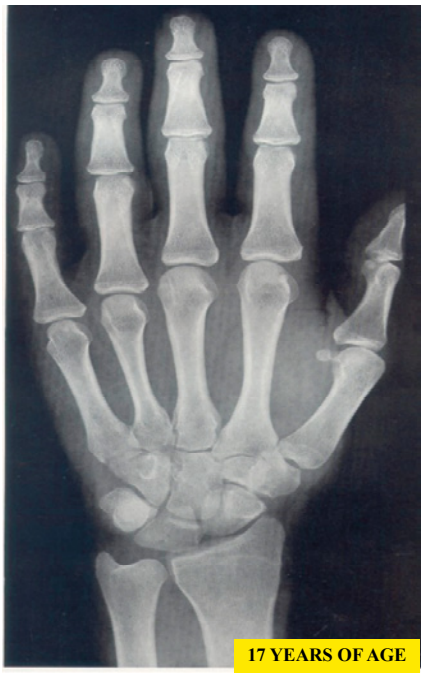
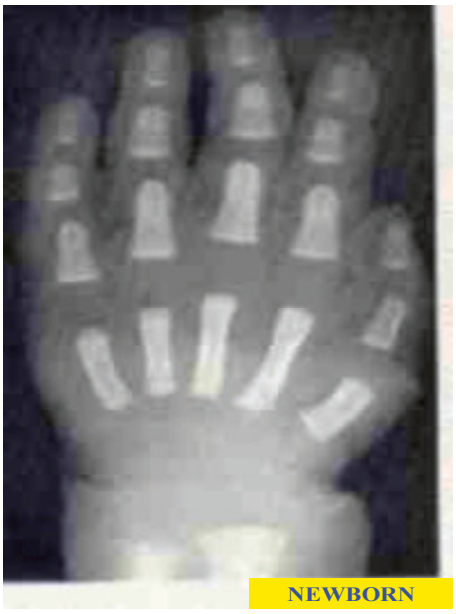
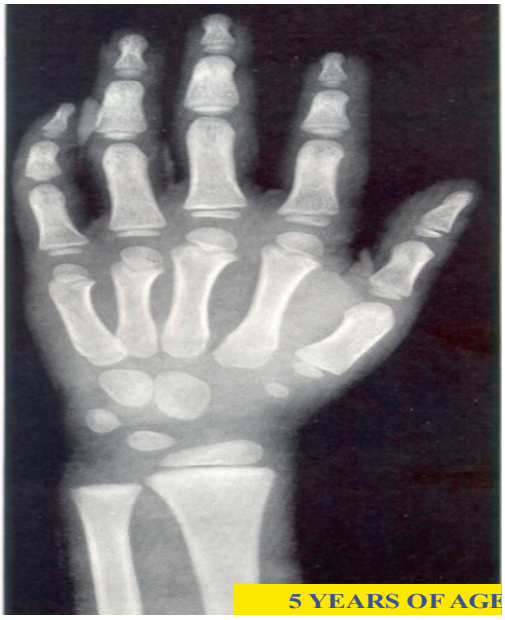
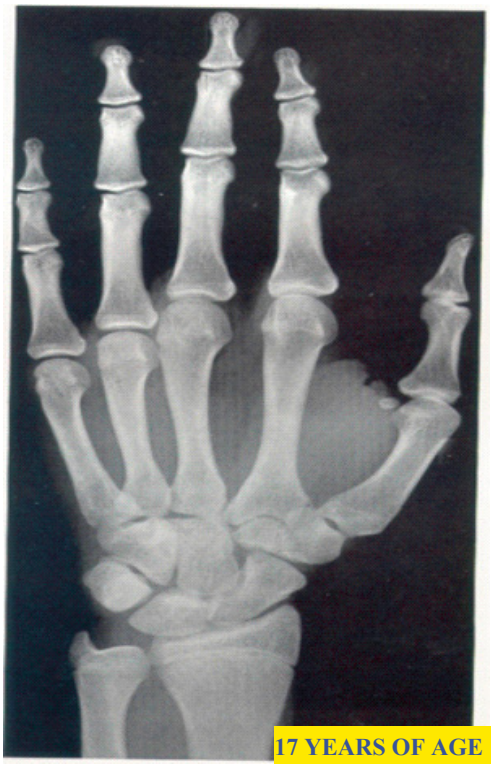


