



Metformin therapy to improve adult height prognosis in growth hormone deficient children treated with growth hormone

A Clinical Trial Intervention

Author: Mireia Català Besa

Mentor: Dr. Abel López Bermejo

End of Term Project

Faculty of Medicine, University of Girona

18/01/2016



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1. ACKNOWLEDGEMENTS

First of all, I would like to express my gratitude to my mentor on this project Dr. Abel López Bermejo for his complete dedication and support on my End of Term Project. His guidance helped me at each moment during the writing of this protocol not only on research stuff –in which his knowledge is well-recognized- but also encourage me with a patient and motivating attitude.

I would like to express my gratitude to the whole paediatric department of Hospital Dr. Josep Trueta of Girona for their dedication during my internship with them and also for letting me enjoy of the magic of paediatrics.

2. ABBREVIATIONS

| | |
|----------------|---|
| SDS | Standard Deviation Score |
| GH | Growth Hormone |
| RhGH | Recombinant Human Growth Hormone |
| GHD | Growth hormone deficiency |
| IGF-I | Insulin-like growth factor I |
| IGFBP-3 | Insulin-like growth factor binding protein 3 |
| HOMA-IR | Homeostatic Model Assessment for Insulin Resistance |
| BMI | Body Mass Index |
| HDL-c | High-density lipoprotein cholesterol |
| LDL-c | Low-density lipoprotein cholesterol |
| TC | Total cholesterol |
| TG | Triglycerides |
| AST | Aspartate aminotransferase |
| ALT | Alanine aminotransferase |
| CIMT | Carotid Intima Media Thickness |
| HbA1c | Glycosylated Haemoglobin |
| PCOS | Polycystic ovary syndrome |

3. ABSTRACT

| | |
|------------------------------|---|
| Background | Growth hormone (GH) deficient children treated with GH experience a gain in adult height prognosis. However, there are a number of patients who may advance their bone age more rapidly than their height gain, which may worsen their adult height prognosis. Moreover, GH treatment causes a secondary hyperinsulinemic state that could increase the cardiovascular risk in treated children in the long-term. |
| Justification | In non GH-deficient children, studies have shown that metformin causes an improvement in height in children treated with high doses and larger periods of time, especially those with insulin resistance at baseline. These effects may be mediated by metformin actions improving insulin sensitivity and inhibiting aromatase activity and the synthesis of oestrogen (the agent responsible for bone age advancement). On the basis, metformin could improve adult height prognosis and could also ameliorate the insulin resistance state caused by GH treatment in these patients. |
| Main objective | The goal of the present work is to determine if metformin use in combination with GH therapy, can potentiate its growth effects and improve adult height prognosis in GH-deficient children with poor adult height prognosis in comparison to GH plus placebo treatment. |
| Design | This protocol is for a multicentre, prospective, phase III/IV, randomized, double blind, placebo controlled, 4-year duration clinical trial in GH-deficient children treated with GH and poor adult height prognosis. |
| Participants | Prepubertal Caucasian isolated GH-deficient children aged 8-10 years treated with GH for at least 2 years with average GH doses (between 0.025-0.035 mg/kg/day) who have poor adult height prognosis (between -1.0 SDS and -3.0 SDS) recruited at the Pediatric Endocrinology Unit at both Hospital Doctor Josep Trueta of Girona and Hospital Sant Joan de Déu of Barcelona. |
| Main outcome variable | Adult height prognosis at the start and the end of GH treatment (Bailey-Pinneau method). |
| Methods | 120 Isolated GH-deficient children treated with GH and poor adult height prognosis will be randomised into treatment or placebo group (1:1) and will be stratified by age, gender and BMI. As an intervention treatment, they will receive a single oral dose of metformin or placebo of 425 mg/day for the first 2 years and a single oral dose of metformin or placebo of 850 mg/day for the last 2 years. Patients will be assessed every 6 months at regular visits scheduled for follow-up of their GH treatment until the study finishes. |
| Data analysis | Data analysis will be performed using SPSS version 22.0. Results for major variables will be performed using Mann-Whitney test (continuous variables) and Fisher exact test (categorical variables). The analysis of response to treatment for endpoints variables will be performed by general linear model (GLM) for repeated measures. A p value <0.05 will be considered statistically significant. |
| Key Words | Growth Hormone deficiency, adult height prognosis, metformin, children |

4. INTRODUCTION

4.1 GROWTH HORMONE DEFICIENCY

Short stature is defined as height below -2 standard deviation score (SDS) for age and gender based on standards for reference population (1). In clinical practice we can divide short patients into 2 subgroups: those with normal variants of growth and those with pathological conditions. The latter can be further divided into proportional and non-proportional pathological conditions(1).

Growth hormone deficiency (GHD) is a condition of postnatal proportional reduced growth which accounts for about 5% of all causes of short stature (1). It can be caused by:

- Pituitary disorders (primary GHD) in which both spontaneous and pharmacological GH secretion are insufficient.
- Supra pituitary disorders (secondary GHD) in which spontaneous GH secretion is abnormal but its response to growth-hormone-releasing hormone (GHRH) stimulus is preserved.
- Peripheral unresponsiveness to GH or insulin-like growth factor type I (IGF-I) in which GH secretion is normal or even increased but the problem lies within the GH receptor, post receptor signals or responsiveness to IGF-I (1).

The etiology of GHD (**Table 1**) includes several causes the most common being idiopathic GHD (for which the cause is still unknown).

Table 1. GH deficiency etiology (1)

| <i>Idiopathic</i> | <i>Congenital</i> | <i>Acquired</i> |
|---|-------------------|---|
| <ul style="list-style-type: none"> <input type="checkbox"/> <u>Genetics</u> <input type="checkbox"/> <u>Related to structural brain disorders</u> (corpus callosum agenesis, septo optic dysplasia, holoprosencephaly, encephalocele) <input type="checkbox"/> <u>Related to midline disorders</u> (palatine fissure, leporine lip, septo optic dysplasia, holoprosencephaly, unique central incisive) | | <ul style="list-style-type: none"> <input type="checkbox"/> <u>Trauma</u> (perinatal or postnatal) <input type="checkbox"/> <u>Infections</u> (meningitis or encephalitis) <input type="checkbox"/> <u>Central Nervous System tumours</u> (craniopharyngioma, pituitary germinoma, pituitary adenoma, optic glioma) <input type="checkbox"/> <u>Others</u> (histiocytosis, granulomatous disease, cranial irradiation after chemotherapy, psychosocial deprivation, hypothyroidism) |

GHD is suspected in children with moderate to severe postnatal growth failure who seek medical advice for short stature. There are some key facts of the medical history that may indicate the presence of GHD (**Table 2**). Acquired GHD can occur at any age, and when it is of acute onset, height can be within the normal range.

Table 2. Key clinical facts of medical history in GHD (1)

| Clinical features |
|--|
| <input type="checkbox"/> Short Stature |
| <input type="checkbox"/> Reduced Growth velocity (at least for a year) |
| <input type="checkbox"/> Hypoglycaemia |
| <input type="checkbox"/> Micropenis |
| <input type="checkbox"/> Excessive subcutaneous adipose tissue |
| <input type="checkbox"/> Delayed bone age |
| <input type="checkbox"/> Delayed puberty |
| <input type="checkbox"/> GH peak below 10.0 ng/mL in stimulation test (glucagon) |
| <input type="checkbox"/> Other pituitary or hormonal deficits |

The diagnosis of Idiopathic GHD is based on clinical, auxological, radiological and biochemical criteria (1–3) including:

a. Clinical criteria:

- No other pathology that can explain the growth delay.
- No clinical signs of malnutrition (especially low BMI values).
- No restrictive eating behaviour disorders.
- Normal thyroid, hepatic, renal and gastrointestinal function.

b. Auxological criteria:

- Height more than two SDS, below the mean (below 3rd centile in charts) for chronological age and gender.
- Growth velocity over 1 year more than one SDS below the mean for chronological age and gender.

c. Radiological criteria:

- Bone age < 1 SDS below the mean.

d. Biochemical criteria:

- A peak GH concentration below 7.4 ng/mL (in other places in Spain below 10.0 ng/mL) in GH stimulation tests (glucagon or others).
- A second stimulation test will be only required if clinical and auxological criteria are accomplished but GH response in the first stimulation test is equal or above 7.4 ng/mL.
- A strong clinical suspicion is important in establishing the diagnosis because laboratory measures of GH sufficiency lack specificity. Observation of low serum levels of IGF-I and the GH-dependent insulin-like growth factor binding protein type 3 (IGFBP-3) can be helpful, but IGF-I and IGFBP-3 levels should be matched for normal values for skeletal age rather than chronological age. Values in the upper part of the normal range for age effectively exclude GH deficiency (4).

Definitive diagnosis of GHD therefore requires demonstration of absent or low levels of GH in response to stimulation test. A variety of provocative tests rapidly increase the level of GH in normal children. In most centres in Catalunya, the stimulation test used is the glucagon test (2). In addition to establishing the diagnosis of GHD, it is necessary to assess other pituitary hormones; levels of thyroid-stimulating hormone (TSH), thyroxine (T4), adrenocorticotrophic hormone (ACTH), cortisol, gonadotropins and gonadal steroids might provide evidence of other pituitary hormonal deficiencies. For the same reason, at diagnose, a magnetic resonance imaging (MRI) should be performed to rule out organic causes (1,4).

In summary, we can establish GHD diagnose after meeting these criteria and having performed a complete study of the short stature in order to exclude other possible causes.

GHD is treated with recombinant human growth hormone (rhGH) which main objective is to normalise height during childhood in order to attain normal adult height closer to the target height and to avoid the negative psychological consequences as a result of short stature. It is indicated when GHD has been diagnosed with the abovementioned criteria (1).

4.2 GROWTH HORMONE TREATMENT

4.2.1 SOMATOTROPIN, INDICATIONS AND CONTRAINDICATIONS

Somatotropin (the name used to designate GH) is a powerful metabolic hormone which is important for lipid, carbohydrate and protein metabolism. It is synthesized and secreted by the somatotrophs cells of the anterior pituitary gland. Its secretion is pulsatile and primarily controlled by GHRH (stimulatory), by somatostatin (inhibitory) and, to a lesser degree, by ghrelin (stimulatory) (5). It stimulates insulin-like growth factor type I production and both are the most important stimulus of linear growth and therefore growth rate. Different actions have been reported (6) on:

- **Lipid metabolism:** somatotropin acts on the liver low-density lipoprotein cholesterol (LDL-c) receptors and affect plasma lipids and lipoproteins. In patients with GHD, GH decreases total cholesterol (TC), LDL-c and B-apolipoprotein serum levels.
- **Carbohydrate metabolism:** somatotropin increases insulin levels but does not change plasma fasting glucose.
- **Mineral metabolism:** somatotropin, especially in adults, can cause sodium, potassium and phosphate retention as it expands extracellular tissue in GHD patients.
- **Bone metabolism:** somatotropin stimulates skeletal bone mass.
- **Physical capacity:** in the long-term, somatotropin can improve muscular strength and physical performance.

rhGH is a protein that is manufactured to be nearly identical to the main form of the naturally occurring human growth hormone (7).

In Spain, GH treatment is indicated mostly in six situations and has four main contraindications(6) (**Table 3**).

Table 3. GH indications and contraindications (6)

| INDICATIONS | CONTRAINDICATIONS |
|--|---|
| <ul style="list-style-type: none"> • GHD. • Growth disorder related to chronic kidney failure. | <ul style="list-style-type: none"> • Hypersensitivity to GH or any of the excipients. • Neoplasia. • Closed epiphysis. |

-
- Growth disorder in children born small for gestational age who do not experience catch-up growth.
 - Turner Syndrome.
 - Prader-Willy Syndrome.
 - Léry-Weill Syndrome.
 - Patients with severe acute diseases who suffer complications after heart or abdominal surgery, multiple trauma, acute respiratory insufficiency or similar conditions.
-

GH treatment in its different indications is administered as a daily subcutaneous injection at night (as a preference, in order to reproduce the physiological circadian rhythm of GH pulse discharge) (1,6).

4.2.2 DOSAGE AND RELATION TO ADULT HEIGHT

GH increases height velocity and adult height in children with GHD but the optimal dose (the lowest dose which can normalize adult height) is unknown (8). Although a higher GH dose increases short-term height velocity more than a lower dose, no statistical differences has been shown in the long-term (8,9).

A. CATALAN AND SPANISH RECOMMENDATIONS

The “*Generalitat de Catalunya*” and Spanish Pediatric Association (AEPED) protocols for GHD recommend mean doses of GH between 0.025-0.035 mg/kg per day (1,2).

B. DURING PUBERTY

Total pubertal growth in adolescents with GHD treated with GH is determined by factors at puberty onset that are not different from those described in children with other short stature causes with no GHD suggesting that total pubertal growth depends mostly on the outcomes achieved at the end of prepubertal growth and less on the dose of GH (in GHD, it has been shown that the effect of the GH is greater in prepubertal years) (10). This observation is probably due to the fact that at the onset of puberty only about 20% of the growth left (10). The determining factors at puberty onset are: age, bone age related to chronological age (especially bone age delay because the expected therapeutic gain in height for a given age is higher in this case), height and mid-parental height and mean dose of GH during puberty. The effect on pubertal growth of these factors is not different between boys and girls. (10).

Although GH secretion and IGF-I levels rise during puberty, the quantitative relationship between these hormones and pubertal growth is unclear (10).

Mauras et al. in 2000 published the results of a study in which the rhGH dose was increased during puberty. This yielded an increment in near adult height when compared with conventional dosage (11). In a new study, *Coelho et al.* found no statistically significant difference between adult heights of children with GHD treated with conventional dosage (between 0.025-0.050 mg/kg/day) when compared with children who received higher doses(11). When accepting higher doses it seems that the efficacy in adult height may be due to the supraphysiological rhGH therapy rather than to the need for hormone replacement (11).

In studies where the rhGH dose-response effect on onset of puberty in children with GHD was evaluated, long-term rhGH treatment among the low, intermediate and high-dose groups did not increase the rate of initiation of puberty and did not show significant differences in adult height depending on puberty onset (9). Previous studies had found that spontaneous puberty started earlier in the higher-dose group than in the standard-dose group suggesting a synergistic effect of rhGH and sex steroids on bone age advancement but results were inconclusive (8,9).

C. RELATION TO IGF-I

GH dosage for children is traditionally based on weight, but this calculation does not account for the individual variation in the response to therapy. The rhGH therapy response can be assessed clinically (by growth response) and also by monitoring the rise in IGF-I levels, the recommended being to maintain them within the normal range during GH therapy (11). If growth velocity has not significantly increased despite a rise in serum IGF-I levels to the upper limits of the normal range further increases in dose may be futile and may increase the possibility of future side effects. On the other hand, if serum IGF-I levels does not rise during rhGH treatment, the growth failure may be due to nutritional deficiencies, GH resistance or poor compliance (11).

4.2.3 EFFICACY

Many studies have shown significantly increases in growth velocity, height SDS and IGF-I and IGFBP-3 serum levels after rhGH treatment in GHD children in a dose-response relationship in comparison to healthy subjects or a control group (3,9,11). In addition, in GHD children, rhGH treatment is able to normalise adult height and is usually safe and well tolerate (9,12).

In order to reach the best improvement in efficacy, as mentioned before, it is important to take into account that the change from baseline in height SDS is greater in prepubertal than in pubertal GHD patients and depends on characteristics at puberty onset (10). Furthermore, during the first 2 years of GH treatment there is a normalisation of IGF-I levels and also a major peak of growth velocity that stabilises to normal values according to children age, sex and pubertal development after the third year of treatment (1,2).

4.2.4 EFFECTS ON BONE AGE

The maturation of bones and their linear growth are due to a combination of two processes known as enchondroplasia and chondral osteogenesis, which occurs under the influence of several hormones and growth factors, with GH and IGF-I playing major roles in these processes(13). During childhood, there are differences in terms of maturation status between bones exhibiting enchondroplasia, such as the radius and ulna (long bones) and metacarpals and phalanges (short bones), and bones exhibiting chondral osteogenesis, such as the carpal bones(13).

In GHD there is a greater delay in bone maturation for carpals than for long and short bones showing that the dominant effect of GH is on chondral osteogenesis with milder effect on enchondroplasia (13). Furthermore, in a study of GH-deficient children, this delay normalises during 2 years of GH treatment. During these 2 years significantly advanced maturation of the carpal cuboid bones was shown on data analysis confirming that separate carpal bone assessment in bone age reading is needed (13). The strongest predictors of maturation for the carpal bones were age at start of treatment (faster maturation as older the children at start of treatment) and gender (girls seemed to mature faster than boys) (13,14).

In summary, skeletal maturation and linear growth are delayed in children with GHD and treatment with GH advances bone maturation as it improved linear growth. The maturation status of the carpal bones is an important variable for the status of other cuboid bones (mostly the vertebrae) that make an important contribution (approximately 40%) to adult height (13). For that reason, the more the bone age delay that children have at the beginning of GH treatment the major the benefit on adult height.

If we go deeper into physiological processes, longitudinal bone growth is organised by complex networks of nutritional, cellular, paracrine, and endocrine factors. The most important ones are the close interplay between oestrogen and GH in the regulation of growth and development in puberty through their role at the growth plate (15). GH, circulating IGF-I, and more importantly, local IGF-I from the circulation and local synthesis at the growth plate –produced by chondrocytes- mediate the elongation of long bones by chondrogenesis. This process results in chondrocyte proliferation, hypertrophy, and extracellular matrix secretion (15). The effects of oestrogens on peripubertal bone growth is biphasic: at low levels they stimulates growth –it involves prepubertal and early pubertal stages-, whereas higher levels of oestrogen (reached at late pubertal stages) have potent inhibitory effects on longitudinal growth by accelerating epiphyseal closure and are therefore essential for epiphyseal fusion (16).

GH treatment increases insulin serum levels (see below) which has an influence on sex steroids production. Thus, by increasing oestrogen production GH may increase their serum levels concentrations and accelerate epiphyseal closure. In summary, GH deficient children that have bone age advancement are unlikely to reach a good response on GH treatment and therefore their target height.

4.2.5 EFFECTS ON INSULIN AND METABOLIC PARAMETERS

GH is a hyperglycaemic and lipolytic hormone and studies have shown that GH increases insulin serum levels, fasting glucose and homeostatic model assessment for insulin resistance (HOMA-IR) index and may cause glucose intolerance and insulin resistance by decreasing insulin sensitivity (6,12,17). Adiponectin levels are inversely correlated to insulin resistance; as expected, low adiponectin values are frequently found in GH-deficient patients; however, men have lower adiponectin levels in comparison to women, suggesting a secondary influence of sex steroids hormones (17). When body fat is decreased, insulin sensitivity and adiponectin levels

rise (17). On the other hand, GH therapy in high doses has been related to an increase of neutrophil count suggesting that insulin resistance is a mechanism linking GH therapy to markers of inflammation (18).

Ghrelin is a gastric peptide that increases appetite, glucose oxidation and lipogenesis and seems to be the strongest factor known today to up-regulate GH secretion. Long-term GH treatment produces a decrease in systemic ghrelin levels which may explain the reduction in food intake observed in GH treated children, which contribute to GH effects on body composition (body fat loss and decreased leptin levels) (17). In summary, GH-treated children have ghrelin and leptin reductions as a result of the negative effect of the GH/IGF-I axis on ghrelin secretion, suggesting an inversely dose-dependent relationship between GH and ghrelin (17). Reduced leptin levels have been associated to improvement in body fat loss, a secondary effect produced by GH (17).

Some studies suggest that patients with childhood-onset GHD are at increased risk of developing early atherosclerosis due to intimal thickening; accelerated progression of atheromatous plaques have been found in the carotid arteries of these patients (3). Impaired lipid metabolism found in GHD children (increase levels of LDL-c and TC), higher carotid intima media thickness (CIMT) and decreased high-density lipoprotein cholesterol (HDL-c) levels may contribute to an increased risk of morbidity and mortality from cardiovascular disease (3). In different studies, it has been demonstrated that GH treatment at average doses (0.030 mg/kg/day) significantly improves lipid profile (it produces a decrease in TC and LDL-c and increase HDL-c) in these children, reducing the atherosclerotic risk (that may worsen when GH treatment is stopped) independently of the known improvement during puberty. Although CIMT showed some improvement, it did not result in a significant difference as compared to controls (3,17).