Image 2: Bone Age for Boys at 0 months, 5 years of age and 17 years of age





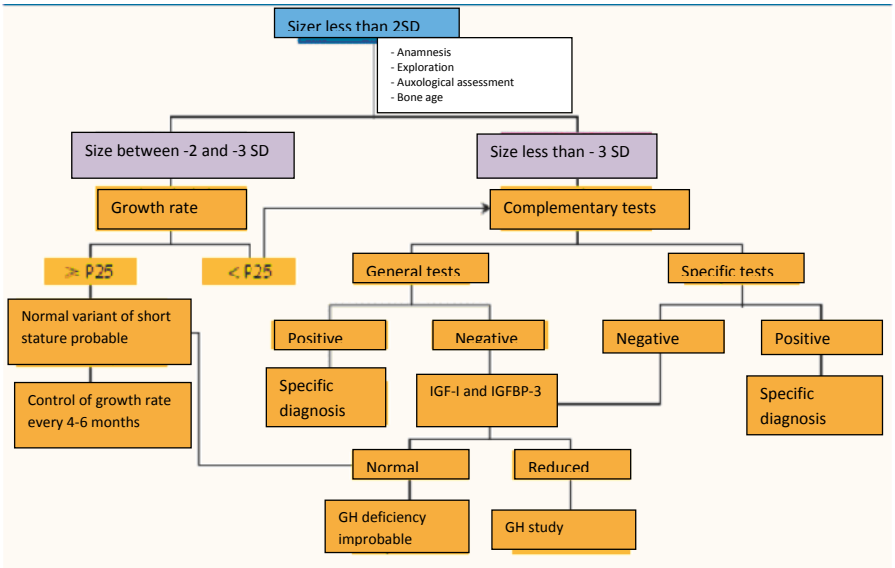


ANNEX D. TABLES

Table 1: Classification of short stature

Pathological	Non-pathological: normal variants of short stature
Harmonic: *Post-natal start:*	Short family stature (SFS)
- Malnutrition - Chronic systemic diseases: - Gastrointestinal - Cardiopulmonary - Renal - Haematological - Infections - Iatrogenic - Lack of affections - Endocrine diseases - Idiopathic	Constitutional delay of growth and puberty. (CDGP) With or without family history
Prenatal start: -Delayed intrauterine growth -without syndromic stigmas -with minimum syndromic stigmas - Prenatal infections - drugs - specific dysmorphic syndromes - chromosome disorders	Association with SFS and CDGP
Disharmonic: - Bone dysplasias - Metabolic bone disorders (rickets) - Congenital/acquired disorder of the spinal column	

Table 2: Algorithm for diagnosis of short stature



SD: standard deviation; GH growth hormone

Table 3: Patients in treatment with GH in the year 2009

	Children						
	Non-idiopathic GH deficiency *1	Idiopathic GH deficiency	Chronic Renal Insufficiency	Turner´s Syndrome	Prader-Willli	Delayed intrauterine growth	Others *2
Patients in treatment	71	1977	16	49	22	484	41

*1 Congenital or acquired GH deficiency

*2 Patients with IGF-I and changes in SHOX gene are included

Table 4: Growth hormone deficiency by age

	Children						
Age group	Non-idiopathic GH deficiency	Idiopathic GH deficiency	Chronic Renal Insufficiency	Turner´s Syndrome	Prader-Willli	Delayed intrauterine growth	Total
less than 3	5	31	4		2	4	46
Between 4-6 years of age	1	102		1	1	60	165
Between 7-9 years of age	2	163		2	1	40	208
Between 10-12 years of age	3	251 *		1		27	282
Between 13-15 years of age	4	147 *		2	1	13	167
Between 16-20 years of age		14					14

* patients with idiopathic GH deficiency who start treatment between the ages of 10 and 15, had shown a delay in their growth before the age of 7 and constitutional delay in growth and development was ruled out.