Finally, regarding body mass index (BMI), no changes have been noticed in adults with GHD after GH treatment (17). However, it has been demonstrate that increases in GH doses can cause an increase in BMI SDS (9).

4.2.6 ADVERSE EFFECTS AND SAFETY

Side effects in children with GHD treated with somatotropin are (6):

- **Very frequent** ($\geq 1/10$): local injection reactions, headache (it is a frequent and nonspecific complaint, but it is hard to come to a definite conclusion of why it is produced) (19).
- **Uncommon** ($\geq 1/1000$ to $< 1/100$): arthralgia.
- **Unknown frequency** (in adults more frequent than in children): diabetes mellitus type 2, paraesthesia, myalgia, extracellular liquid and ion retention, decrease in peripheral cortisol and autoimmunity against rhGH. In this subgroup there are two side effects that should be discussed, although they are more common in organic GHD or other central nervous system disorders:
 - **Idiopathic Intracranial Hypertension:** defined as intracranial hypertension in the absence of a space-occupying lesion which has been reported predominantly in patients with GHD and chronic renal insufficiency. It is characterised by increased cerebrospinal fluid (CSF) pressure with normal CSF composition, bilateral papilledema, visual changes such as diplopia, headaches, nausea and vomiting, strabismus and stiff neck (the last ones are more frequent in children). It had been related to several medications, such as L-thyroxine, glucocorticoids, vitamins A and D and tetracycline. Treatment consists of discontinuation of GH and reduction of CSF pressure, which may include administration of dexamethasone or acetazolamide or lumbar puncture (6,19). For that reason, annually eye fundus exams by a paediatric ophthalmologist are recommended.
 - **Slipped Capital Femoral Epiphysis (SCFE):** it is a disorder of the femoral head growth plate leading to a displacement of the femoral head epiphysis from its natural alignment that occurs frequently in the peripubertal period and it is more common in males. It is commonly associated with obesity and trauma. With GH treatment, a significant increase in the proliferative and hypertrophied cell zones occurs in rats. GH contributes to the widening of the weakest zone of the ephypyseal plate and thus may increase the risk of SCFE in GHD children

treated with GH (19). Pain in the hip or knee and a limb are the major symptoms of SCFE and X-ray of the hip is the best diagnostic tool. Treatment consists of correcting the displacement of the epiphysis with GH therapy being resumed after orthopaedic evaluation.

Somatotropin can reduce insulin sensitivity and increase extratiroideal conversion of T4 to T3 that can lead to hypotiroidism. For that reason, patients with glucose intolerance or diabetes need to be monitored and thyroid function has to be checked in every follow up (6). Related to somatotropin use it is important to be careful when it is combined with glucocorticoids because it can interfere in its growth effects (6).

Although all these side effects have been reported, many studies and clinical practise have shown that GH is a safety treatment (6,9,11,19).

4.3 METFORMIN

4.3.1 CONCEPT AND INDICATIONS

Metformin is a biguanide with antihyperglycaemic effects that reduce postprandial and basal glucose in plasma acting by means of at least 3 different mechanisms (20):

- Reduction of glucose liver production by inhibiting two processes: gluconeogenesis and glycogenolysis.
- Increasing insulin sensitivity (especially muscle) thereby improving peripheral use of glucose and its metabolism (it increases the capacity of transport of all glucose membrane transporters known nowadays and up-regulates anaerobic synthesis acting on glycogen synthase).
- Delays glucose intestinal absorption.

Metformin therapeutic indication in children is for Diabetes Mellitus type 2 treatment (especially those patients with overweight) in children aged above 10 years alone or in combination with insulin (it has been proved that improves metabolic profile in diabetic patients) (20). It is also approved in Polycystic Ovary Syndrome (PCOS).

4.3.2 EFFECTS ON INSULIN RESISTANCE

Metformin causes significant improvements in insulin sensitivity by decreasing insulin and IGF-I circulating concentrations as well as HOMA-IR index in those populations with predisposition or demonstrated insulin resistance (PCOS, low-birth-weight history, metabolic syndrome and glucose intolerance) (21–24) .

Metformin effects improving insulin resistance is thought to be related to an effect on inflammatory process apart from enhancing glucose homeostasis that could explain in part why it delays the onset of type 2 diabetes mellitus (21). *Gómez-Díaz et al.* performed a study whose objective was to determine the effect of metformin on the concentrations of different markers of insulin resistance (especially resistin) or inflammation (C-reactive protein, cytokines, body weight, HbA1c among others) in children with glucose intolerance (21). Results showed that

metformin caused significant reductions of plasma resistin, HOMA-IR index, insulin and HbA1c levels independently of body weight and other covariates in comparison to placebo. Resistin is an adipokine that is predominantly expressed in peripheral blood mononuclear cells, macrophages and bone marrow cells in humans, all being molecules involved in inflammatory process. The decrease in resistin concentrations is thought to be an additional mechanism to improve glucose utilization, due to its association with inflammation (21). Furthermore, metformin has shown to reduce neutrophil count in patients small for gestational age who have insulin resistance (18).

4.3.3 EFFECTS ON METABOLIC PARAMETERS

Metformin reduces leptin serum levels as interacts with the AMPK system that regulate all these molecules (21). The reduction of leptin levels could minimise the gonadotropin-releasing hormone (GnRH) pulsatile discharge and enhance the luteinizing hormone (LH) negative feedback thereby causing a decrease in aromatase enzyme activity on ovarian granulose cells. Thus, it could decrease oestrogen serum levels decreasing its effect on growth plate that may allow more growth and better adult height (22).

Metformin has demonstrated significant improvements in BMI and weight centiles in children as well as improvements in TC, LDL-c and non-HDL-c thus increasing its cardiovascular benefits (22,25). Furthermore, it reduces total, visceral and hepatic fat percentage leading to a further expansion of subcutaneous adipose tissue especially in girls with low-birth-weight (23,24).

4.3.4 SAFETY IN CHILDREN

Many studies with metformin have been performed in children without experiencing severe side effects, which demonstrates its safety in this population. Most frequent side effects found were gastrointestinal intolerance or headache (20).

4.4 LATEST OUTCOMES

4.4.1 METFORMIN EFFECT ON AROMATASE

Insulin enhances oestradiol production in granulosa cells from normal and polycystic ovaries. In PCOS girls, the hyperinsulinaemic state secondary to insulin resistance is the principal cause of abnormal steroidogenesis and defective follicle development which results in dysfunctional ovarian and menstrual cycles. For that reason, metformin –an insulin-sensitizing agent- was introduced in order to diminish PCOS symptoms (26). Metformin effects were attributed to the systemic anti-hyperglycaemic and insulin-sensitizing actions but it has been demonstrated that it is also able to exert direct effects on the ovary. This is due to metformin inhibition of basal and insulin-stimulated E2 prostaglandin (which induces aromatase activity) and progesterone production in ovarian granulosa cells by reducing the activity of several of the steroidogenic enzymes without reductions in circulating insulin (26,27).

These findings were corroborated after demonstrating that metformin has a direct effect on ovarian granulosa cells as it has been shown that it significantly attenuates basal and insulin-stimulated P450 aromatase mRNA expression and protein activity, by silencing some key promoters. This occurs via activation of MEK/ERK pathway which are negative regulators of aromatase synthesis (26). Furthermore, metformin is thought to act primarily upregulating AMPK (28). This mechanism of action is important because it support a possible therapeutic indication in oestrogen-dependent breast and endometrial cancers which is nowadays a matter of investigation (26,28).

In addition to reducing insulin-induced aromatase concentrations and its activity, metformin decreases gonadal oestrogen production and serum levels decreasing its effect on the growth plate, which may allow more growth and a better adult height.

Furthermore, metformin reduces leptin levels, which could exert an indirect effect on aromatase activity. Leptin down-regulation could minimise GnRH discharge and enhance LH negative feedback causing a decrease in aromatase enzyme activity on ovarian granulose cells (22). This is thought to be a synergic effect added to metformin direct effects on the ovary.

4.4.2 METFORMIN AND ITS RELATION TO HEIGHT

Metformin studies in low-birth-weight girls with precocious puberty supports that insulin is a major co determinant of the pubertal chronology and pubertal height gain. They conclude that, in children, an early insulin-sensitizing intervention is important because it can delay the onset of puberty, attenuate body adiposity and normalise the age at menarche (causing a delay of about a year in these patients) resulting in more optimal postmenarcheal stature and endocrine-metabolic state. All these conditions, especially higher total, visceral and hepatic adiposity caused by the hyperinsulinemic/insulin resistance state, are thought to be major factors of early maturation and thus can affect adult height (22–24). *Ibañez et al* suggested that the effect of metformin during puberty on adult height is expected to be slightly more pronounced as they found that metformin treated girls were still growing at a greater velocity than control groups, who seemed to have almost stopped growing. Furthermore, most non-treated girls ended attaining heights below their target mid-parental height (22,24).

Biochemically, metformin also increases sex hormone binding globulin concentrations (22). Thus, an increase in sex hormone-binding globulin as a result of increased insulin sensitivity with metformin could lead to a lower fraction of circulating free steroids which in turn may be followed by a later closure of the epiphyses (22,29).

In order to better understand the heterogeneous changes in BMI of children in response to metformin some authors performed a meta-analysis that took into account not only weight but also height changes. That is because BMI is calculated from both components and in youth linear growth is still preserved and may interfere as a confounding variable. Overall, results showed that metformin reduced BMI but did not significantly affect height or weight. However, when studies were divided into two subgroups based on cumulative metformin doses, those with higher metformin doses demonstrated a decrease in BMI and an increase in height (but no effect on weight) and those with low amounts of metformin did not exhibit changes in any of these variables (29). Thus, this meta-analysis suggests that metformin may increase height in children compared to control subjects, particularly when there is a combination of larger doses and longer treatment duration (29).

4.4.3 FRENCH ALERT ON GH USE

In December 2010 the US Food and Drug Administration (FDA) warned of possible increased risk for death in somatotropin treated patients. This was derived from published results from a French study (*Santé Adulte GH Enfant Study*) that found that persons with idiopathic GHD and small-for-gestational age subjects treated with rhGH for a long-term during childhood had slightly higher risk for death in comparison to individuals from the general French population; specifically, a 30% increased risk(7). This risk for death appeared to be dose-related and was observed in individuals receiving higher doses than those that were commonly prescribed in paediatric GHD (7). A year later, the FDA published that this evidence regarding rhGH and increased risk of death was inconclusive as they identified some study design flaws that limited the interpretation of the study results (30).

4.4.4 METFORMIN AND GH

Metabolic syndrome has similarities to the condition observed in untreated GHD caused by pituitary or hypothalamic pathologies. The core findings in both are abdominal obesity and insulin resistance suggesting that reduced GH action may play a role in the pathogenesis of metabolic syndrome (31). Based on its effect on body mass, *Herrmann et al* studied if rhGH could have favourable effects on patients with metabolic syndrome receiving also metformin. Additionally, metformin could reduce the antagonistic effect of rhGH on insulin. The results of this study showed that apart from metformin, rhGH did not significantly improve glucose metabolism or insulin sensitivity. It is unclear if GH effect decreasing cardiovascular risk exists only in GHD patients or in patients with metabolic syndrome or others pathologies, or whether its effect is additional to those of metformin on metabolism (31). Main side effects observed in the metformin plus rhGH group were arthralgia and peripheral oedema at the beginning of treatment. These side effects improved after reducing treatment doses (31). However, the additional administration of rhGH to metformin in patients with metabolic syndrome has shown to increase adiponectin levels in comparison to controls treated with metformin alone. It seems that synergic reductions on body fat produced by both therapies can increase insulin sensitivity(32).

5. JUSTIFICATION

rhGH treatment has demonstrated its efficacy improving adult height in children with GHD allowing them to reach final heights that are closer to their target height. However, several GH and non-GH dependent factors can influence growth and some children fail to reach adequate adult heights. In addition, it is known that rhGH improves growth velocity but it also can accelerate bone maturation as it increases insulin levels that may stimulate oestrogen production in gonadal cells, oestrogens being the principal stimulus for epiphyseal cartilage maturation on the growth plate (15,16).

Metformin has demonstrated to exert an effect on aromatase enzyme (responsible for oestrogen synthesis) by directly inhibiting its production and activity in ovarian granulosa cells and also by possible indirect effects reducing leptin levels that could minimise GnRH pulsatile secretion and enhance LH negative feedback, eventually causing a decrease in enzyme activity. Thus, a reduction of aromatase activity means less gonadal oestrogen production which could decrease oestrogen serum levels and its effect on the growth plate and may allow for more growth and better adult height (22). On the other hand, metformin has demonstrated to increase SHBG concentrations which could decrease free oestrogen concentrations minimising its effects on peripheral tissues (22).

In girls with precocious puberty an early insulin-sensitizing intervention with metformin has proved to delay the onset of puberty, attenuate body adiposity and normalise the menarcheal timing as well as the postmenarcheal stature and endocrine-metabolic state. All these conditions, especially those on total, visceral and hepatic adiposity caused by hyperinsulinemic insulin resistance state, are thought to be major factors influencing early maturation and therefore can affect adult height (18).

To the best of our knowledge, there are no studies that directly investigate the relationship between metformin and height if we search published papers and protocol databases (European and American). However, some studies using metformin as an interventional drug performed in girls with precocious puberty, polycystic ovarian syndrome or other conditions where BMI was studied, have shown that patients experienced height gains compared to control subjects. Furthermore, the combination of metformin and GH as a treatment has only been performed in order to analyse its effects on metabolic parameters but none on height or growth and more

importantly no study of such combination exist in children with GHD (there is only a protocol registered that is going to study the effects of a short-term combination of metformin and rhGH on metabolic parameters in children born small for gestational age; it can be available at the following webpage: <https://www.clinicaltrialsregister.eu/ctr-search/trial/2009-016246-12/ES>).

Recently, a meta-analysis of different trials where metformin was used as an interventional drug in children and adolescents reported favourable effects on heights as a secondary endpoint. They concluded that metformin use may increase height in children compared to control subjects, particularly when there is a combination of larger doses and longer treatment duration(29). Moreover, they mentioned the need to perform further studies in children younger than 10 years and for longer periods of time because metformin effects could have been underestimated due to the short duration of studies - and the inclusion of older adolescents who potentially had epiphyseal growth plate closure (29). In addition, no studies have been performed in mixed populations of boys and girls so far.

Last but not least, people may think that being one centimetre taller or shorter is not important but it is because this is thought from an adult mind's perspective. For children, and especially adolescents, every stage in their lives is crucial and is the most important thing for them. Being shorter can cause a huge psychological problem in children and even more in those that suffer from GHD and in whom treatment does not seem to work, because they always feel different to their partners or friends. Adults can deal with their own problems or worries in their daily routine but children cannot and for them their worries and fear to not fit well dominate all aspects of their lives, and they can greatly affect their psychological well-being. Therefore, helping them to reach an adequate adult height even if it is only a few centimetres can make a huge difference in their lives.

6. HYPOTHESES

6.1 MAIN HYPOTHESIS

The addition of Metformin to GH treatment improves adult height prognosis in comparison to GH treatment alone in GH deficient children treated with GH and poor adult height prognosis.

6.2 SECONDARY HYPOTHESES

- The addition of Metformin decreases the hyperinsulinemic state secondary to GH treatment.
- The addition of Metformin improves metabolic and cardiovascular risk markers in GH treated children.

7. OBJECTIVES

7.1 MAIN OBJECTIVE

Determinate if metformin use in combination with GH improves adult height prognosis in GH-deficient children with poor adult height prognosis in comparison to GH plus placebo treatment.

7.2 SECONDARY OBJECTIVES

- Determinate if metformin use in combination with GH treatment decreases the hyperinsulinemic state observed in GH treated children.
- Determinate if metformin use in combination with GH treatment improves metabolic and cardiovascular risk markers, such as:
 - BMI
 - Waist circumference
 - CIMT
 - Blood Pressure
 - Serum lipids (HDL-c, LDL-c and TG)
 - C-reactive protein

8. METHODOLOGY

8.1 STUDY DESIGN

This protocol is for a multicentre, prospective, phase III/IV, randomized, double blind, placebo controlled, 4-year duration clinical trial in GH-deficient children treated with GH and poor adult height prognosis.

The study will be conducted at:

- Hospital Universitari Dr. Josep Trueta of Girona. Av. de França, s/n 17007 Girona. Telephone number: 972 94 02 00. Fax: 972 94 02 70.
Email: hospital.girona.ics@gencat.cat
- Principals investigators: Dr. Abel López Bermejo (Pediatric Endocrinology Department) and Ms. Mireia Català Besa.
- Hospital Sant Joan de Déu of Barcelona. Passeig Sant Joan de Déu, 2 08950 Esplugues de Llobregat, Barcelona. Telephone number: 93 253 21 00. Fax: 93 203 39 59.
Email: info@hsjdbcn.org.
- Principal investigator: Dra. Lourdes Ibáñez (Pediatric Endocrinology Department).

A Steering Trial Committee will be created by principals investigators in order to ensure and enhance communication between centres.

8.2 STUDY POPULATION

This is a multicentric study of GH deficient children aged 8-10 years who have been treated with GH for at least 2 years and have a poor adult height prognosis. The participating centres were consulted regarding the actual number of GH-deficient patients who accomplish inclusion and exclusion criteria in order to evaluate the viability of this protocol:

- Dr. Josep Trueta Hospital: 60
- Hospital Sant Joan de Déu: 100

8.3 SAMPLE SELECTION

Table 4. Inclusion and exclusion criteria.

| <u>INCLUSION CRITERIA</u> |
|---|
| ✓ GH deficient children (at diagnosis: height below -2.0 SDS, growth velocity below 25 th centile, GH peak in GH provocative tests below 7.4 ng/mL and normal pituitary MRI). |
| ✓ Age between 8 and 10 years. |
| ✓ Prepubertal patients (no breast development in girls and no testicular growth in boys). |
| ✓ Previous GH treatment for at least 2 years. |
| ✓ Current GH doses between 0.025-0.035 mg/kg/day. |
| ✓ Adult height prognosis between -1.0 SDS and -3.0 SDS. |
| ✓ BMI equal or above -1.5 SDS and equal or below +3.0 SDS. |
| ✓ Birthweight equal or above -2.0 SDS and equal or below +2.0 SDS. |
| ✓ Caucasian ethnicity. |
| <u>EXCLUSION CRITERIA</u> |
| ✗ Chronic endocrine diseases other than GH deficiency (especially thyroid dysfunction). |
| ✗ Chronic non-endocrine diseases (especially celiac disease, Cystic Fibrosis, Inflammatory Bowel Disease, Malnutrition, Anaemia). |
| ✗ Genetic conditions associated with short stature (such as <i>SHOX</i> or <i>AGGRECAN</i> mutations, Turner, Prader-Willi, Silver-Russell or Noonan syndrome, other genetic defects, bone dysplasia). |
| ✗ Other causes of short stature: adoption or emotional deprivation. |
| ✗ Use of chronic medications. |
| ✗ Contraindications to metformin therapy. |
| ✗ Tobacco smoking or use of illicit drugs. |
| ✗ Non-Caucasian ethnicity. |
| ✗ Poor response to GH during the first two years of GH treatment prior to start of trial (increase in Growth Velocity (GV) below 3 cm/year during the first year or/and GV below 6 cm/year during the second year). |

8.3.1 INCLUSION CRITERIA

- ***GH deficient children (at diagnosis: height below -2.0 SDS, growth velocity below 25th centile, GH peak in GH provocative tests below 7.4 ng/mL and normal pituitary MRI).***

The study protocol is based on GH-deficient children and therefore diagnostic criteria from the Spanish Pediatric Association (*Asociación Española de Pediatría, AEPED*) will be used (1). However, GH peak value in GH provocative tests in Catalonia below 7.4 ng/mL instead of 10.0 ng/mL is accepted as a criterium (2). Our clinical trial will be performed in two Catalan hospitals, thus the 7.4 ng/ml cut-off value for GH peak will be used in our patients. Furthermore, a normal brain MRI at diagnosis is needed in order to exclude organic pituitary causes or other cerebral disorders that could affect GHRH-GH axis (1,2,4).

- ***Age between 8 and 10 years.***

Only subjects aged between 8 to 10 years will be included. Lower limit was selected because it is the lower age used in studies performed with metformin in children. These studies showed that metformin was both efficacious and safe similarly to metformin results in children above 10 years of age (22,23,29). On the other hand, upper limit is established in order to avoid epiphyseal cartilage closure in patients before the study concludes as it lasts 4 years and that phenomenon is evidenced at a mean age of 14 years in girls and 16 years in boys (33). Thus, we can avoid confounding results of metformin effects on height as well as the possibility of being able to underestimate its effects just because those children are unable to keep growing.

- ***Prepubertal patients (no breast development in girls and no testicular growth in boys).***

During puberty children experience a growth spurt due to the activation of gonadal function. By including children in all pubertal stages even if we do not change GH doses, we could cause confounding in the interventional drug effects analysed in the trial, so including only prepubertal patients establishes the same conditions for all subjects. Furthermore, as mentioned above, total pubertal growth is determined by factors at puberty onset depending mostly on the outcomes achieved at the end of prepubertal growth, allowing for a greater effect of GH in this period of steady growth (10).

- ***Previous GH treatment for at least 2 years.***

At the beginning of GH treatment, an increase in growth velocity is expected in order to confirm its efficacy; after the first year, an increase greater than 3 cm/year in growth velocity and after the second year, an increase equal or greater than 6 cm/year in growth velocity is expected on follow-up. From the third year of follow-up on, a normal growth velocity adjusted by age, gender and pubertal development is expected (2,11). We wish to evaluate metformin effects at a steady state of growth during GH treatment; by including children who have been treated for at least 2 years instead of naïve ones, we are avoiding including subjects during the initial catch-up growth following GH treatment.

- ***Current GH doses between 0.025-0.035 mg/kg/day.***

The Catalan Health Department and the Spanish Pediatric Association recommendations on doses of GH treatment in GH-deficient children are to use average doses between 0.025 to 0.035 mg/kg/day (1,2). During the clinical trial, children will be treated with an average dose of 0.030 mg/kg/day to standardise GH treatment in all groups. We will include children treated with these average doses in order to minimise changes in basal treatment.

- ***Adult height prognosis between -1.0 SDS and -3.0 SDS.***

Adult height can be assessed once the epiphyseal cartilages are completely closed. Usually, this is observed at approximately 18 years of age this is why we need to use adult height prognosis instead of a precise adult height. Children with good or reasonable adult height prognosis will be not included in order to avoid the addition of a second drug to their treatment; only children with poor adult height prognosis will be included in order to determine if additional treatment with metformin [which has shown to cause an improvement in height as a secondary end-point in other studies (22,23,29)] can also improve heights in these children and allow them to attain final heights closer to their mid-parental height. This explains the upper limit of the criteria. On the other hand, the lower limit is selected to avoid the mistakenly inclusion of a child with other rare causes of short stature (2).

- ***BMI equal or above -1.5 SDS and equal or below +3.0 SDS.***

Higher BMI is related to bone age advancement and it can minimise rhGH effect by reducing its sensitivity (14). Furthermore, these patients have higher risk of metabolic syndrome and insulin resistance that could confound the results regarding metformin effects on metabolism. This explains the upper limit of the criteria. On the other hand, the lower limit is selected in order to exclude those patients extremely thin to avoid excessive fat or weight loss during metformin treatment.

- ***Birthweight equal or above -2.0 SDS and equal or below +2.0 SDS.***

Low-birth weight has demonstrated to affect the initial growth response to GH treatment in GHD children by influencing the first year of auxological response. Furthermore, this influence seems to persist over time (34). In addition, low-birth-weight patients experience catch-up growth that has been associated with insulin resistance and higher risk for type 2 diabetes mellitus. For this reason, we need to exclude these patients in order to avoid different responses to GH treatment and the possible effect of the catch-up growth. On the other hand, the higher limit is selected in order to avoid including patients with higher risk of metabolic syndrome and diabetes that could confound our results.

- ***Caucasian ethnicity.***

Depending on the ethnicity, the most frequent causes of short stature vary and, most importantly, the growth charts and values to evaluate the main parameters of children (height, weight and BMI) are different (1). We include only Caucasian ethnicity in order to avoid a heterogeneous group and limit confounding variables.

8.3.2 WITHDRAWAL CRITERIA

Subjects may be withdrawn from the study because of the following reasons:

- Patient is not willing to comply with the protocol and instructions provided by the investigators.
- For medical reasons, as assessed by the investigators: adverse event or sudden important disease or condition that could affect metformin effect.
- Patient with BMI changes above or below 1 SDS during the study period.
- Patient who has poor treatment adherence rate (adherence below 80%).
- Participant declines consent to continue in the study.

Subjects withdrawn from the trial will not be replaced.

8.4 SAMPLE SIZE

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 55.0 subjects are needed in the first group (metformin plus GH treatment) and 55.0 in the second (placebo plus GH treatment) to be able to detect as statistically significant a difference greater than or equal to +0.6 units (+0.6 SDS) in the projected adult height. The common standard deviation has been computed as being 1 (about 5 cm in girls and 6 cm in boys) (**See Annex 1: Height Charts**). A drop-out rate of 20% has been estimated.

Considering the results of studies on metformin in girls with low-birth-weight aged 8-12 we expect to observe a minimum difference of +0.8 SDS in the projected adult height (23,29). However, as there are not studies performed in boys we wish to detect a difference of at least +0.6 SDS in this subjects. Therefore, a more conservative difference of +0.6 SDS (about 3 cm in girls and 3.5 cm in boys) has been selected for the purpose of this study.

For randomization purposes, we will split the sample in three strata (age, gender and BMI; see below) in order to avoid having differences in these variables at baseline between groups. We therefore need 60 subjects in each group, which yields an estimated sample size of 120 patients.

The following website was used to calculate the sample size;

<http://www.imim.cat/ofertadeserveis/software-public/granmo/>

8.5 ENROLLMENT AND PATIENT SELECTION

We will perform a consecutive non-probabilistic sampling due to the fact that we will not have a census of possible candidates at the beginning of the study. Potential research subjects will be determined from the 2015/16 lists of GH treatment Approval at the two participating centres, based on inclusion and exclusion criteria retrieved from the clinical history. After that, we will schedule a first visit with each possible candidate and their parents or legal tutors in which the investigator will provide detailed information about the study. If the patient and parents agree with the protocol procedure, a written informed consent will be signed (**See Annex 4: Information for patient and Informed Consent**).

BMI is the principal covariate we will have during the study period because it may affect growth response to treatment. For that reason, we also need to determine that variable at the first visit in order to allocate each patient to the correct stratum.

In order to accomplish the inclusion and exclusion criteria and especially ensure that there is no contraindication to metformin therapy, a complete history and physical examination –including Tanner stage - will be performed in a second visit 4 weeks before the study starts. At this visit the investigator will order baseline labs, including complete blood count, fasting glucose, HbA1c, creatinine, transaminases, B12 vitamin, serum albumin levels, serum lipids (LDL, HDL and triglycerides), C-reactive protein, anti-transglutaminase antibodies and hormone profile (fasting insulin, IGF-I and IGFBP-3 levels, HOMA-IR index, HMW-adiponectin, TSH, free T4, prolactin, cortisol, LH, FSH, testosterone and oestradiol). In addition, a left hand radiography and internal carotid ultrasonography will be scheduled for the next visit to assess bone age advancement and intima-media thickness, respectively.

A week before the onset of the study, we will schedule a third visit where we will check laboratory results and assess weight, height, waist circumference, blood pressure, growth velocity, bone age and adult height prognosis at the beginning of the study.

The estimated time of recruitment will be of 6 months. Due to the fact that we divide our patients into three strata, the rate of inclusion may be slower for the last few subjects, therefore a period of time of 6 months is expected to be needed to complete the inclusion of all subjects.

8.6 RANDOMISATION

Participants will be 1:1 randomized using block randomisation into metformin and placebo groups. The randomization will be made according to a randomization list generated by nQuery Advisor 7.0 (Statistical Solutions Ltd., Cork, Ireland), in which patients remain into 12 blocks of 10 subjects balanced by age, gender, BMI and treatment (**See Annex 3: Example of Randomisation**). This will ensure the comparability of treatment groups by main covariates:

- **Age** (a first group with age between 8 to 9 years and a second group with age between 9 to 10 years). This stratification is important in order to avoid a disproportion of patients younger or older between study groups. This could produce a difference in mean bone age (14,33) –and indeed time to growth- and puberty onset between groups that could affect the study results.
- **Gender** (male and female). This stratification is important in order to ensure that values of height are comparable between groups. That is because in terms of height male and females have different mean and SDS values for height (mean SDS for adult height indeed are: 5cm for female and 6cm for male subjects) (**see Annex 1**). In addition, the onset of puberty and possibly also the response to treatment vary between boys and girls.
- **BMI** (a first group with BMI-SDS between -1.5 and 0.0 SDS, a second group with BMI-SDS between 0.0 and +1.5 SDS and a third group with BMI-SDS between +1.5 to and +3.0) (**See BMI charts in Annex 2**). This stratification is important because differences in this variable can change bone age advancement (the higher BMI –or weight/height ratio- the more adipose tissue available. This allows for higher androgen conversion into oestrogens and possibly faster bone maturation) (14,35). Furthermore, increases in BMI could produce higher fat mass and serum leptins that may advance puberty onset (14).

8.7 VARIABLES AND INSTRUMENTATION

Table 5. Variables and instrumentation.

| | VARIABLE | TYPE | INSTRUMENTATION | UNITS | |
|----------------------------------|---|--|-----------------------------|---|-------------------|
| Independent Variable | Metformin or placebo as an additional treatment to GH | DcQV | None. | mg/day | |
| Main Dependent variable | Adult height prognosis at the end of study | CQV | Bailey-Pinneau method (36). | cm | |
| Other Dependent Variables | Related to height | Height | CQV | Harpenden Stadiometer (Holtain Ltd, Crymych, UK). | cm |
| | | Height Gain | CQV | Harpenden Stadiometer (Holtain Ltd, Crymych, UK). Calculating the difference between final and initial height measured. | cm |
| | | Growth Velocity | CQV | Harpenden Stadiometer (Holtain Ltd, Crymych, UK). Calculating the difference between final and initial height measured and dividing by 4 years of study duration. | cm/year |
| | | Bone age | CQV | Greulich and Pyle radiographic atlas (33). It will be determined by main investigators according to the same criteria. | years |
| | Related to metabolic profile | BMI | CQV | Height will be measured by Harpenden Stadiometer (Holtain Ltd, Crymych, UK) and weight by calibrated scale (SECA, Hamburg, Germany). Body weight divided by the square of the body height. | kg/m ² |
| | | Waist circumference | CQV | Measuring tape. It will be measured at a level midway between the lowest rib and the iliac crest. | cm |
| | | Blood Pressure | CQV | Electronic sphygmomanometer (Dinamap Pro 100, GE Healthcare, Chalfont St Giles, United Kingdom). | mmHg |
| | | Carotid intima-media thickness | CQV | High-resolution ultrasonography (MyLab25; Esaote, Firenze, Italy). As ultrasonography is observer-dependent, measurements will be read by the same investigator for both hospitals. | mm |
| | | C-reactive protein | CQV | Ultrasensitive latex immunoassay (CRP Vario; Sentinel Diagnostics, Abbot Diagnostics Europe, Milan, Italy). | mg/L |
| | | HDL-cholesterol, LDL-c and triglycerides | CQV | Cobas Integra 711 model (Roche Diagnostics, Indianapolis, IN, EE.UU). | mg/dL |

| | | | | | |
|---|------------------|---------------------------------|------|--|-------------------|
| | | Fasting insulin | CQV | Insulin-automated assay IMMULITE 2000 System (Siemens, Healthcare Diagnostics, Deerfield, IL, USA). | mIU/l |
| | | HOMA-IR | CQV | Homeostasis model assessment for insulin resistance. | mg/dL |
| | | HbA1c | CQV | Siemens DCA Vantage Analyzer. | % |
| | | HMW-adiponectin | CQV | Radioimmunoassay (RIA) (LincoResearch, Inc., St. Charles, Missouri, EE.UU.) | mg/L |
| | Related to basal | IGF-I levels | CQV | Enzyme-amplified immunoassay (DIAsource ImmunoAssays, Belgium) (3). | mg/dL |
| | | IGFBP-3 levels | CQV | Enzyme-amplified immunoassay (DIAsource ImmunoAssays, Belgium) (3). | mg/dL |
| Safety | | Fasting glucose | CQV | Hexokinase method (AEROSET c8000). | mIU/l |
| | | Creatinine | CQV | Synchron CX analyser (Beckman Systems, Fullerton CA)(21). | mg/dL |
| | | Liver function tests (AST, ALT) | CQV | Synchron Cx analyser (Beckman Systems, Fullerton CA)(21). | mg/dL |
| | | B12 vitamin | CQV | Immunochemiluminiscence. | pg/ml |
| | | Haemoglobin | CQV | Immunochemiluminiscence. | pg/ml |
| | | Eye funduscopy | DcQV | Normal or Abnormal | - |
| Covariates | | Mid-parental height | CQV | It will be measured by established formulas based on father's and mother's height: father's height+mother's height + 13 (boys) or -13 (girls) and the results is divided by 2. | cm |
| | | BMI | CQV | Body mass divided by the square of the body height. Height will be measured by Harpenden Stadiometer (Holtain Ltd, Crymych, UK) and weight by calibrated scale (SECA, Hamburg, Germany). | kg/m ² |
| | | Gender | DcQV | Clinical examination: male/female. | - |
| | | Age | CQV | Clinical examination. | years |
| | | Pubertal stages | NQV | Tanner stages based on testicular volume in boys using an orchidometer and breast development in girls: Tanner I through to V. | - |
| <p>*DQV: Discrete quantitative variable. *CQV: Continuous quantitative variable. *NQV: Nominal qualitative variable.</p> <p>*DcQV: Dichotomy qualitative variable</p> | | | | | |

All measures will be done by the same observer at each centre (nurse or physician) in order to avoid interobserver variability. All laboratory samples from participating centres will be analysed at one single laboratory (Hospital Dr. Josep Trueta) by one analyst. Finally, all radiological tests will be also read at a single centre (Hospital Dr. Josep Trueta) by the same radiologist.

Height, waist circumference and BMI will be measured in their appropriate units –cm and kg/m² respectively- and will be transformed into SDS values according to age and gender (**See Annex 1 and 2**). At the beginning of the study all patients will be prepubertal (Tanner stage I).

9. INTERVENTION

9.1 STUDY TREATMENT

9.1.1 INTERVENTION DRUG

The selected experimental drug will be metformin 850 mg, produced by Kern Pharma (Terrassa, Barcelona), and with expertise preparing metformin and placebo pills in previous studies performed by both hospitals participating in this protocol.

9.1.2 METFORMIN DOSAGE

In *Agencia Española del Medicamento y Productos Sanitarios* in paediatric population it is recommended to give metformin as single dose because of its proved efficacy in previous studies and the lack of efficacy results for multiple doses (20). In order to improve gastrointestinal tolerability it is recommended to start with low doses and to reach a maximum dose after 10-15 days (20) and to take metformin with or after meals.

Several clinical trials have been performed with different metformin doses administration regimes (once or twice per day) in children with mean ages between 8 to 16 years. As mentioned above, in a Meta-analysis of Randomized Clinical Trials using metformin versus placebo, it was shown that there is greater increase of height and decrease in BMI with metformin when given at largest cumulative doses but not in those in which metformin was given at lowest doses as compared to the control group (in whom there were not statistically significant differences) suggesting a dose-response relationship (29). This increment seems to be more significant when there is a combination of larger doses and longer treatment duration (29).

In order to achieve at least the same results of a 4-year clinical trial with largest cumulative metformin and avoid overdosing in children between 8 to 10 years (22), the study treatment will be divided into a single oral dose of 425 mg/day for the first 2 years and a single oral dose of 850 mg/day for the last 2 years. Furthermore, metformin doses during the first 10-15 days at the beginning of treatment will be progressively up-scaled in order to minimise gastrointestinal adverse effects.

The maximum recommended dose of metformin hydrochloride is 2g/day administered twice or three times per day. This dose will not be achieved in the current protocol.

9.1.3 TREATMENT DURATION

As mentioned above, in the few metformin studies where height is taken into account as a secondary variable, it has been suggested that largest cumulative doses plus longer treatments durations are needed to achieve better outcomes in height and metabolic profile in comparison to a control group (29). Furthermore, when height has been studied with shorter metformin treatment durations, it did not show greater differences as compared to the control group, but significant differences were shown after a follow-up period in the metformin group (23).

For that reason, the trial will be performed during 4 years in order to achieve at least the same height improvement as that described in published studies assessing metformin effects on height (22,23,29) and on metabolic outcomes (24). The study will not be extended over 4 years because of the lack of evidence of metformin treatment in children above this period of time and also because of the possibility that after that time some of the patients will have reached epiphyseal growth plate closure. In that condition we will not be able to evaluate growth or height changes due to metformin which could lead to confounding results regarding metformin effects on height.

9.1.4 DRUG CHARACTERISTICS

CONTRAINDICATIONS (20)

- Hypersensitivity to metformin or any of the excipients.
- Diabetic ketoacidosis, diabetic precoma.
- Kidney failure or dysfunction (estimated creatinine clearance < 60 ml/min).
- Acute situations with the potential to produce kidney impairments such as dehydration, severe infection or shock. In these cases, metformin treatment will be discontinued to be resumed once the patient recovers from the disease.
- Acute or chronic disease that could produce tissue hypoxia such as heart failure, respiratory failure or shock.
- Liver failure, acute alcoholic intoxication or alcoholism.

INTERACTIONS

Plasma protein binding is negligible since it is distributed in erythrocytes. For that reason, metformin has no known pharmacokinetic interactions (20). The main interactions are:

- **Alcohol:** acute alcoholic intoxication is associated with increasing risk of lactic acidosis, especially in case of fasting or malnutrition and liver failure. It can also be seen with drugs containing alcohol so it is better to avoid them.
- **Iodine contrast:** intravascular administration of iodine contrast can produce kidney failure producing blood metformin accumulation and higher risk of lactic acidosis.
- **Drugs with intrinsic hyperglycaemic activity (corticoids, sympathomimetics):** It is recommended to perform closer blood glucose controls, especially at the beginning of treatment. If necessary, metformin posology should be adjusted during therapy with the other drug and after it is discontinued.
- **Diuretics, especially loop ones:** They can increase lactic acidosis risk as they can decrease kidney function.

The use of any of these drugs will be a reason for excluding a subject from the current protocol.

ADVERSE EFFECTS

Frequencies of adverse reactions (20) are defined as:

Very common ($\geq 1/10$)

- Gastrointestinal disorders, such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These disorders tend to appear at the beginning of treatment and in most cases tend to disappear spontaneously. To avoid them it is recommended to take metformin with or after meals as well as to slowly increase metformin doses.

Common ($\geq 1/100$ to $< 1/10$)

- Nervous system disorders especially taste disorder.

Uncommon ($\geq 1/1.000$ to $< 1/100$)

Rare ($\geq 1/10.000$ to $< 1/1.000$)

Very rare (<1/10,000)

- Lactic acidosis. Metformin inhibits gluconeogenesis and its accumulation can lead to this rare metabolic complication that needs emergency treatment and metformin discontinuation. Most of described cases were observed in diabetic patients with severe kidney failure.
- Megaloblastic anaemia. The use of large periods of metformin therapy reduces absorption and B12 vitamin serum levels.
- Hepatobiliary disorders. Isolated cases of liver function disorders or hepatitis have been described and those disappear when metformin has been discontinued.
- Skin and subcutaneous tissue disorders such as erythema, pruritus or urticarial.

Metformin use in children is indicated in type 2 diabetes or PCOS (**See Annex 7: Metformin Datasheet**). Growth or pubertal negative effects of metformin use have not been described in clinical trials so far but the recommendations are to perform a carefully follow-up (especially in children between 10-12 years old even though metformin efficacy and safety have not significant differences from adults). Although the use of metformin is not indicated in children younger than 10 years there are several studies evaluating its efficacy in puberty onset and in BMI changes in children aged 8 years, showing the same safety characteristics (22–25,29) .

However, it is important to report suspected adverse drug reactions after approval. This allows for continuous monitoring of the benefit/risk of the drug. If suspected new adverse reactions are detected, they ought to be reported through the Spanish Pharmacovigilance System for Medicinal Products for Human Use: www.notificaRAM.es

OVERDOSE

Metformin treatment should be discontinued when rare or very rare adverse effects appears, especially lactic acidosis (20). This condition is a medical emergency and should be treated in hospital by haemodialysis and haemodynamic support.