Table 5: Incidence and Prevalence in children with GHD in Cataluña

Children and adolescents between 0 and 20 years of age		
New cases	Incidence children/year (per 100,000 children)	Prevalence (per 100,000 children)
899	50.43	172.9

Data from 2009 population census . Source: IDESCAT

Total population 7,475,420 Between 0 and 20 years of age: 1,538,386

Over the age of 20: 5,937,034

Table 6: Incidence & Prevalence of GHD cases in Cataluña, as a function of diagnosis

Children (according to diagnosis)			
New cases		Incidence children/year (per 100,000 children)	Prevalence (per 100,000 children)
Non-idiopathic GH	15	0.97	4.61
Idiopathic GH deficiency	708	46.02	128.51
Chronic Renal Insufficiency	4	0.26	1.04
Turner´s Syndrome	6	0.39	3.18
Prader-Willli	5	0.32	1.43
Delayed intrauterine growth	144	9.36	31.46

Table 7: Important aspects to consider in adherence to treatment with growth hormone, and assessment area by author

Authors	*Publication year*	***Número de muestra estudiado***	**Variable(s) used to measure adherence and/or compliance**	**Type of evaluation**	**Evaluation areas**
Gacs et al (29)	1991	78 patients	Parent´s educational level	Clinical History Questionnaires	Socioeconomic Psychological environment of child
Lieberman et al (30)	1993	96 patients	Degree of satisfaction with treatment	Questionnaire with 50 items	Perception about medical problem Satisfaction with treatment and results obtained
Smith et al (31)	1993	188 patients	Understanding of r-GH treatment prescribed Assessment of number of doses missed	Questionnaire with 22 items	Cognitive
Lopez-Siguero, et al (32)	1995	90 patients	Understanding of r-GH treatment prescribed Knowledge about the disease Acceptance of therapy	Questionnaire with 21 items	Psychological environment of child Cognitive
Oyarzabal et al (33)	1998	473 patients	Assessment of number of doses missed Type of device used Understanding of r-GH treatment prescribed	Questionnaire with 28 items	Cognitive Technological innovation
Desrosiers et al (27)	2005	631 patients	Type of device used (Electronic, with and without a needle)	Questionnaire	Technological innovation
Wickramasuriya et al (25)	2006	125 patients	Type of device used Factors which affect choice of device	Questionnaire	Technological innovation
Haverkamp et al (34)	2008		Type of device used Understanding of r-GH treatment prescribed Doctor - patient relationship	Bibliographic review	Technological innovation Cognitive
Rosenfeld et al (18)	2008	724 patients	Understanding of r-GH treatment prescribed Training and administration technique for r-GH Doctor - patient relationship Motivation, acceptance and satisfaction with therapy Type of device used	Questionnaire 134 items	Cognitive Emotional / Psychological Technological innovation
Kapoor et al (35)	2008	75 patients	Treatment duration	Questionnaires	

Authors	*Publication year*	***Número de muestra estudiado***	**Variable(s) used to measure adherence and/or compliance**	**Type of evaluation**	**Evaluation areas**
Norgren et al (28)	2009		Type of device used	Bibliographic review	Technological innovation
			Parent´s and family´s educational level		Socioeconomic
			Duration of medical consultation		Psychological
			Type of health professional who provides training to patient		Educational
			Understanding of r-GH treatment prescribed		Cognitive
			Acceptance of therapy		Psychological / Emotional
			Acceptance of type of device used		
			Acceptance of results obtained		
			Doctor - patient relationship		
			Motivation, acceptance and satisfaction with therapy		
			Family surrounding		
			Educational level		Socioeconomic level
			Training and administration technique for r-GH		
			Age		
Fuchs et al (21)	2009	70 patients	Type of device used (Ease of use)	Questionnaire with 21 items	Technological innovation
			Acceptance of device used		Psychological
Pfutzner et al (26)	2010	56 patients	Type of device used (Ease of use)	Questionnaire with 21 items	Technological innovation
			Acceptance of device used		
Bozzola et al (36)	2011	824 patients	Type of device used (Ease of use)	Data registered in electronic device	Technological innovation
			Acceptance of device used	Questionnaire with 15 items	
Kappelgaard et al (68)	2012	50 patients	Type of device used (Ease of use) Acceptance of device used	Questionnaire with 47 items	Technological innovation