Lactic acidosis is manifested with unspecific signs such as muscle cramps with digestive disorders (abdominal pain) and severe asthenia. Massive overdoses can lead to acidotic dyspnoea, abdominal pain, hypothermia and coma.

9.2 TREATMENT MONITORING

Metformin overdose can be monitoring through safety variables related to metformin main adverse effects. At each 6-month follow-up visit fasting glucose, serum creatinine, transaminases, haemoglobin and B12 vitamin levels will be checked in order to rule out most severe side effects. Furthermore, the patient and their guardians will be informed about possible side effects before starting the trial and they will be asked at each visit for their presence (including possible new side effects). In positive cases, a side-effect report form will be filled notifying its presence (**See Annex 6: Side-effects Report Form**). If there are new side-effect they will be reported to an appropriate institution as mentioned above.

9.3 MASKING

The study will be double-blinded (patient and researchers) and the pharmacist will be the person responsible for masking the intervention and randomly dispensing the intervention according to the abovementioned list. Thus, neither the patient nor the researchers will be able to know the interventional drug assigned to any patient until the study concludes. It may be only be disclosed in case of emergency regarding the need for the patient's treatment.

9.3.1 PATIENT MASKING: PLACEBO

Control group will receive placebo. Placebo looks like metformin pill and it has the same ingredients except from the active ingredient. Like the interventional drug it will be produced by Kern Pharma (Terrassa, Barcelona).

9.3.2 INVESTIGATOR MASKING

If, in follow-up measurements, insulin levels and metabolic parameters were assessed on a regular basis, it would become clear which subjects were receiving treatment and which were not. Therefore, serum samples will be frozen, in order to be analysed at the end of the study in Hospital Josep Trueta, to where all samples will be sent by means of a courier service. Variables to be analysed will be serum lipids, fasting glucose, fasting insulin, HOMA-IR index, HbA1c and HMW-adiponectin levels. This way, several advantages are gained. The most clear one being

blinding the investigators, but also, analysing serum in badges and in one single laboratory which will reduce variability produced by different lab techniques.

9.4 BASAL TREATMENT

Our study population are GH-deficient children treated with rhGH as a basal treatment. There are different GH brands with different devices for drug administration. Furthermore, as mentioned before rhGH can be prescribed at different doses although Spanish and Catalan recommended doses are average ones (between 0.025 to 0.035 mg/kg/day).

In order to homogenise basal treatment in all participants, rhGH will be administered only using a *Saizen easypod* (a device from Merck-Serono used for GH administration) and using a mean dose of 0.030 mg/kg/day with weight adjustments every six months at each visit. In those patients who do not use this brand and device, a replacement at the third pre-selection visit will be performed and rhGH dosage will be adjusted before starting the study. The reason to select this brand is because the device allows to evaluate adherence to treatment by monitoring daily hormone administration and allows also to know whether a full dose or a partial has been given.

This procedure will provide the same basal conditions in all patients and avoid that rhGH dose acts as a covariate confounding the results of the interventional drug.

rhGH side effects are rare as mentioned before, but in order to monitor the severe ones annual eye fundus examination will be scheduled for each participant. Furthermore, all patients will be monitored by means of hormonal profiles and thyroid function at each follow-up visit as established on protocols (1,2,6) to detect hormonal disorders during treatment. On the other hand, overdose can be monitored by means of two different variables included in the blood tests performed at each visit: IGF-I and IGFBP-3 serum levels. In case IGF-I levels are above 2 SDS (for age, gender and Tanner stage) or they are higher than 100 times the corresponding IGFBP-3 values, the dose of GH will be adjusted.

9.5 ORGANISATION AND DATA COLLECTION

The intervention visits will take place during the routine follow-up visits for GH-deficient children appointed every 6 months. By not adding new visits, the trial should not affect patients' routine; therefore, fewer drop-outs are expected.

In order to optimise study adherence, metformin or placebo will be taken at dinner time or before giving the GH injection. In addition, guardians and subjects will receive text message or e-mail reminders on a weekly basis to take the metformin/placebo during the treatment period. Also, 1 week in advance, guardians and subjects in both groups will receive text message or e-mail reminders about their upcoming appointments. Counting the number of pills remaining at each visit will be performed by the pharmacist as an indicator of adherence. At each visit investigators will also monitor basal treatment adherence checking the *Saizen easypod* application of the device.

At each visit, the follow-up measurements described below (**Table 6**) will be assessed:

Table 6. Follow-up measurements

| Auxological (every 6 months) | Laboratory tests (every 6 months) | Other parameters (yearly) |
|---|---|--------------------------------------|
| - Height | - C-reactive protein | - Bone age |
| - Weight | - Serum lipids (HDL-c, LDL-c and triglycerides) | - Adult height prognosis |
| - BMI | - Fasting glucose | - CIMT |
| - Waist circumference | - HbA1c | - Eye fundus |
| - Blood pressure | - Fasting insulin | |
| - Pubertal stage (Tanner scale) | - HOMA-IR | |
| - Growth velocity | - HMW-adiponectin | |
| | - IGF-I and IGFBP-3 | |
| | - Creatinine | |
| | - Liver function (AST and ALT) | |
| | - B12 vitamin | |
| | - Complete blood count (including haemoglobin) | |

The follow-up measurements should not be performed when the patient presents acute symptomatology (such as any pulmonary infection, very common in children). Acute symptomatology increases stress hormones needs such as cortisol and secondary increases insulin production; therefore it needs to be taken into account when collecting data. If this situation happens, follow-up visit will be rescheduled in within two weeks in order to collect follow-up measures and avoid to have missing data.

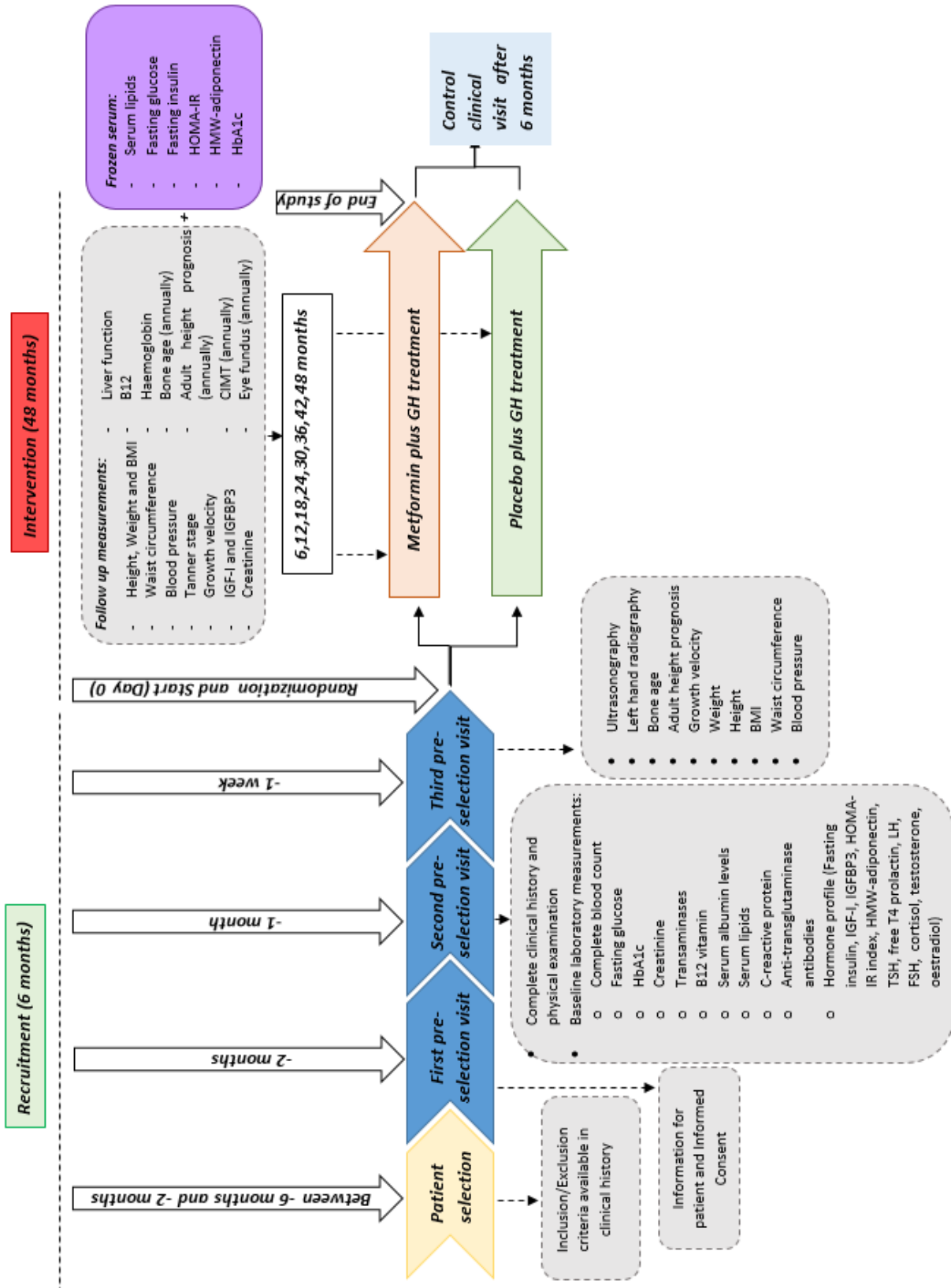
As established by the protocol, venous blood sampling will be drawn with the child in the fasting state. All serum samples will be obtained between 8.00 a.m. and 10.00 a.m. in order to avoid variability produced by circadian hormones. Blood tests will be performed every 6 months in order to have safety parameters and those that allows us to adjust GH treatment dosage (IGF-I and IGFBP-3). Blood tests will be performed the same visit day and when results are available main investigators will contact families in order to inform from the results and any change in basal treatment.

Measurements will be taken during follow up visits in all children and will be performed by the same observer who will be unaware of the subjects' clinical and laboratory metformin parameters. All data will be collected in standard forms in order to ensure all parameters (**See Annex 5: Case Report Form**).

- **Height** will be measured with the child wearing no shoes on a Harpenden stadiometer. It will be measured standing with the back and ankles touching the surface and the head in neutral position. Feet and legs must be straight and remain together. Three measures will be performed in order to avoid measurements mistakes that could lead to information bias. The average of two similar measurements will be used in the study.
- **Weight** will be measured with the child wearing underwear on a calibrated scale.
- **BMI** will be calculated as weight divided by the square of height in meters. Age and sex adjusted z-score values for current weight, height, and BMI will be calculated using regional normative data (**See Annex 1 and 2**).
- **Waist circumference** will be measured at the umbilical level with the child standing with a measuring tape. It will be measured at a level midway between the lowest rib and the iliac crest.

- **Blood pressure** will be measured before venous blood sampling with the child supine on the right arm after a 10-minute rest, using an electronic sphygmomanometer with a cuff of appropriate size for the child's arm circumference.
- **cIMT** will be measured by high-resolution ultrasonography. For cIMT, diastolic images will be obtained using a linear 12-MHz transducer on the right side at the level of the distal common carotid artery, 1 cm away from its bifurcation. Averages of 5 cIMT measurements on the far wall of the artery will be used in the study. The intra-subject coefficient of variation for ultrasound measurements is <6%. It will be performed annually by a radiologist in each participating center under consensus criteria previously established in organisation meetings and images will be sent to Hospital Dr. Josep Trueta in order to be read by the same radiologist.
- **Bone age** will be determined by a left hand radiography following Greulich and Pyle radiographic atlas (33). It will be determined by the main investigators according to the same criteria previously established in organisation meetings. Radiography will be scheduled annually at a follow up visit. Once we have the bone age we can predict adult height prognosis by Bailey-Pinneau method (36) so we will calculate it annually. Estimations of adult height prognosis will be done by one single investigator with ample expertise in reading bone age films.
- **Growth velocity** will be calculated by the difference between final and initial height measured at each follow up visit and adjusted z-score values for age and sex (37).
- **Eye fundus** will be scheduled annually in order to evaluate GH side effects. The presence of massive oedema or hypertension signs will be a reason to discontinue basal treatment and to withdraw the subject from the study.

10. FLOW CHART



11. STATISTICAL ANALYSIS

UNIVARIATE DESCRIPTIVE ANALYSIS

Results for categorical variables will be described as frequencies (n) and percentages for each category. Quantitative variables assuming a normal distribution will be summarized as mean \pm standard deviation, and those for variables without a normal distribution will be expressed as median and interquartile range. Non-parametric variables will be mathematically transformed to improve symmetry.

BIVARIATE ANALYSIS

Results for main variables will be compared in order to ensure that comparable treatment groups were generated through the randomisation process. Categorical variables will be compared in a 2x2 contingency tables and evaluated by χ^2 test or Fisher's exact test. Continuous variables that assume a normal distribution will be compared by Student T test (to compare 2 groups) or ANOVA's test (to compare three groups). Mann-Whitney test will be used to compare continuous variables that do not follow a normal distribution.

MULTIVARIATE ANALYSIS

General linear model (GLM) for repeated measures will be applied in order to perform the analysis of response to treatment for endpoint variables (see below) between independent treatment and control groups (main and secondary objectives of the proposal). The interaction term among the intervention variable and the endpoint variables of the study will be applied in order to highlight differences in 4-years changes across intervention groups. Models will be adjusted for potential confounders (see "covariates" in **Table 5**). For adult height prognosis, covariates will be age, gender, BMI-SDS, mid-parental height, height SDS at baseline, GH treatment duration, current GH dose, pubertal stage, change in HOMA-IR, change in HMW-adiponectin and treatment (metformin or placebo). For HOMA-IR and HMW-adiponectin, covariates will be age, gender, BMI-SDS, waist circumference SDS, GH dose, pubertal stage, treatment (metformin or placebo) and HOMA-IR/HMW-adiponectin in each one. For other

endpoints (changes in BMI-SDS, waist-SDS, CIMT, blood pressure, serum lipids and C-reactive protein), covariates will be age, gender, GH dose, pubertal stage, change in HOMA-IR (and when applicable also, changes in BMI-SDS and waist-SDS), change in HMW-adiponectin, treatment (metformin or placebo) and the corresponding value of the parameter to be tested at baseline.

“Intention-to-treat” (ITT), “as treated” and “per protocol” analyses will be applied, in case of:

- Protocol violations.
- Losses to follow up.
- Withdrawals from the study.
- Non-compliance.
- Refusal of the allocated treatment.
- Other deviations from established protocol.

Imputation of missing values for endpoints variables will be performed using the latest observed values for each variable and subject.

A p value <0.05 will be considered statistically significant.

12. ETHICAL CONSIDERATIONS

The clinical trial will be conducted in accordance with the medical ethics requirements defined on the Declaration of Helsinki involving Ethical Principles for Medical Research Involving Human subjects (last update October 2013) **(See Annex 8: Helsinki Declaration)**.

All patients and guardians, as all will be under 18 years of age, will be properly informed about the trial. Written informed consent **(See Annex 4)** will be provided to their guardians and must be signed before taking part in the project. However, we will obtain informed assent from all children, in order to enrol them in the study. On the other hand, every investigator will have to declare no conflict of interest.

The research project will be performed in accordance with the legal framework related to clinical trials: “Real Decreto Legislativo 1/2015, de 24 de julio, por el que se aprueba el texto refundido de la Ley de garantías y uso racional de los medicamentos y productos sanitarios”, “Ley 14/2007, de 3 de julio, de investigación biomédica” and “Reglamento (UE) n°536/2014 del Parlamento Europeo y del Consejo, de 16 de abril de 2014, sobre los ensayos clínicos de medicamentos de uso humano”.

All patient data obtained during the trial will be confidential and the anonymity of the patients will be guaranteed according to: “Ley orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal”.

The clinical trial will be submitted to a European database of clinical trials (<http://www.clinicaltrialregister.eu>). As postulated by current recommendations, the trial will also be registered with an International Standard Randomized Controlled Trial Number (<http://www.controlled-trials.com>).

The trial will be submitted to the “Comité de Ética de Investigación Clínica (CEIC)” of Hospital Dr. Josep Trueta of Girona following the guidelines subscribed, in order to be reviewed and approved before any further procedure. Then, we will apply for the approval of the responsible person at each centre participating in the trial. As a final step, the protocol must be approved by the European Medical Agency (EMA) and “Asociación Española de Medicamentos y Productos Sanitarios (AEMPS)” before final approval of the clinical trial.

13. LIMITATIONS

- Regarding the patient selection, a consecutive non-probabilistic method will be applied. An appointment will be scheduled instead of waiting for the follow-up visit to describe the study to patients. It is expected to reach about 75% of selected patients. Therefore, a non-response rate should be taken into account. However, this would not be a limitation because if we cannot reach all sample size with the two participating centres, a third centre will be added to the trial. Contact with Hospital Vall Hebron of Barcelona has been established and they accept to participate if this situation happens.
- BMI is our main covariate in the study as children are constantly changing their weight as well as their height. As mentioned before, small BMI changes influence growth. Although randomisation usually distributes variables equally in both groups we have stratified sample into three BMI groups in order to avoid this confounding effect. Moreover, all participants will be informed about the importance of maintain a stable weight during the study which will be of help not only for the study results but also for their growth. The same measure of stratification has been performed for those unmodifiable covariates: gender and age.
- Regarding follow up measurements, as this is a multicentre study, there always will exist variability between main investigators and selected personnel when collecting data. Furthermore, there are some examinations that are observer-dependent like Tanner stage, bone age and CIMT measured by ultrasonography. To minimise this interobserver variability, all personnel involved in collecting data will be trained in the same way to perform examinations and they will perform meetings in order to put in common all procedures. On the other hand, CIMT will be read by the same radiologist of Hospital Dr. Josep Trueta in all study patients. Appointments will be scheduled and recalled to patients.
- Differences between measurements techniques could cause lack of comparability between the different centres participating in the study. For that reason, as mentioned in masking section, frozen serum analyses will be performed only in Hospital Josep Trueta of Girona.
- All participants have a basal treatment inherent to its pathological condition. Different methods in rhGH treatment application and dosage can confound the results of the effects of the interventional drug on height. Therefore, all patients will change their devices to

Saizen easypot in order to avoid variability between rhGH devices and a mean dose will be established in all patients at each follow up visit based on weight.

- The study lasts 4 years so there is a risk of drop-out or non-compliance of the treatment. This has been taken into account when calculating the sample size.
- Inherent to the study design which have strict inclusion and exclusion criteria that do not represents all GH-deficient population, we will not be able to extrapolate the study results to the general population. Therefore, further studies will be needed with greater sample sizes and other study populations in order to increase the external validity of our results. It would be convenient that other researchers performed similar studies in order to confirm the results of our study.
- According to the current literature, it is possible that larger doses and longer periods of study would be necessary in order to reach better results in endpoint variables, especially in height gain and adult height. However, we have selected our criteria based on previous experience with metformin and we expect to have statistically significant results.
- Regarding the budget, as this is a clinical trial, it is a high cost study although metformin has a low cost. However, if we want to answer our hypothesis this is the best study design to be performed.

14. WORK PLAN

Personnel:

- Investigators: as discussed previously, a principal investigator will be assigned at each of the participating centres: Hospital Universitari Dr. Josep Trueta de Girona and Hospital Sant Joan de Déu de Barcelona. They will constitute the Trial Steering Committee (TSC). TSC is responsible for trial overall supervision. Research associates (RA) will be selected at each centre.
- Collaborators: statistician (ST), pharmacist (PH), laboratory (LA), radiologist (RAD), ophthalmologist (OP), nurse staff (NU) and data manager (DA).

The trial has been designed in 5 phases:

PHASE 1 – Coordination phase. Development of theoretical framework (6 months): TSC and RA centre will be involved in this phase.

1. *PROTOCOL ELABORATION* (Accomplished): first objectives have been established in order to answer a formulated hypothesis. A comprehensive and exhaustive literature search have been conducted, followed by a detailed definition of study variables and study design. Theoretical methodology of data collection have been elaborated.
2. *ORGANISATIONAL MEETING* will be performed in order to further delineated the study chronogram and establish a timeline. Data collection circuits and communication systems between the involved centres will be set up.
3. *PILOT TEST* will be performed in order to evaluate the protocol. It will help to identification of problems and allow us to apply corrections in order to solve them.
4. *AUTHORISATIONS*: administrative and ethical authorisations will be obtained before any further activity.

PHASE 2 - Field research (54 months): All the study staff from each centre will be involved.

1. *RECRUITMENT PERIOD* (6 months): sample selection will be made in a non-consecutive way, based on inclusion and exclusion criteria. All preselection visits with their respective tests will be performed to help in the process. A member in charge of patient flow analysis evaluates the recruitment time in order to prove that the rate of inclusion of patients is being fulfilled. Guardians and subjects must have access to information documents regarding the study and informed consent must be signed before any further activity in the trial.
2. *GROUP ASSIGNMENT*: randomisation procedure, masking method and allocation type will be performed.
3. *INTERVENTION* (48 months): study variables will be recorded in a shared database by the involved centres. At each follow-up visit, all follow-up measurements will be taken and serum samples of the patients will be frozen. Critical parameters that can unmask the treatment arm will be assessed at the end of the trial.

PHASE 3 – Database processing and statistical analysis (4 months): TSC and RA from each centre along with DA will be involved.

1. *DATABASE PROCESSING* (4 months): results will be screened for possible errors during data collection.

PHASE 4 – Analysis of the results (4 months): TSC and RA from each centre along with ST will be involved.

1. *INTERIM ANALYSIS*: at the middle of the intervention process (at the end of 24 month), an interim analysis of the results by an external agent will be performed in order to ensure that there are not huge differences in benefits between interventional and control groups. However, we expect not to find significant differences because in growth studies two years is a short period of time in order to elicit significant results.

2. *STATISTICAL ANALYSIS* (2 months): appropriate statistical tests will be applied for all collected data. As previously described, descriptive and bivariate analyses will be performed followed by the multivariate analyses.
3. *INTERPRETATION OF THE RESULTS* (2 months): The outcomes of the trials will be interpreted and conclusions will be derived thereof, written and discussed. TSC will be involved.

PHASE 5 – Finalisation and publication of results (3 months): TSC will be involved.

A report with the final results of the study will be elaborated. Whether results support or not initial hypothesis will not affect their publication. Dissemination strategy consists on an open access online publication and study results presentation in Conferences from *Sociedad Española de Endocrinología Pediátrica* and European Society for Paediatric Endocrinology.

15. TIMELINE

| | Activity | Personnel | 2015 | | | 2016 | | | 2017 | | | 2018 | | | 2019 | | | 2020 | | | 2021 | | | | | |
|----------|------------------------|----------------|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|-----|------|-----|--|--|--|--|
| | | | N-D | G-M | A-J | J-S | O-D | G-M | A-J | J-S | O-D | G-M | A-J | J-S | O-D | G-M | A-J | J-S | O-D | G-M | A-J | J-S | | | | |
| 1 | Protocol Elaboration | TSC and RA | | | | | | | | | | | | | | | | | | | | | | | | |
| | Organisational Meeting | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Pilot Test | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Authorisations | | | | | | | | | | | | | | | | | | | | | | | | | |
| 2 | Recruitment Period | All | | | | | | | | | | | | | | | | | | | | | | | | |
| | Group Assignment | | | | | | | | | | | | | | | | | | | | | | | | | |
| 3 | Intervention | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Database Processing | TSC, RA and DA | | | | | | | | | | | | | | | | | | | | | | | | |
| 4 | Interim Analysis | TSC, RA, ST | | | | | | | | | | | | | | | | | | | | | | | | |
| | Statistical Analysis | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Interpretation | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Conclusions | | | | | | | | | | | | | | | | | | | | | | | | | |
| 5 | Final Trial Report | TSC | | | | | | | | | | | | | | | | | | | | | | | | |
| | Publications | | | | | | | | | | | | | | | | | | | | | | | | | |

16. BUDGET

Table 7. Budget

| 1. STAFF COSTS | | | | |
|--|-------------|--------------------|-----------------|--------------|
| | Cost | Nº persons | Time | Total |
| - Statistical consultant | 35 €/h | 1 | 100 h | 3500 € |
| - Data manager | 20 €/h | 1 | 80 h | 1600 € |
| - Meetings organisation | 50 €/h | 2 | 20 h | 2000 € |
| | | | | 7100 € |
| 2. IMPLEMENTATION COSTS | | | | |
| | Cost | Nº patients | Quantity | Total |
| <i>Inventory material costs</i> | | | | |
| - Saizen easypot device | 0 € | 120 | 1 | 0 € |
| <i>Services and disposable items costs</i> | | | | |
| - Laboratory parameters: | | | | |
| o Complete Blood Count (Serum) | 3,54 €/u | 120 | 9 | 3823,2 € |
| o IGF-I (Serum) | 0 € | 120 | 9 | 0 € |
| o IGFBP3 (Serum) | 0 € | 120 | 9 | 0 € |
| o Fasting glucose (Serum) | 1,27 €/u | 120 | 9 | 1371,6 € |
| o Fasting insulin (Serum) | 6,98 €/u | 120 | 9 | 7538,4 € |
| o HOMA-IR index | - | 120 | 9 | - |
| o HMW-adiponectin (Serum) | 850 €/80 u | 120 | 9 | 11475 € |
| o HbA1c (Serum) | 6,35 €/u | 120 | 9 | 6858 € |
| o Lipid profile (Serum) | 10,43 €/u | 120 | 9 | 11264,4 € |
| o C-reactive protein (Serum) | 6,59 €/u | 120 | 9 | 7117,2 € |
| o Creatinine (Serum) | 1,27 €/u | 120 | 9 | 1371,6 € |
| o ALT/AST (Serum) | 7,84 €/u | 120 | 9 | 8467,2 € |
| o B12 vitamin (Serum) | 6,98 €/u | 120 | 9 | 7538,4 € |
| o Albumin (Serum) | 2,23 €/u | 120 | 9 | 2408,4 € |
| o TSH (Serum) | 0 € | 120 | 9 | 0 € |
| o Free T4 (Serum) | 0 € | 120 | 9 | 0 € |
| o Prolactin (Serum) | 0 € | 120 | 9 | 0 € |
| o LH (Serum) | 0 € | 120 | 9 | 0 € |
| o FSH (Serum) | 0 € | 120 | 9 | 0 € |

| | | | | |
|---|------------|----------------|-----------------|-----------------|
| ○ Cortisol (Serum) | 0 € | 120 | 9 | 0 € |
| ○ Anti-transglutaminase antibodies (Serum) | 0 € | 120 | 1 | 0 € |
| - Left hand radiography | 0 € | 120 | 5 | 0 € |
| <i>Liability insurance</i> | - | 120 | 1 | 17000 € |
| <i>Drug purchase</i> | | | | |
| - Metformin 850 mg 50 pills/box | 1,52 €/box | 120 | 22 | 4012,8 € |
| - Placebo 50 pills/box | 7,35 €/box | 120 | 22 | 19404 € |
| - Basal rhGH treatment | 0 € | 120 | - | 0 € |
| <i>Administrative permits (AGEMED)</i> | 3948,1 € | 120 | - | 3948,1 € |
| <i>MRW couriers to ship serum samples to Hospital Dr. Josep Trueta (Girona)</i> | - | - | - | 500 € |
| | | | | 114098,3 € |
| 3. DISSEMINATION OF THE RESULTS | | | | |
| | | Cost | Quantity | Total |
| <i>Congress of the Spanish Society of Paediatric Endocrinology:</i> | | 800 €/pers. | 2 pers. | 1600 € |
| <i>Congress of the European Society of Paediatric Endocrinology:</i> | | 1000 €/pers. | 2 pers. | 2000 € |
| <i>Publication fees</i> | | | | |
| - Translation services | | 30 €/h | 50 h | 1500 € |
| - Open access | | 1500 € | - | 1500 € |
| <i>Software and bibliography</i> | | 1000 € | - | 1000 € |
| | | | | 7600 € |
| 4. SUBCONTRACTING OF PROFESSIONAL SERVICES | | | | |
| - Contracting of nursing services | | 20 €/ subject | 2 | 4800 € |
| - Contracting of echography services | | 25 € / subject | 2 | 6000 € |
| | | | | 10800 € |
| 5. INDIRECT COSTS | | | | |
| | | | | 27919,7 € |
| TOTAL COSTS | | | | 167518 € |

No budget will be needed for CEIC and the pharmacy department because the promoter of the study will be IDIBGI. IDIBGI research centre receives a 20% of the total expenses, in order to cover the account management services at the research institute and for the use of research offices, examination rooms and laboratory.

BUDGET SPECIFIC ASPECTS

- ***Implementation costs:***

All devices, laboratory parameters and radiography evaluated by protocol during the follow up of GH-deficient children due to its basal treatment with rhGH will be free cost for the trial because they are inherent to the basal condition of the patients and are therefore paid by the hospital. The measurements included are: IGF-I and IGFBP3 levels, TSH, free T4, prolactin, cortisol, LH, FSH and anti-transglutaminase antibodies. *Saizen easypot devices* will be provided by the company with free cost.

MRW courier will ship serum samples to Hospital Josep Trueta when the study concludes in order to be analysed by the same laboratory.

- ***Subcontracting of personal services:***

Two nurses will be hired during the trial in order to help main investigators to perform follow up measurements. A radiologist at each centre will perform carotid echography to determine CIMT after previous consensus criteria agreed upon in organisation meetings. However, images all will be sent to Hospital Josep Trueta to be read by one single radiologist.

17. HEALTH IMPACT OF THE PROJECT

As discussed previously, not all GH-deficient children treated with rhGH achieve a full improvement in adult height prognosis that may allow them reach their target height. Metformin studies in non GH-deficient children have shown an improvement in height gain and adult height. The objective of this study is determine if metformin in GH-deficient children has also these effects on height and may help those children with poor adult height prognosis to reach an adequate adult height. By reaching this goal, we would not only establish a new therapeutic option for these children but will also avoid all the psychological consequences that can affect important aspects of their lives, which could mean a major health impact on these subjects.

Furthermore, we will also analyse metabolic parameters and insulin resistance improvements during the interventional period as a secondary objective. These results will set the basis for further studies in order to establish if the addition of metformin in GH-children not only improves growth but also decreases the cardiovascular risk in long-term.

18. BIBLIOGRAPHY

1. Pombo M, Rodríguez PC. El niño de talla baja. *Protoc diag ter pediatr* [Internet]. 2011 [cited 2015 Nov 13];1:236–54. Available from: http://www.aeped.es/sites/default/files/documentos/20_el_nino_de_talla_baja.pdf
2. Criteris d'indicació i seguiment del tractament amb hormona del creixement de la Circular 1/2002, per la qual s'estableix el procediment de tramitació de les sol·licituds de tractament farmacològic. Modificació de l'Annex III. [Internet]. Barcelona: Generalitat de Catalunya Departament de Salut Direcció General de Salut Pública; 1966 [cited 2015 Nov 13]. Available from: http://canalsalut.gencat.cat/web/.content/home_canal_salut/professionals/participacio/grups_de_treball/consells_assessors_sobre_lus_racional_dels_medicaments/consell_aseessor_sobre_utilitzacio_lhormona_creixement_i_substancies/documents/arxiu/ins truc1-201
3. Binay C, Simsek E, Yıldırım A, Kosger P, Demiral M, Kılıç Z. Growth hormone and the risk of atherosclerosis in growth hormone-deficient children. *Growth Horm IGF Res* [Internet]. 2015 Dec 12 [cited 2015 Dec 1];25(6):294–7. Available from: <http://www.growthhormoneigfresearch.com/article/S1096637415300253/fulltext>
4. Parks JS, Felner EI. Sistema endocrino. In: Kliegman RM, Stanton BF, St. Geme JW, Schor NF, Behrman RE, editors. *Nelson Tratado de Pediatría*. 19th ed. Barcelona: Elsevier España; 2013. p. 1948–53.
5. Reh CS, Geffner ME. Somatotropin in the treatment of growth hormone deficiency and Turner syndrome in pediatric patients: a review. *Clin Pharmacol* [Internet]. 2010 Jan [cited 2016 Jan 17];2:111–22. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3262362/pdf/cpaa-2-111.pdf>
6. Ficha técnica Genotonorm [Internet]. Madrid: Agencia Española del Medicamento y Productos Sanitarios; 2014 [cited 2015 Dec 23]. Available from: http://www.aemps.gob.es/cima/pdfs/es/ft/61815/FT_61815.pdf
7. FDA Drug Safety Communication: Ongoing safety review of Recombinant Human Growth Hormone (somatotropin) and possible increased risk of death [Internet]. Rockville: Food and Drug Administration; 2010 [cited 2015 Dec 28]. Available from: <http://www.fda.gov/Drugs/DrugSafety/ucm237773.htm>
8. Sas TCJ, de Ridder MAJ, Wit JM, Rotteveel J, Oostdijk W, Reeser HM, et al. Adult height in children with growth hormone deficiency: a randomized, controlled, growth hormone dose-response trial. *Horm Res pædiatrics* [Internet]. 2010 [cited 2015 Dec 28];74(3):172–81. Available from: <http://www.karger.com/Article/FullText/281323>
9. Rogol AD, Cohen P, Weng W, Kappelgaard A-M, Germak JA. Prepubertal children with growth hormone deficiency treated for four years with growth hormone experience dose-dependent increase in height, but not in the rate of puberty initiation. *Horm Res pædiatrics* [Internet]. 2013 Jan 29 [cited 2015 Dec 23];80(1):28–37. Available from: <http://www.karger.com/Article/FullText/353429>

10. Ranke MB, Lindberg A. Observed and predicted total pubertal growth during treatment with growth hormone in adolescents with idiopathic growth hormone deficiency, Turner syndrome, short stature, born small for gestational age and idiopathic short stature: KIGS analysis and rev. *Horm Res pædiatrics* [Internet]. 2011 [cited 2015 Dec 21];75(6):423–32. Available from: <http://www.karger.com/Article/FullText/324117>
11. Collett-Solberg PF. Update in growth hormone therapy of children. *J Clin Endocrinol Metab* [Internet]. 2011 [cited 2015 Dec 28];96(3):573–9. Available from: http://press.endocrine.org/doi/10.1210/jc.2010-1131?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed
12. Lebl J, Lebenthal Y, Kolouskova S, Steensberg A, Jøns K, Kappelgaard A-M, et al. Metabolic impact of growth hormone treatment in short children born small for gestational age. *Horm Res pædiatrics* [Internet]. 2011 [cited 2015 Dec 1];76(4):254–61. Available from: <http://www.karger.com/Article/FullText/329729>
13. Even L, Andersson B, Kriström B, Albertsson-Wikland K, Hochberg Z. Role of growth hormone in enchondroplasia and chondral osteogenesis: evaluation by X-ray of the hand. *Pediatr Res* [Internet]. 2014 [cited 2015 Dec 14];76(1):109–14. Available from: <http://dx.doi.org/10.1038/pr.2014.56>
14. Klein KO, Newfield RS, Hassink SG. Bone maturation along the spectrum from normal weight to obesity: a complex interplay of sex, growth factors and weight gain. *J Pediatr Endocrinol Metab* [Internet]. 2015 Nov 13 [cited 2016 Jan 13]; Available from: <http://www.degruyter.com/view/j/jpem.ahead-of-print/jpem-2015-0234/jpem-2015-0234.xml>
15. Shim KS. Pubertal growth and epiphyseal fusion. *Ann Pediatr Endocrinol Metab* [Internet]. 2015 Mar [cited 2015 Dec 8];20(1):8–12. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4397276/pdf/apem-20-8.pdf>
16. Xu L, Wang Q, Wang Q, Lyytikäinen A, Mikkola T, Völgyi E, et al. Concerted actions of insulin-like growth factor 1, testosterone, and estradiol on peripubertal bone growth: a 7-year longitudinal study. *J Bone Miner Res* [Internet]. 2011 Sep [cited 2016 Jan 17];26(9):2204–11. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21590732>
17. Edén Engström B, Burman P, Holdstock C, Karlsson FA. Effects of growth hormone (GH) on ghrelin, leptin, and adiponectin in GH-deficient patients. *J Clin Endocrinol Metab* [Internet]. 2003 Nov 2 [cited 2015 Nov 9];88(11):5193–8. Available from: http://press.endocrine.org/doi/10.1210/jc.2003-030713?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed
18. Ibáñez L, Fucci A, Valls C, Ong K, Dunger D, de Zegher F. Neutrophil count in small-for-gestational age children: contrasting effects of metformin and growth hormone therapy. *J Clin Endocrinol Metab* [Internet]. 2005 Jun 2 [cited 2016 Jan 17];90(6):3435–9. Available from: http://press.endocrine.org/doi/10.1210/jc.2005-0049?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed
19. Darendeliler F, Karagiannis G, Wilton P. Headache, idiopathic intracranial hypertension and slipped capital femoral epiphysis during growth hormone treatment: a safety update from the KIGS database. *Horm Res* [Internet]. 2007 [cited 2015 Dec 23];68(Suppl. 5):41–7. Available from: <http://www.karger.com/Article/FullText/110474>

20. Ficha técnica Dianben 850 mg [Internet]. Madrid: Agencia Española del Medicamento y Productos Sanitarios; 2010 [cited 2015 Nov 17].
Available from: http://www.aemps.gob.es/cima/pdfs//ft/55211/FT_55211.pdf
21. Gómez-Díaz RA, Talavera JO, Pool EC, Ortiz-Navarrete FV, Solórzano-Santos F, Mondragón-González R, et al. Metformin decreases plasma resistin concentrations in pediatric patients with impaired glucose tolerance: a placebo-controlled randomized clinical trial. *Metabolism* [Internet]. 2012 [cited 2015 Dec 2];61(9):1247–55. Available from: <http://www.metabolismjournal.com/article/S0026049512000728/fulltext>
22. Ibáñez L, Valls C, Ong K, Dunger DB, de Zegher F. Metformin therapy during puberty delays menarche, prolongs pubertal growth, and augments adult height: a randomized study in low-birth-weight girls with early-normal onset of puberty. *J Clin Endocrinol Metab* [Internet]. 2006 Jun 2 [cited 2015 Nov 11];91(6):2068–73.
Available from: <http://press.endocrine.org/doi/pdf/10.1210/jc.2005-2329>
23. Ibáñez L, Lopez-Bermejo A, Diaz M, Marcos MV, de Zegher F. Early metformin therapy to delay menarche and augment height in girls with precocious pubarche. *Fertil Steril* [Internet]. 2011 Feb [cited 2015 Nov 9];95(2):727–30. Available from: <http://www.sciencedirect.com/science/article/pii/S0015028210024660>
24. Ibáñez L, López-Bermejo A, Díaz M, Marcos MV, de Zegher F. Metformin Treatment for Four Years to Reduce Total and Visceral Fat in Low Birth Weight Girls with Precocious Pubarche. *J Clin Endocrinol Metab* [Internet]. 2008 May 2 [cited 2015 Nov 19];93(5):1841–5.
Available from: <http://press.endocrine.org/doi/pdf/10.1210/jc.2008-0013>
25. Luong DQ, Oster R, Ashraf AP. Metformin treatment improves weight and dyslipidemia in children with metabolic syndrome. *J Pediatr Endocrinol Metab* [Internet]. 2015 [cited 2015 Nov 18];28(5-6):649–55. Available from:
<http://www.degruyter.com/view/j/jpem.2015.28.issue-5-6/jpem-2014-0201/jpem-2014-0201.xml>
26. Rice S, Pellatt L, Ramanathan K, Whitehead SA, Mason HD. Metformin inhibits aromatase via an extracellular signal-regulated kinase-mediated pathway. *Endocrinology* [Internet]. 2009 Oct 1 [cited 2015 Nov 9];150(10):4794–801.
Available from: <http://press.endocrine.org/doi/pdf/10.1210/en.2009-0540>
27. Vrbikova J, Hill M, Starka L, Cibula D, Bendlova B, Vondra K, et al. The effects of long-term metformin treatment on adrenal and ovarian steroidogenesis in women with polycystic ovary syndrome. *Eur J Endocrinol* [Internet]. 2001 Jun 1 [cited 2015 Nov 11];144(6):619–28. Available from: <http://www.eje-online.org/content/144/6/619>
28. Zhou Y, Xu J-N, Zeng C, Li X, Zhou Y-F, Qi Y, et al. Metformin Suppresses Prostaglandin E2-Induced Cytochrome P450 Aromatase Gene Expression and Activity via Stimulation of AMP-Activated Protein Kinase in Human Endometriotic Stromal Cells. *Reprod Sci* [Internet]. 2015 Sep [cited 2015 Nov 11];22(9):1162–70.
Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26058395>