Table 8: Comparison of variables considered by their authors for evaluation of results after GH therapies

Authors	*N*	*Doses*	*Device used*	*Age (in years)*	*Follow up*	*Height with SD*	*Total cm2 gained*	*Adult Height with SD*	*Final height*	*Growth rate (cm/year)*
	16									
Rosenbloom et al 1988 (37)	11 boys	0.3mg/kg/week	SC injection	9.5 ± 3.4	2 years				7.7 + 1.2 (cm gained in 1st year)	9.1 + 2.6 : 1st year
	5 girls									8.2+1.8 :2nd year
	121									
Blethen et al , 1997 (38)	72 Boys	0.3mg/kg/week	SC injection	11.3 ± 2.1	6.4 ± 1.7 years		46.6 ± 11.8	(-)0.7 ± 1.3	171.6 ± 8.2	
	49 Girls			10.1 ± 2.8	5.7 ± 2.0		41.6 ± 16.5	(-)0.7 + 1.1	158.5 ± 7.1	
	49									
Rappaport et al, 1997 (39)	27 Boys	0.2mg/kg/week	SC injection. Saizen, serono		Group A* 2- 5 years	From 1.1 ± 0.6 to 0.35 ± 1.0				* Group A < 2 SD
	22 Girls				Group B**5 years	De -3.6 + 1.0 a- 0.9 ± 1.2(12 months).-1.1 (24 months)-1.1 (36 months);-0.9(48 months).-0.8(60 months)				** Delay in growth
	83									
Cacciari et al 1997 (40)	51 Boys	0.5mg/kg/week	SC injection	12.7 ± 1.7	2 - 7 years	(-)2.2 a (-)1.3				
	32 Girls									
Grumbach et al 1998 (41)	Pre-puberty children	0.175mg/kg/week	SC injection					On average -1 SD of the standard population		
	Boys					Increased – 2 SD				
	Girls	0.035 mg/kg/week				Increased -3 SD				
	51									

Authors	N	Doses	Device used	Age (in years)	Follow up	Height with SD	Total cm2 gained	Adult Height with SD	Final height	Growth rate (cm/year)
Iyoda et al 1999 (42)	15 (Group A: Patients with no previous treatment)	0.16 mg/kg/week	SC injection	7.5	6 months	From (-)2.6 ± 0.6 to (-) 2.1 ± 0.5				From ± 4.0 ± 2.4 to 9.2 ± 2.9
	36 (Group B: Change from powder to liquid rGH)			8.7		From (-)2.0 + 0.6 to (-) 1.9 + 0.9				From + 7.0 ± 2.4 to 6.7 ± 1.9
Saenger et al 2000 (44)	Boys	0.3/mg/kg/week	SC injection			(-)0.7 ±1.3			1.71 ± 8.2	
	Girls					(-)0.7 ± 1.1			1.58 + 7.1	
	74					Initial: (-)2.9 ± 1.0				Initial: 4.5± 2.3
Reiter et al 2001 (45)	50 Boys	0.37mg/kg/week	SC injection	7.4 years	12 months	0.5 ± 0.4				8.4 ± 2.1 (0-6 months)
	24 Girls									7.8 ± 1.8(6-12months)
	GHD = 36									
	56									
Silverman et al 2002 (46)	11 Boys	1.5 mg/kg/ once a month (0.37mg/kg/week)	SC injection	5.7 ± 2.9	0 - 12 months	(-)2.3				8.3 + 1.5
	11 Girls				12-24 months	(-)1.9				7.2 ± 2.0
	26 Boys	0.75mg/kg twice a week ((0.37mg/kg/week)		7.4 ± 2.6	0 - 12 months	(-)2.6				8.2 ± 2.0
	8 Girls				12-24 months	(-)2.2				6.9 ± 1.5
	104									
Cohen et al 2002(47)	33	Low =0.175mg/kg/week	SC injection	7.8 + 2.9	2 years	2.6 + 0.9	1.4 + 0.6			
	37	Average = 0.35mg/kg/week		7.8 + 3.0		2.1 + 0.9	1.9 + 1.0			
	34	High = 0.7mg/kg/week		7.7 + 2.7		1.1 + 0.9	2.2 + 0.8			