29. Kuzik N, Myette-Côté É, Carson V, Slater L, Boulé NG. Evaluating the Effects of Metformin Use on Height in Children and Adolescents. *JAMA Pediatr* [Internet]. 2015 [cited 2015 Nov 19];169(11):1. Available from: <http://archpedi.jamanetwork.com/article.aspx?articleid=2446192>
30. FDA Drug Safety Communication: Safety review update of Recombinant Human Growth Hormone (somatropin) and possible increased risk of death [Internet]. Rockville: Food and Drug Administration; 2011 [cited 2015 Dec 30]. Available from: <http://www.fda.gov/Drugs/DrugSafety/ucm265865.htm>
31. Herrmann BL, Berg C, Vogel E, Nowak T, Renzing-Koehler K, Mann K, et al. Effects of a combination of recombinant human growth hormone with metformin on glucose metabolism and body composition in patients with metabolic syndrome. *Horm Metab Res* [Internet]. 2004 [cited 2015 Nov 9];36:54–61. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/14983408>
32. Herrmann BL, Saller B, Stratmann M, Berg C, Mann K, Janssen OE. Effects of a combination of rhGH and metformin on adiponectin levels in patients with metabolic syndrome. *Horm Metab Res* [Internet]. 2005 Jan 28 [cited 2016 Jan 17];37(1):49–52. Available from: <https://www.thieme-connect.com/DOI/DOI?10.1055/s-2005-861036>
33. Greulich W, Pyle S. *Radiographic Atlas of Skeletal Development of the Hand and Wrist*. 2nd ed. California: Stanford University Press; 1959.
34. Wasniewska M, Arrigo T, Cisternino M, De Luca F, Ghizzoni L, Maghnie M, et al. Birth weight influences long-term catch-up growth and height prognosis of GH-deficient children treated before the age of 2 years. *Eur J Endocrinol* [Internet]. [cited 2015 Dec 21];142:460–5. Available from: <http://www.eje-online.org/content/142/5/460.long>
35. Lee HS, Shim YS, Jeong HR, Kwon EB, Hwang JS. The Association between Bone Age Advancement and Insulin Resistance in Prepubertal Obese Children. *Exp Clin Endocrinol Diabetes* [Internet]. 2015 Nov [cited 2016 Jan 14];123(10):604–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26600056>
36. Bayley N, Pinneau SR. Tables for predicting adult height from skeletal age: Revised for use with the greulich-pyle hand standards. *J Pediatr* [Internet]. 1952 [cited 2016 Jan 13];40(4):423–41. Available from: <http://www.sciencedirect.com/science/article/pii/S0022347652802057>
37. Carrascosa A, Fernández JM, Ferrández Á. *Estudios Españoles de Crecimiento 2010* [Internet]. Madrid: Asociación Española de Pediatría; 2010. Available from: http://www.aeped.es/sites/default/files/eecweb14_09_10.pdf

19. ANNEX

ANNEX 1 – HEIGHT CHARTS

ANNEX 2 – BMI CHARTS

ANNEX 3 – EXAMPLE OF RANDOMISATION

ANNEX 4 – INFORMATION FOR PATIENT AND INFORMED CONSENT

ANNEX 5 – CASE REPORT FORM

ANNEX 6 – SIDE-EFFECTS REPORT FORM

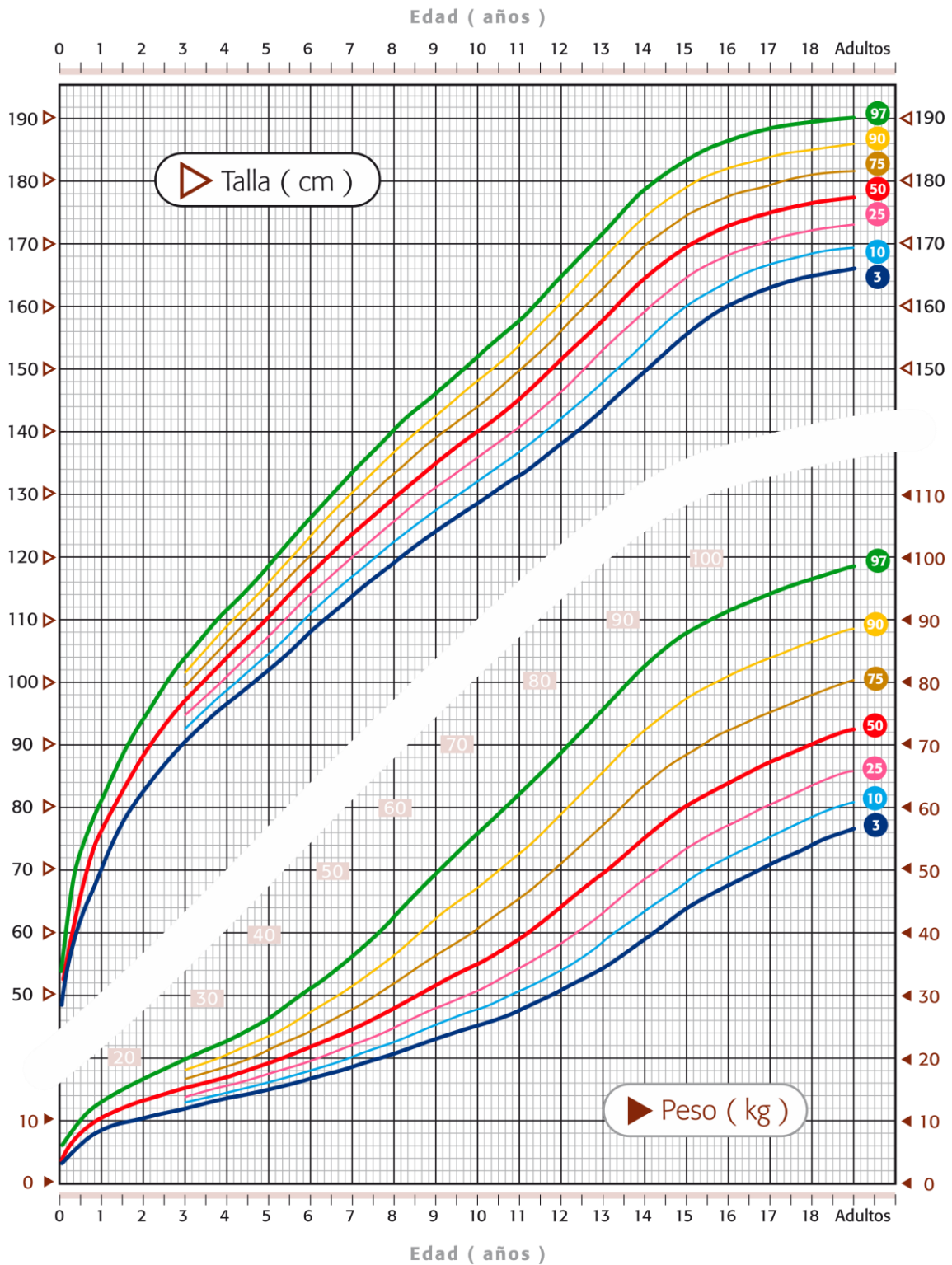
ANNEX 7 – METFORMIN DATASHEET

ANNEX 8 – HELSINKI DECLARATION

ANNEX 1: HEIGHT CHARTS

Estudio Transversal Español de Crecimiento 2010

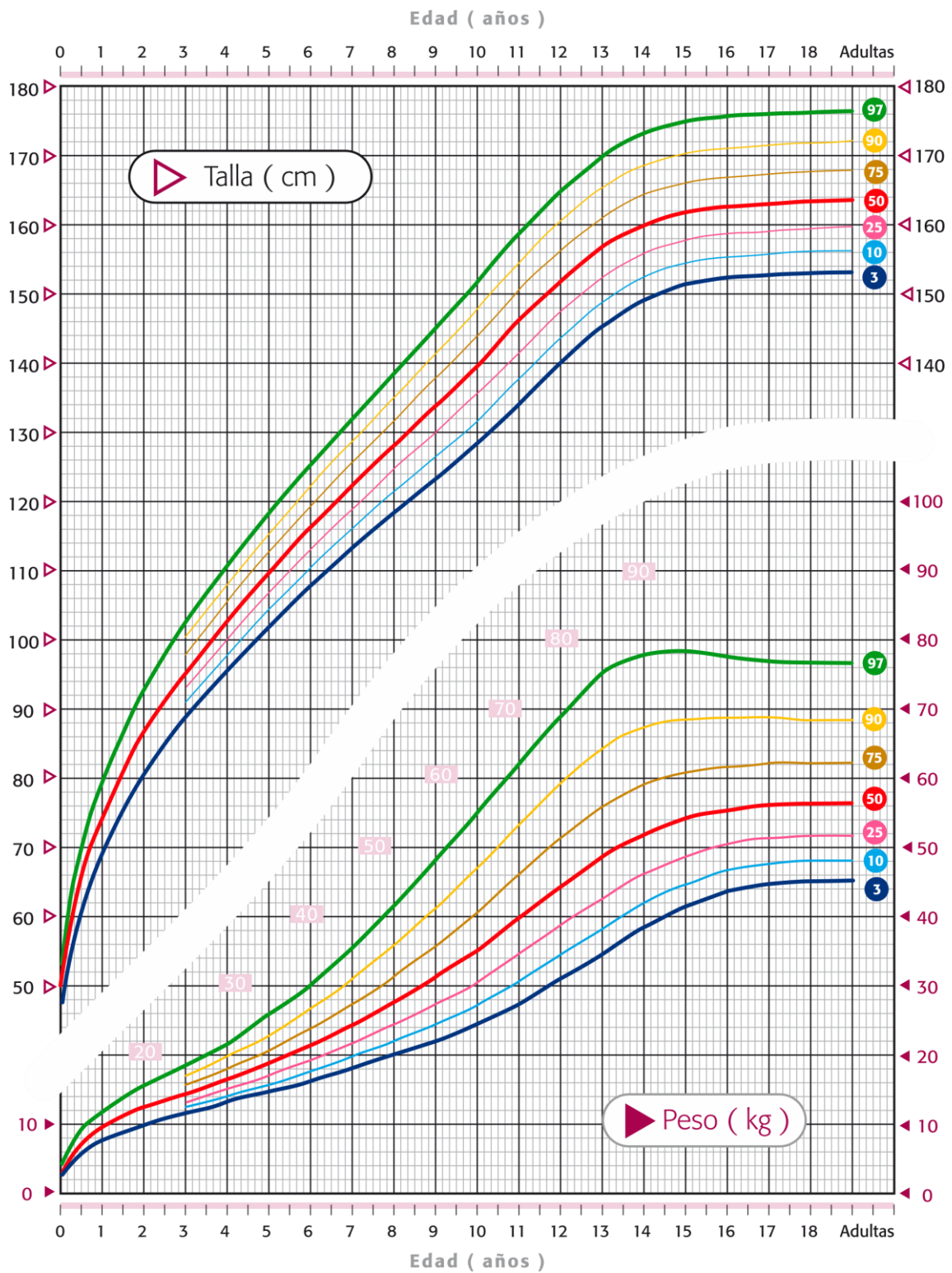
VARONES 



Carrascosa A, Fernández JM, Fernández C, Ferrández A, López D, López-Siguero JP, Sánchez E, Sobradillo B, Yeste D. y Grupo Colaborador Español
 An Pediatr (Barc) 2008;68:552-69. An Pediatr (Barc) 2010; en prensa.

Estudio Transversal Español de Crecimiento 2010

MUJERES



Carrascosa A, Fernández JM, Fernández C, Ferrández A, López D, López-Siguero JP, Sánchez E, Sobradillo B, Yeste D. y Grupo Colaborador Español. *An Pediatr (Barc)* 2008;68:552-69. *An Pediatr (Barc)* 2010; en prensa.

Talla (cm) de cada uno de los cinco grupos maduradores puberales. (M ± DE)

VARONES 

| Edad (años) | Muy temprano N = 25 | Temprano n = 59 | Intermedio n = 106 | Tardío n = 52 | Muy tardío n = 17 | Toda la muestra n = 259 |
|-----------------|------------------------|--------------------|-----------------------|--------------------|----------------------|----------------------------|
| 0 | 50,5 ± 1,4 | 50,7 ± 1,5 | 50,6 ± 1,2 | 50,5 ± 1,5 | 50,3 ± 1,1 | 50,5 ± 1,4 |
| 1 | 76,6 ± 2,1 | 76,1 ± 2,4 | 75,7 ± 2,5 | 75,6 ± 2,5 | 75,7 ± 2,4 | 75,9 ± 2,4 |
| 2 | 88,8 ± 2,7 | 88,2 ± 2,8 | 87,8 ± 3,2 | 87,4 ± 2,8 | 87,5 ± 2,6 | 87,9 ± 3,0 |
| 3 | 98,0 ± 2,8 | 97,2 ± 3,0 | 96,5 ± 3,6 | 95,8 ± 3,2 | 96,0 ± 3,5 | 96,6 ± 3,4 |
| 4 | 105,6 ± 3,0 | 104,5 ± 3,5 | 103,8 ± 4,0 | 103,0 ± 3,5 | 103,5 ± 3,7 | 103,9 ± 3,7 |
| 5 | 112,6 ± 3,6 | 111,4 ± 3,8 | 110,6 ± 4,4 | 109,8 ± 3,8 | 110,2 ± 4,2 | 110,8 ± 4,1 |
| 6 | 119,3 ± 4,2 | 118,2 ± 4,3 | 117,0 ± 4,6 | 116,2 ± 4,0 | 116,5 ± 4,6 | 117,3 ± 4,5 |
| 7 | 125,6 ± 4,6 | 124,4 ± 4,4 | 123,1 ± 5,3 | 122,2 ± 4,2 | 122,6 ± 4,8 | 123,4 ± 4,7 |
| 8 | 131,8 ± 4,8 | 130,4 ± 4,7 | 128,8 ± 5,4 | 128,0 ± 4,2 | 128,3 ± 5,0 | 129,2 ± 5,1 |
| 9 | 137,5 ± 5,0 | 136,0 ± 4,9 | 134,3 ± 5,5 | 133,5 ± 4,4 | 133,5 ± 5,6 | 134,8 ± 5,2 |
| 10 ^a | 142,5 ± 5,2 | 141,5 ± 4,9 | 139,6 ± 5,8 | 138,6 ± 4,4 | 138,6 ± 5,7 | 140,0 ± 5,4 |
| 11 ^b | 149,3 ± 5,6 | 146,1 ± 5,1 | 144,7 ± 6,1 | 143,7 ± 4,6 | 143,3 ± 6,2 | 145,2 ± 5,7 |
| 12 ^c | 158,5 ± 6,0 | 152,6 ± 5,3 | 149,0 ± 6,3 | 148,4 ± 4,8 | 147,8 ± 6,3 | 150,5 ± 6,5 |
| 13 ^d | 166,0 ± 5,7 | 161,6 ± 5,7 | 155,5 ± 6,7 | 152,5 ± 4,9 | 152,2 ± 6,7 | 157,1 ± 7,4 |
| 14 ^e | 171,5 ± 5,6 | 169,1 ± 5,2 | 164,3 ± 7,2 | 159,1 ± 4,9 | 156,2 ± 7,0 | 164,5 ± 7,6 |
| 15 ^f | 174,3 ± 5,3 | 173,4 ± 5,3 | 170,9 ± 6,8 | 167,0 ± 4,9 | 163,0 ± 7,3 | 170,5 ± 6,8 |
| 16 ^g | 175,8 ± 5,3 | 175,8 ± 5,6 | 174,2 ± 6,6 | 172,5 ± 5,0 | 170,2 ± 7,2 | 174,1 ± 6,2 |
| 17 ^h | 176,6 ± 5,2 | 176,9 ± 5,8 | 176,0 ± 6,6 | 175,0 ± 5,5 | 174,9 ± 6,6 | 176,0 ± 6,1 |
| 18 ⁱ | 176,9 ± 5,1 | 177,4 ± 5,9 | 176,7 ± 6,5 | 176,1 ± 5,7 | 177,3 ± 7,0 | 176,8 ± 6,1 |
| 19 ^j | 176,9 ± 5,1 | 177,6 ± 5,9 | 176,8 ± 6,9 | 176,4 ± 5,9 | 177,4 ± 7,3 | 177,0 ± 6,3 |

En **negrita**: talla y edad al inicio del brote de crecimiento puberal.

- a: NS
b: p<0.001 muy temprano vs intermedio, tardío y muy tardío.
c: p<0.0001 muy temprano vs cada uno de los otros grupos; p=0.002 temprano vs intermedio.
d: p<0.0001 muy temprano vs cada uno de los otros grupos; temprano vs intermedio, tardío y muy tardío.
e: p<0.0001 muy temprano y temprano vs intermedio, tardío y muy tardío; intermedio vs tardío y muy tardío.
f: p<0.0001 muy temprano y temprano vs tardío y muy tardío; p<0.002 intermedio vs tardío y muy tardío.
g: p=0.002 temprano vs muy tardío.
h, i, j: NS

Talla (cm) de cada uno de los cinco grupos maduradores puberales. (M ± DE)

MUJERES 

| Edad (años) | Muy temprano N = 27 | Temprano n = 75 | Intermedio n = 101 | Tardío n = 59 | Muy tardío n = 19 | Toda la muestra n = 281 |
|-----------------|------------------------|--------------------|-----------------------|--------------------|----------------------|----------------------------|
| 0 | 50,0 ± 1,6 | 49,7 ± 1,1 | 50,0 ± 1,4 | 49,9 ± 1,4 | 50,3 ± 1,4 | 50,0 ± 1,3 |
| 1 | 74,8 ± 2,2 | 74,3 ± 2,4 | 73,8 ± 2,3 | 73,7 ± 2,1 | 74,2 ± 1,9 | 74,0 ± 2,3 |
| 2 | 87,0 ± 2,0 | 86,5 ± 2,4 | 85,9 ± 3,0 | 85,7 ± 2,6 | 86,1 ± 3,7 | 86,1 ± 2,7 |
| 3 | 96,0 ± 2,2 | 95,5 ± 2,9 | 95,0 ± 3,6 | 94,3 ± 2,9 | 94,1 ± 3,6 | 95,0 ± 3,2 |
| 4 | 103,5 ± 2,5 | 103,3 ± 3,5 | 102,5 ± 4,1 | 101,8 ± 3,2 | 101,5 ± 3,6 | 102,6 ± 3,6 |
| 5 | 110,6 ± 2,9 | 110,3 ± 3,9 | 109,3 ± 4,5 | 108,5 ± 3,5 | 108,3 ± 4,2 | 109,5 ± 4,0 |
| 6 | 117,6 ± 3,2 | 116,9 ± 4,0 | 115,7 ± 4,9 | 114,9 ± 3,8 | 114,6 ± 4,5 | 115,9 ± 4,3 |
| 7 | 123,8 ± 3,5 | 123,1 ± 4,4 | 121,6 ± 5,1 | 120,7 ± 4,0 | 120,5 ± 4,7 | 122,0 ± 4,6 |
| 8 ^a | 128,8 ± 3,8 | 129,1 ± 4,6 | 127,3 ± 5,3 | 126,2 ± 4,1 | 126,3 ± 4,8 | 127,6 ± 4,8 |
| 9 ^b | 135,5 ± 4,1 | 134,0 ± 4,8 | 132,7 ± 5,5 | 131,1 ± 4,3 | 131,9 ± 4,8 | 133,1 ± 5,0 |
| 10 ^c | 143,6 ± 5,4 | 140,6 ± 5,1 | 137,4 ± 5,8 | 136,8 ± 4,3 | 137,2 ± 5,1 | 138,7 ± 5,6 |
| 11 ^d | 150,8 ± 5,2 | 148,4 ± 5,8 | 143,9 ± 6,1 | 141,2 ± 4,4 | 142,0 ± 5,5 | 145,1 ± 6,4 |
| 12 ^e | 156,3 ± 4,7 | 154,7 ± 5,6 | 151,5 ± 6,3 | 147,5 ± 4,6 | 146,2 ± 5,8 | 151,6 ± 6,4 |
| 13 ^f | 159,5 ± 4,2 | 158,9 ± 5,3 | 157,1 ± 6,1 | 154,4 ± 4,8 | 152,0 ± 6,1 | 156,9 ± 5,9 |
| 14 ^g | 161,0 ± 4,0 | 161,0 ± 5,2 | 160,4 ± 5,7 | 158,7 ± 4,5 | 158,4 ± 6,3 | 160,1 ± 5,3 |
| 15 ^h | 161,8 ± 3,9 | 161,9 ± 5,3 | 161,9 ± 5,7 | 160,9 ± 4,8 | 162,3 ± 5,7 | 161,7 ± 5,2 |
| 16 ⁱ | 162,2 ± 3,8 | 162,4 ± 5,2 | 162,7 ± 5,7 | 162,3 ± 5,0 | 164,1 ± 5,5 | 162,5 ± 5,3 |
| 17 ^j | 162,4 ± 3,8 | 162,6 ± 5,2 | 163,0 ± 5,8 | 162,4 ± 5,0 | 165,1 ± 5,8 | 162,9 ± 5,3 |
| 18 ^j | 162,6 ± 3,8 | 162,7 ± 5,1 | 163,2 ± 5,8 | 162,7 ± 5,0 | 165,4 ± 5,8 | 163,0 ± 5,3 |

En negrita: altura y edad al inicio del brote de crecimiento puberal.

a: p=0,002 temprano vs tardío.

b: p=0,002 muy temprano vs tardío y muy tardío.

c: p<0,0001 muy temprano vs intermedio, tardío y muy tardío; p<0,0005 temprano vs intermedio y tardío.

d: p<0,0001 muy temprano y temprano vs cada uno de los otros grupos.

e: p<0,0001 muy temprano vs intermedio, tardío y muy tardío; temprano vs tardío, muy tardío y intermedio vs tardío y muy tardío; p=0,004 temprano vs intermedio.