Authors	N	Doses	Device used	Age (in years)	Follow up	Height with SD	Total cm2 gained	Adult Height with SD	Final height	Growth rate (cm/year)
	70 Boys					1.4 + 0.1	21 ± 5			
	34 Girls						21 ± 5			
	631									
Desroseirs et al 2005 (45)	222 Boys		Needless device	10.6	2 years					0 -6 M: 9.2 (n=214)
	104 Girls									6 - 12 M: 9.1 (n=151)
										12 - 24 M: 8.2 (n=18)
	204 Boys		Device with a needle	10.1						0-6 M: 9.1 (n=216)
	101 Girls									6-12M. 8.7 (n=189)
										12-24M: 8.1 (n=107)
	747									
Reiter et al 2006 (49)	351 Caucasian Boys	0.22mg/kg/week	SC injection (Genotropin)	18.2	7.5 years	1.6 (increase)		(-)0.8		
	200 Caucasian Girls	0.20 mg/kg/week		16.6	6.9 years	1.6 (increase)		(-)1.0		
	128 Japanese Boys	0.15 mg/kg/week		18.3	6.7 years	0.7 (increase		(-)1.6		
	68 Japanese Girls	0.16 mg/kg/week		16.8	7.0 years	0.6 (increase)		(-)2.1		
	75									
Kapoor et al 2008 (35)	45 boys	0.4mg/kg/week	SC injection	12.3	1.9 years					7.8
	30 girls									

Authors	*N*	*Doses*	*Device used*	*Age (in years)*	*Follow up*	*Height with SD*	*Total cm2 gained*	*Adult Height with SD*	*Final height*	*Growth rate (cm/year)*
	401									
Westphal et al 2008 (50)	294 Boys	0.24mg/kg/week		18.57	8.43 years	(-)0.93			172.55	
	107 Girls	0.24mg/kg/week		17.4	8.51 years	(-)0.80			159.76	
	57 Boys (Severe GH)	0.022mg/kg/week	SC injection (Genotropin)	19.37	10.7 years	(-) 0.36			1st year: 8.5cm;	
	24 Girls (Severe GH)	0.021mg/kg/week		18.39	11.77 years	(-)0.21			163.92	
	237 Boys (Partial GH)	0.025mg/kg/week		18.38	7.88 years	(-)1.07			171.58	
	83 Girls (Partial GH)	0.025mg/kg/week		17.11	7.57 years	(-)0.97			158.56	
	1716	0.21-0.75mg/kg/week	Pre-filled pen Syringes	112						1st year : 8.5 (n=575) 2nd year: 7.6 (n=243) 3rd year: 7.6 (n= 52) 4th year: 9.4 (n=5) 5th year: 8.1 (n=5)
Plotnick et al 2009 (51)	1183 Boys									
	533 Girls									
	980 GHD									
	5797					Initial: (-)2.2 + 0.89				
Ross et al 2010 (52)	2918 Boys	0.32mg/kg/week	SC injection	10.8 ± 3.54	2 years	(-)2.1 ± 0.85		From 0.6 to -1 SD		
	952 Girls					(-)2.4 ±0.94				