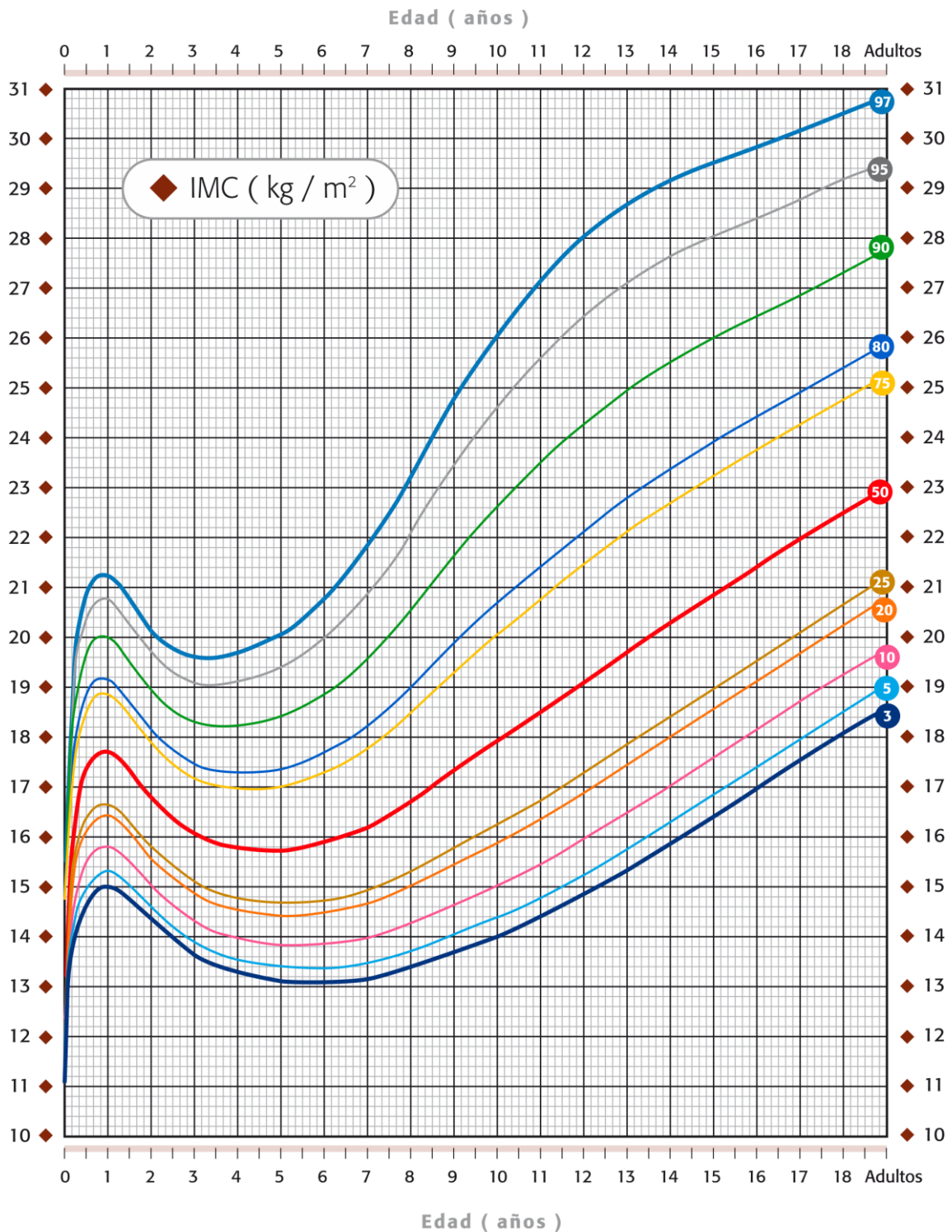
f: p<0,0004 muy temprano vs tardío y muy tardío; p<0,0001 temprano vs tardío y muy tardío,

g: intermedio vs muy tardío; p=0,003 intermedio vs tardío.

h, i, j: NS

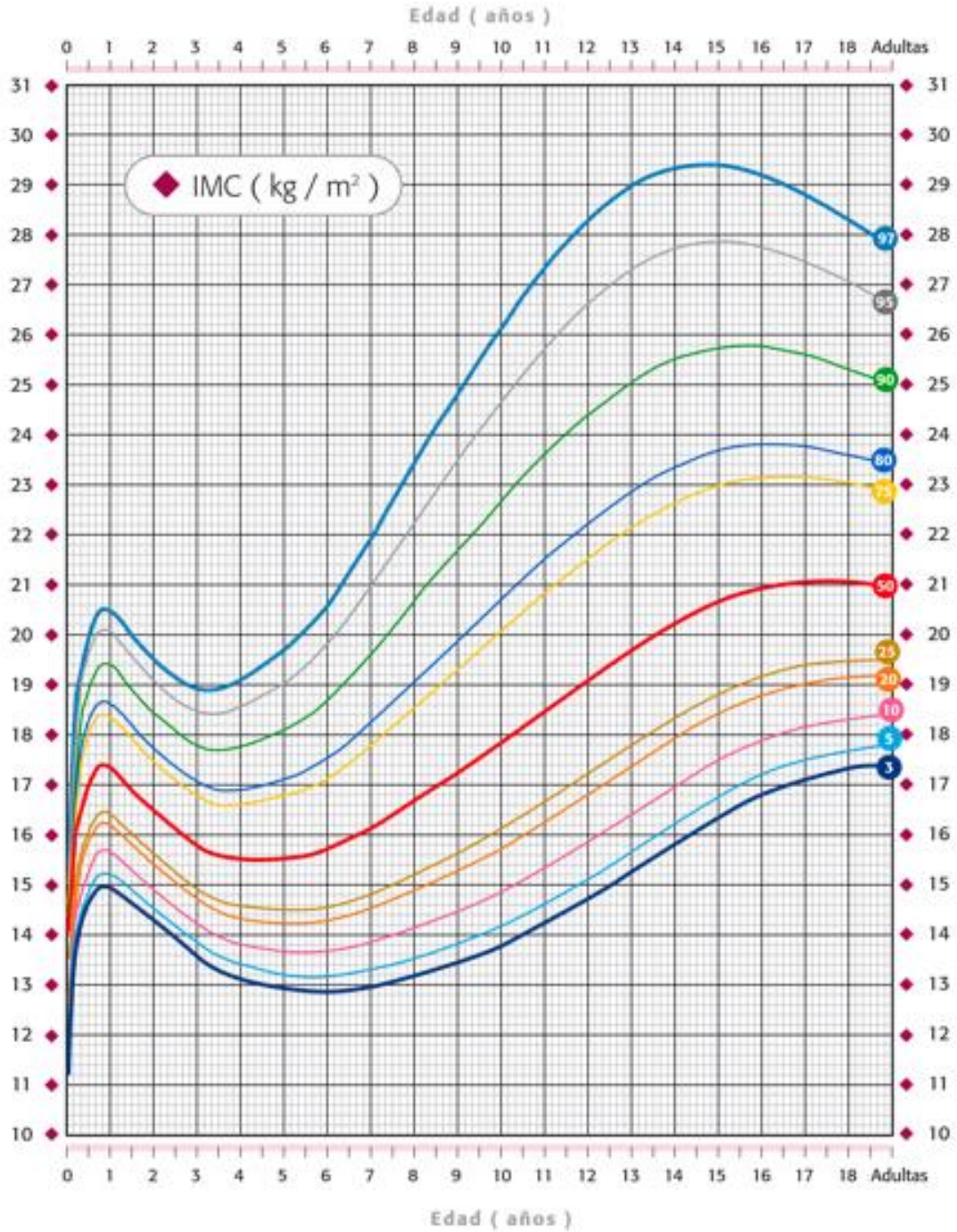
ANNEX 2: BMI TABLES

VARONES



Carrascosa A., Fernández JM., Fernández C., Ferrández A., López D., López-Siguero JP., Sánchez E., Sobradillo B., Yeste D. y Grupo Colaborador Español
An Pediatr (Barc) 2008;68:552-69. *An Pediatr (Barc)* 2010; en prensa.

MUJERES



Carrascosa A, Fernández JM, Fernández C, Ferrández A, López D, López-Siguero JP, Sánchez E, Sobradillo B, Yeste D. y Grupo Colaborador Español
An Pediatr (Barc) 2008;68:552-69. An Pediatr (Barc) 2010; en prensa.

ANNEX 3: EXAMPLE OF RANDOMISATION

Table Example of the randomisation process.

| PATIENT | GENDER | AGE | BMI | TREATMENT |
|----------------|---------------|------------------|-------------------------|------------------|
| 10001 | Male | ≥8 and < 9 years | ≥-1.5 SDS and ≤0 SDS | ? |
| 10002 | Male | ≥8 and < 9 years | ≥-1.5 SDS and ≤0 SDS | ? |
| 10003 | Male | ≥8 and < 9 years | ≥-1.5 SDS and ≤0 SDS | ? |
| 10004 | Male | ≥8 and < 9 years | ≥-1.5 SDS and ≤0 SDS | ? |
| 10005 | Male | ≥8 and < 9 years | ≥-1.5 SDS and ≤0 SDS | ? |
| 10006 | Male | ≥8 and < 9 years | ≥-1.5 SDS and ≤0 SDS | ? |
| 10007 | Male | ≥8 and < 9 years | ≥-1.5 SDS and ≤0 SDS | ? |
| 10008 | Male | ≥8 and < 9 years | ≥-1.5 SDS and ≤0 SDS | ? |
| 10009 | Male | ≥8 and < 9 years | ≥-1.5 SDS and ≤0 SDS | ? |
| 10010 | Male | ≥8 and < 9 years | ≥-1.5 SDS and ≤0 SDS | ? |
| <hr/> | | | | |
| 20001 | Male | ≥8 and < 9 years | >0 SDS and ≤+1.5 SDS | ? |
| 20002 | Male | ≥8 and < 9 years | >0 SDS and ≤+1.5 SDS | ? |
| 20003 | Male | ≥8 and < 9 years | >0 SDS and ≤+1.5 SDS | ? |
| 20004 | Male | ≥8 and < 9 years | >0 SDS and ≤+1.5 SDS | ? |
| 20005 | Male | ≥8 and < 9 years | >0 SDS and ≤+1.5 SDS | ? |
| 20006 | Male | ≥8 and < 9 years | >0 SDS and ≤+1.5 SDS | ? |
| 20007 | Male | ≥8 and < 9 years | >0 SDS and ≤+1.5 SDS | ? |
| 20008 | Male | ≥8 and < 9 years | >0 SDS and ≤+1.5 SDS | ? |
| 20009 | Male | ≥8 and < 9 years | >0 SDS and ≤+1.5 SDS | ? |
| 20010 | Male | ≥8 and < 9 years | >0 SDS and ≤+1.5 SDS | ? |
| <hr/> | | | | |
| 30001 | Male | ≥8 and < 9 years | >+1.5 SDS and ≤+3.00 SD | ? |
| 30002 | Male | ≥8 and < 9 years | >+1.5 SDS and ≤+3.00 SD | ? |
| 30003 | Male | ≥8 and < 9 years | >+1.5 SDS and ≤+3.00 SD | ? |
| 30004 | Male | ≥8 and < 9 years | >+1.5 SDS and ≤+3.00 SD | ? |
| 30005 | Male | ≥8 and < 9 years | >+1.5 SDS and ≤+3.00 SD | ? |
| 30006 | Male | ≥8 and < 9 years | >+1.5 SDS and ≤+3.00 SD | ? |
| 30007 | Male | ≥8 and < 9 years | >+1.5 SDS and ≤+3.00 SD | ? |
| 30008 | Male | ≥8 and < 9 years | >+1.5 SDS and ≤+3.00 SD | ? |
| 30009 | Male | ≥8 and < 9 years | >+1.5 SDS and ≤+3.00 SD | ? |
| 30010 | Male | ≥8 and < 9 years | >+1.5 SDS and ≤+3.00 SD | ? |

| | | | | |
|-------|--------|------------------------------|----------------------------------|---|
| 40001 | Male | ≥ 9 and ≤ 10 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 40002 | Male | ≥ 9 and ≤ 10 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 40003 | Male | ≥ 9 and ≤ 10 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 40004 | Male | ≥ 9 and ≤ 10 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 40005 | Male | ≥ 9 and ≤ 10 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 40006 | Male | ≥ 9 and ≤ 10 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 40007 | Male | ≥ 9 and ≤ 10 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 40008 | Male | ≥ 9 and ≤ 10 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 40009 | Male | ≥ 9 and ≤ 10 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 40010 | Male | ≥ 9 and ≤ 10 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 50001 | Male | ≥ 9 and ≤ 10 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 50002 | Male | ≥ 9 and ≤ 10 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 50003 | Male | ≥ 9 and ≤ 10 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 50004 | Male | ≥ 9 and ≤ 10 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 50005 | Male | ≥ 9 and ≤ 10 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 50006 | Male | ≥ 9 and ≤ 10 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 50007 | Male | ≥ 9 and ≤ 10 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 50008 | Male | ≥ 9 and ≤ 10 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 50009 | Male | ≥ 9 and ≤ 10 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 50010 | Male | ≥ 9 and ≤ 10 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 60001 | Male | ≥ 9 and ≤ 10 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 60002 | Male | ≥ 9 and ≤ 10 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 60003 | Male | ≥ 9 and ≤ 10 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 60004 | Male | ≥ 9 and ≤ 10 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 60005 | Male | ≥ 9 and ≤ 10 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 60006 | Male | ≥ 9 and ≤ 10 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 60007 | Male | ≥ 9 and ≤ 10 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 60008 | Male | ≥ 9 and ≤ 10 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 60009 | Male | ≥ 9 and ≤ 10 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 60010 | Male | ≥ 9 and ≤ 10 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 70001 | Female | ≥ 8 and < 9 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 70002 | Female | ≥ 8 and < 9 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |

| | | | | |
|--------|--------|------------------------------|----------------------------------|---|
| 70003 | Female | ≥ 8 and < 9 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 70004 | Female | ≥ 8 and < 9 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 70005 | Female | ≥ 8 and < 9 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 70006 | Female | ≥ 8 and < 9 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 70007 | Female | ≥ 8 and < 9 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 70008 | Female | ≥ 8 and < 9 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 70009 | Female | ≥ 8 and < 9 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 70010 | Female | ≥ 8 and < 9 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 80001 | Female | ≥ 8 and < 9 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 80002 | Female | ≥ 8 and < 9 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 80003 | Female | ≥ 8 and < 9 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 80004 | Female | ≥ 8 and < 9 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 80005 | Female | ≥ 8 and < 9 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 80006 | Female | ≥ 8 and < 9 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 80007 | Female | ≥ 8 and < 9 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 80008 | Female | ≥ 8 and < 9 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 80009 | Female | ≥ 8 and < 9 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 80010 | Female | ≥ 8 and < 9 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 90001 | Female | ≥ 8 and < 9 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 90002 | Female | ≥ 8 and < 9 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 90003 | Female | ≥ 8 and < 9 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 90004 | Female | ≥ 8 and < 9 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 90005 | Female | ≥ 8 and < 9 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 90006 | Female | ≥ 8 and < 9 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 90007 | Female | ≥ 8 and < 9 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 90008 | Female | ≥ 8 and < 9 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 90009 | Female | ≥ 8 and < 9 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 90010 | Female | ≥ 8 and < 9 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 100001 | Female | ≥ 9 and ≤ 10 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 100002 | Female | ≥ 9 and ≤ 10 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 100003 | Female | ≥ 9 and ≤ 10 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 100004 | Female | ≥ 9 and ≤ 10 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 100005 | Female | ≥ 9 and ≤ 10 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |

| | | | | |
|--------|--------|------------------------------|----------------------------------|---|
| 100006 | Female | ≥ 9 and ≤ 10 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 100007 | Female | ≥ 9 and ≤ 10 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 100008 | Female | ≥ 9 and ≤ 10 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 100009 | Female | ≥ 9 and ≤ 10 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| 100010 | Female | ≥ 9 and ≤ 10 years | ≥ -1.5 SDS and ≤ 0 SDS | ? |
| <hr/> | | | | |
| 110001 | Female | ≥ 9 and ≤ 10 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 110002 | Female | ≥ 9 and ≤ 10 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 110003 | Female | ≥ 9 and ≤ 10 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 110004 | Female | ≥ 9 and ≤ 10 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 110005 | Female | ≥ 9 and ≤ 10 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 110006 | Female | ≥ 9 and ≤ 10 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 110007 | Female | ≥ 9 and ≤ 10 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 110008 | Female | ≥ 9 and ≤ 10 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 110009 | Female | ≥ 9 and ≤ 10 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| 110010 | Female | ≥ 9 and ≤ 10 years | > 0 SDS and $\leq +1.5$ SDS | ? |
| <hr/> | | | | |
| 120001 | Female | ≥ 9 and ≤ 10 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 120002 | Female | ≥ 9 and ≤ 10 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 120003 | Female | ≥ 9 and ≤ 10 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 120004 | Female | ≥ 9 and ≤ 10 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 120005 | Female | ≥ 9 and ≤ 10 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 120006 | Female | ≥ 9 and ≤ 10 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 120007 | Female | ≥ 9 and ≤ 10 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 120008 | Female | ≥ 9 and ≤ 10 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 120009 | Female | ≥ 9 and ≤ 10 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |
| 120010 | Female | ≥ 9 and ≤ 10 years | $> +1.5$ SDS and $\leq +3.00$ SD | ? |

ANNEX 4: INFORMATION FOR PATIENT AND INFORMED CONSENT

| | | |
|--|---|--|
| Hospital Dr. Josep Trueta, Av. França s/n 17007 Girona | INFORMACIÓ AL PACIENT | Metformin therapy to improve adult height prognosis in growth hormone deficient children treated with growth hormone |
|--|---|--|



INFORMACIÓ AL PACIENT

L'equip d'investigadors clínics del Servei de Pediatria de l'Hospital Josep Trueta de Girona i l'Hospital Sant Joan de Déu de Barcelona proposa la realització d'aquest estudi, basat en observacions pròpies i en treballs científics d'investigació mèdica. El període de l'estudi serà de QUATRE ANYS durant el qual es realitzaran algunes proves i es recolliran dades clíniques del seu fill/filla coincidint aproximadament amb els controls de salut de l'Endocrinòleg Infantil.

INTRODUCCIÓ

El dèficit aïllat d'hormona del creixement és un problema mèdic que afecta al 5% dels nens amb baixa estatura i es defineix com una insuficient producció o secreció d'hormona del creixement per part de la hipòfisi (una glàndula situada al cervell). Es tracta de nens que sempre es troben en percentils de talla baixos, usualment per sota del percentil 3, i que, sense tractament tenen un major risc tant d'obtenir un mal pronòstic de talla adulta com de tenir alteracions metabòliques que incrementarien el risc cardiovascular (per la manca d'acció de l'hormona). El tractament amb hormona del creixement recombinada ha suposat un gran avenç donat que no només permet que es substitueixi la funcionalitat de l'hormona que a aquests nens els falta si no que també ha demostrat millorar el perfil metabòlic en quasi tots els seus aspectes. Tot i que la majoria amb tractament quasi assoleixen la talla diana adulta ajustada per talla genètica hi ha un conjunt de nens en els que els persisteix un mal pronòstic de talla adulta (les causes exactes avui en dia encara no es coneixen) amb un fracàs en l'eficàcia de l'hormona. Aquests nens es mantenen en una talla baixa sempre comportant un impacte psicològic sobretot durant el transcurs del període escolar.

El propòsit d'aquest estudi consisteix en veure si l'addició d'un segon fàrmac, la metformina, al tractament d'hormona del creixement en aquests nens amb mal pronòstic de talla adulta, permet millorar aquells aspectes que poden fer que l'hormona falli en el seu propòsit. Estudis previs han demostrat que la metformina pot tenir un efecte beneficiós en el creixement i, a més a més, aporta efectes que podrien ser beneficiosos en la protecció cardiovascular.

Com a resultat de l'estudi, esperem tenir un millor coneixement de com tractar aquests nens que tenen mal pronòstic de talla adulta tot i estar tractats degudament amb hormona del creixement. Aquests resultats poden ser útils per formular noves hipòtesis i dissenyar noves metodologies terapèutiques en altres poblacions de nens.

Aquest estudi comporta la realització d'un seguiment més estret del que habitualment presenten els nens amb dèficit d'hormona del creixement i alguna prova més durant el transcurs de l'estudi que és indolora i no perjudicial pel nen/a.

| | | |
|--|----------------------------------|--|
| Hospital Dr. Josep Trueta, Av. França s/n 17007 Girona | INFORMACIÓ AL PACIENT | Metformin therapy to improve adult height prognosis in growth hormone deficient children treated with growth hormone |
|--|----------------------------------|--|

OBJECTIU I REALITZACIÓ DE L'ESTUDI

L'estudi actual vol corroborar que el tractament amb un fàrmac conegut, la metformina, en nens i nenes amb dèficit aïllat d'hormona de creixement que tenen un mal pronòstic de talla adulta, alenteix la progressió de l'edat òssia i millora el perfil d'algunes hormones (insulina, estrògens, GH i IGF-I) que influeixen en el creixement assolint així una millora d'aquest pronòstic i, per tant, més talla adulta que fent únicament el tractament d'hormona del creixement. També és important determinar l'efecte del tractament amb metformina sobre alguns paràmetres metabòlics (nivells de colesterol, glucosa, insulina i altres) així com el gruix de l'artèria caròtida (per mitjà d'ecografia), que reflexa l'estat del cor, per tal d'avaluar si exerceix una millora positiva així com protecció cardiovascular a llarg termini.

PROCEDIMENT

El medicament objecte d'aquest estudi, la metformina, pertany al grup dels denominats medicaments que milloren l'acció de la insulina. Aquest producte s'utilitza des de fa anys en el tractament de la diabetis tipus 2 en adults i adolescents. Posteriorment s'han demostrat els seus efectes positius en adolescents amb síndrome de l'ovari poliquístic, i en dones amb problemes de fertilitat per induir l'ovulació.

Un cop realitzada una visita de primer contacte, es realitzarà una exploració més completa que inclou determinacions antropomètriques (mesures de talla, pes, IMC...), analítiques i radiològiques per tal de conèixer l'estat actual en el tractament amb hormona del creixement. També s'efectuarà una ecografia de les artèries caròtides del coll per verificar el seu estat.

Els pacients que es considerin candidats per l'assaig, seran distribuïts a l'atzar en dos grups. A la meitat d'ells se'ls administrà metformina (425 mg durant els primers dos anys d'estudi i 850 mg als dos últims anys) en forma d'un comprimit a prendre per boca un cop al dia durant 4 anys. L'altra meitat rebrà, durant el mateix període, un comprimit similar al medicament però que conté només lactosa (sucre) enlloc de metformina; a aquest comprimit se'l denomina placebo. L'assaig està previst que duri 4 anys. Als dos anys de tractament, es comprovarà si els pacients que reben metformina milloren més que els que reben placebo. Als sis mesos de finalitzar el tractament es realitzarà una visita de seguiment clínic.

A la següent taula s'indica el calendari de les visites i proves a efectuar:

Mesures i determinacions a efectuar

| Mesures clíniques | Inicial | 6m | 12m | 18m | 24m | 30m | 36m | 42m | 48m | Final |
|---|----------------|-----------|------------|------------|------------|------------|------------|------------|------------|--------------|
| Pes, talla, índex de massa corporal, perímetre abdominal | X | X | X | X | X | X | X | X | X | |
| Pressió arterial | X | X | X | X | X | X | X | X | X | |
| Edat òssia (radiografia mà) | X | | X | | X | | X | | X | |
| Analítica de sang: recompte de cèl·lules, perfil lipídic, glucosa, insulina, funció hepàtica i renal, funció tiroidea i altres. | X | X | X | X | X | X | X | X | X | |
| Hormones de seguiment del tractament d'hormona del creixement | X | X | X | X | X | X | X | X | X | |

| | | |
|--|----------------------------------|--|
| Hospital Dr. Josep Trueta, Av. França s/n 17007 Girona | INFORMACIÓ AL PACIENT | Metformin therapy to improve adult height prognosis in growth hormone deficient children treated with growth hormone |
|--|----------------------------------|--|

| | | | | | | | | | | |
|---|---|--|---|--|---|--|---|--|---|--|
| Gruix de la paret arterial (ecografia del coll) | X | | X | | X | | X | | X | |
|---|---|--|---|--|---|--|---|--|---|--|

Les proves analítiques i l'ecografia no tenen efectes secundaris coneguts i s'utilitzen de manera rutinària en el diagnòstic i control dels pacients tractats amb metformina. Les radiografies tenen un efecte negatiu produït per la radiació ionitzant però aquest és perjudicial si s'instaura a dosis molt altes i a moltes zones i nosaltres ens limitarem a una única zona i la quantitat de radiació que utilitzarem és mínima. Totes les extraccions als nens es realitzaran en un ambient tranquil, després d'haver aplicat crema anestèsica en la pell (crema EMLA, d'ús habitual en pediatria) i amb personal experimentat que minimitzaran les molèsties al seu fill/a. D'aquestes s'analitzarà una analítica general i es congelaran algunes mostres per al posterior anàlisi al final de l'estudi (donat que conèixer la possible millora dels mateixos suposaria conèixer si el nen està o no tractat durant el transcurs de l'estudi i això podria afectar als resultats del mateix). Totes les mostres biològiques recollides s'emmagatzemaran a l'Hospital Dr Josep Trueta fins a l'esgotament de les mateixes. Les mostres s'utilitzaran per a la finalitat de l'estudi i s'introduiran en el biobanc de l'hospital (en cas que així ho consenti).

POSSIBLES BENEFICIS

La participació a l'estudi implica la presa de medicació de manera cega, és a dir, que ningú sabrà si el seu fill/a prendrà la medicació d'estudi: metformina, o bé placebo (preparat similar però sense medicació). Encara que no podem saber si el seu fill/a prendrà un o l'altre fins que finalitzi l'estudi, es preveu que aquells nens que rebin metformina presentin una millora en alguns paràmetres hormonals com hem predit a dalt i, per aquest motiu, les mostres analítiques seran congelades per ser analitzades quan finalitzi l'estudi. Els nens tractats amb metformina és possible que experimentin una mica més de guany en talla adulta i a llarg termini pugui disminuir el risc de desenvolupar diabetis tipus 2 i malaltia cardiovascular.

RISCS I INCONVENIENTS

La medicació objecte d'estudi és ben tolerada, encara que a vegades poden produir-se lleus molèsties digestives, trastorns del gust o bé disminuir lleugerament la glucosa en sang. En persones grans i amb problemes de deshidratació, s'han descrit trastorns de l'acidesa de la sang que no s'espera que es produeixin en nens. Tots els pacients estaran estrictament vigilats pel que fa a la seguretat del tractament.

Durant l'estudi, es realitzaran controls clínics i analítics cada 6 mesos. Si en qualsevol dels controls es detectés una mínima alteració de la funció del fetge, ronyons, de la glucosa o de les xifres de glòbuls vermells i blancs, es suspendria immediatament la medicació, i es prendrien les mesures necessàries.

Tots els pacients de l'assaig tenen una assegurança d'assaig clínic segons el RD 223/2004 per fer front a possibles eventualitats derivades de l'assaig. Tots els esdeveniments greus que es manifestin durant l'estudi, es considerin o no relacionats amb el mateix ho han de comunicar a l'investigador principal.

PARTICIPACIÓ VOLUNTÀRIA

La seva participació i la del seu fill/a en aquest estudi és voluntària, pel que, encara que inicialment acceptés participar, vostè pot demanar als seus responsables de l'estudi, en qualsevol moment i sense necessitat d'especificar el motiu, l'eliminació de totes les mostres recollides que es trobin emmagatzemades i de la informació relacionada amb aquestes, sense que això repercuteixi en les seves cures mèdiques.

| | | |
|--|---|--|
| Hospital Dr. Josep Trueta, Av. França s/n 17007 Girona | INFORMACIÓ AL PACIENT | Metformin therapy to improve adult height prognosis in growth hormone deficient children treated with growth hormone |
|--|---|--|

Pot comentar la informació rebuda amb la seva família, amb el seu metge o amb qualsevol que consideri oportú per sentir-se ben aconsellat. El metge d'estudi li contestarà a qualsevol pregunta o dubte que no hagi quedat clara.

COMPENSACIÓ

Els investigadors no tenen benefici econòmic amb aquest estudi que està patrocinat pel Ministeri de Salut i Política Social dins del programa de promoció de la investigació Clínica no Comercial.

La seva participació en l'estudi no li suposarà cap cost i li seran reintegrats els costos addicionals (per exemple menjars i trasllats) si vostè ho sol·licita. Vostè no haurà de pagar pels medicaments ni per les proves de l'estudi.

CONFIDENCIALITAT

La informació recollida en aquest estudi serà introduïda en una base de dades computeritzada (en un ordinador) per a la seva anàlisi. Els resultats d'aquest estudi s'utilitzaran per a la seva presentació en congressos mèdics o la publicació en revistes científiques.

Totes les dades de caràcter personal i informació recollida o generada en l'estudi queden protegides d'acord amb la legislació vigent sobre protecció de dades de caràcter personal (Llei Orgànica 15/1999 de 13 de desembre). Ningú, excepte el seu metge i el personal directament relacionat amb aquest estudi, podrà conèixer la identitat. Únicament les autoritats sanitàries poden tenir accés a les seccions rellevants de l'estudi, si així ho sol·licitessin.

Moltes gràcies per la seva atenció.

Si us plau, no dubti en fer-nos qualsevol pregunta al respecte.

Telèfon de contacte: 972-941404 (de 9:00 a 15:00h).

Comitè Directiu de l'Assaig Clínic



FULL D'INFORMACIÓ PER AL PACIENT

UTILITZACIÓ DE MOSTRES BIOLÒGIQUES ROMANENTS D' UN PROJECTE D'INVESTIGACIÓ I CONSERVACIÓ FINAL AL BIOBANC- IDIBGI

Al Hospital Josep Trueta (HJT), l'Institut d'Investigació Biomèdica de Girona (Idibgi) i/o altres centres hospitalaris adscrits es realitza investigació biomèdica, a més de l'assistència als pacients. La finalitat d'aquesta investigació és progressar en el coneixement de les malalties, la seva prevenció, diagnòstic, pronòstic i tractament. Aquesta investigació biomèdica requereix recollir dades clíniques i mostres biològiques dels pacients o donants per analitzar-les amb l'objectiu de conèixer millor i avançar en el diagnòstic i/o tractament de les malalties.

En aquest sentit, les mostres obtingudes per al diagnòstic o control de les malalties, un cop utilitzades amb aquesta finalitat, resulten també molt útils i necessàries per a la investigació. De fet, molts dels avenços científics obtinguts en els darrers anys en medicina són fruit d'aquest tipus de mostres. Si no fossin cedides per a investigació, aquestes mostres biològiques sobrants o excedents del procés assistencial serien destruïdes.

D'acord amb les normes de bioètica i la legislació vigent, sol·licitem la vostra autorització per a la cessió de les mostres biològiques i la informació clínica associada per prosseguir amb la investigació biomèdica, una vegada hagi finalitzat el projecte d'investigació següent:

..... (indiqueu la ref. del projecte).

Seguint el que estableix la Llei 14/2007 de Recerca Biomèdica, la Llei Orgànica 15/1999 de Protecció de Dades Personals i les seves normes de desenvolupament (RD 1716/2011 i RD 1720/2007, respectivament), us demanem que llegiu detingudament aquest document d'informació i el consentiment informat que s'adjunta al final perquè el pugueu signar, si s'escau.

FINALITAT DE LA INVESTIGACIÓ: progressar en el coneixement de les malalties

La finalitat de la investigació és millorar el nostre coneixement de les malalties. Les mostres, les dades clíniques i analítiques i les proves d'imatge s'utilitzaran per a la recerca biomèdica.

Tot això permetrà progressar en el coneixement de la prevenció, diagnòstic, pronòstic i/o tractament de les malalties.

MOSTRES BIOLÒGIQUES I DADES CLÍNiques: una vegada finalitzat el projecte d'investigació es custodien i conserven al Biobanc fins a la seva extinció

És a les vostres mans decidir si una vegada finalitzat el projecte d'investigació abans descrit, les dades clíniques recollides i les mostres biològiques sobrants d'aquest projecte passen a ser custodiades i conservades al biobanc (banc de mostres biològiques), fins a la seva extinció.

Aquest biobanc és un establiment legalment autoritzat, sense ànim de lucre, acull col·leccions organitzades de mostres biològiques i informació associada a les condicions i garanties de qualitat i seguretat que exigeix la legislació ja referida i els codis de conducta aprovats pels comitès d'ètica. Aquestes mostres i la seva informació associada queden disponibles per a aquells centres o institucions de recerca nacionals o internacionals que ho sol·licitin oficialment al biobanc.

Qualsevol estudi d'investigació per al qual se sol·liciti la utilització d'aquestes dades o mostres ha de disposar sempre de l'aprovació del Comitè d'Ètica de la Investigació (CEI) competent, que vetlla perquè els investigadors desenvolupin els seus estudis seguint sempre les més estrictes normes ètiques i legals, i perquè l'aprovi un comitè científic que en garanteixi la utilitat científica.



A partir de les mostres donades, en els casos en què la investigació ho requereixi, es realitzaran estudis genètics, i a partir d'aquests es pot obtenir informació sobre la vostra salut i la dels vostres familiars. Sempre s'actuarà vetllant per la protecció d'aquesta informació (vegeu l'apartat de protecció de dades i confidencialitat).

En cas de ser necessària alguna mostra addicional, la institució sanitària es podria posar en contacte amb vosaltres per sol·licitar novament la vostra col·laboració.

PROTECCIÓ DE DADES I CONFIDENCIALITAT: les mostres es conserven codificades

Les dades personals que es recullin seran obtingudes, tractades i emmagatzemades complint en tot moment el deure de confidencialitat, d'acord amb la legislació vigent en matèria de protecció de dades de caràcter personal.

La identificació de les mostres biològiques del biobanc és sotmesa a un procés de codificació. A cada mostra se li assigna un codi d'identificació, que és el que utilitzen els investigadors. Únicament el personal autoritzat pel biobanc pot relacionar la vostra identitat amb els esmentats codis. Mitjançant aquest procés, els investigadors que sol·licitin mostres al biobanc no podran conèixer cap dada que reveli la vostra identitat. Així mateix, encara que els resultats obtinguts de la investigació realitzada amb les vostres mostres es publiquin en revistes científiques, la vostra identitat no és facilitarà.

Les dades clíniques i la informació de les mostres biològiques dels donants passen a formar part del fitxer del biobanc, inscrit en l'agència de protecció de dades sota la responsabilitat de Idibgi.

Aquestes dades són tractades i cedides amb l'única i exclusiva finalitat de dur a terme recerca biomèdica. Les dades de les mostres, sense dades personals, podran ser compartides en el si de xarxes cooperatives de biobancs i grups cooperatius de recerca.

Podreu exercir els vostres drets d'accés, rectificació, cancel·lació i oposició (ARCO) de les vostres dades dirigint-vos a la Direcció del Biobanc Idibgi per correu electrònic (biobanc@idibgi.cat) o via postal a l'adreça següent:

| | |
|--|---|
| DIRECTOR DEL BIOBANC IDIBGI Hospital Josep Trueta Planta -9 | Av. França s/n 17007 Girona Tel. 972 94 02 82 biobanc@idibgi.cat |
|--|---|

En cas de dubte o impossibilitat per dur a terme el procediment, podeu contactar a través del telèfon d'atenció indicat.

CARÀCTER ALTRUISTA DE LA DONACIÓ: la cessió de mostres biològiques que realitzeu al Biobanc Idibgi és gratuïta

No obtindreu cap benefici econòmic directe per la cessió de la mostra i dades associades ni per participar en els estudis d'investigació. Tampoc tindreu drets sobre possibles beneficis comercials dels descobriments que es puguin aconseguir com a resultat de la investigació biomèdica.

PARTICIPACIÓ VOLUNTÀRIA: la vostra negativa no afectarà la vostra assistència mèdica, present o futura

La vostra participació és totalment voluntària. Podeu negar-vos a participar o retirar el vostre consentiment en qualsevol moment posterior a la signatura sense haver d'explicar els motius. Això no repercutirà negativament en la vostra assistència mèdica, present o futura.



REVOCACIÓ DEL CONSENTIMENT: si decidiu firmar aquest consentiment, també podreu cancel·lar-lo lliurement. Això comportarà la destrucció de les vostres mostres

Si en un futur volguéssiu anul·lar o cancel·lar el vostre consentiment, les mostres biològiques serien destruïdes i les dades associades a aquestes serien retirades del biobanc. També podríeu sol·licitar que les mostres siguin anònimes, la qual cosa significa que s'eliminarà la relació entre les vostres dades personals (que revelen la vostra identitat) i les mostres biològiques i dades clíniques associades. Els efectes d'aquesta cancel·lació o anonimat no es podrien estendre a la investigació que ja s'hagués dut a terme. Si desitgeu cancel·lar el consentiment, hauríeu de sol·licitar-ho per escrit a la direcció del Biobanc Idibgi, a l'adreça indicada anteriorment.

INFORMACIÓ SOBRE ELS RESULTATS DE LA INVESTIGACIÓ: se us proporcionarà informació si la desitgeu rebre

En cas que ho demaneu expressament, el biobanc us pot proporcionar informació sobre quines són les investigacions en què s'han utilitzat les vostres mostres i dels resultats globals d'aquestes investigacions, excepte en cas de cancel·lació o anonimat.

Els mètodes utilitzats en investigació biomèdica solen ser diferents dels aprovats per a la pràctica clínica, per la qual cosa no els heu de considerar amb valor clínic. Però, en cas que aquestes investigacions proporcionin dades que poguessin ser tant clínicament com genèticament rellevants per a la vostra salut o la de la vostra família, se us comunicarien si així ho creieu oportú. Així mateix, podríeu obtenir informació rellevant per a la vostra família. Us correspon a vosaltres decidir si voleu o no que us les comuniquem. Si voleu que sigui així, ho heu de consignar a la casella que apareix al final d'aquest full.

Si no desitgeu rebre aquesta informació, tingueu en compte que la llei estableix que quan la informació obtinguda sigui necessària per evitar un greu perjudici per a la salut dels vostres familiars biològics, un comitè d'experts estudiarà el cas i haurà de decidir si és convenient informar els afectats o els seus representants legals.

Si teniu qualsevol dubte, ara o en el futur, en relació amb aquest consentiment, no dubteu a preguntar el que calgui al personal sanitari que us ha donat aquesta informació. També podeu comentar els dubtes amb el vostre metge, que us posarà en contacte amb el personal sanitari autoritzat.

Moltes gràcies per la vostra col·laboració.

Biobanc Idibgi

Format de full d'informació del pacient adaptat de Institut d'Investigació Biomèdica de Bellvitge (HUB -ICO -IDIBELL)

| | | |
|---|---------------------------------|---|
| <p>Hospital Dr. Josep Trueta, Av. França s/n 17007 Girona</p> | <p>FULL DE CONSENTIMENT</p> | <p>Metformin therapy to improve adult height prognosis in growth hormone deficient children treated with growth hormone</p> |
|---|---------------------------------|---|

CONSENTIMENT PER ESCRIT DELS PARES/TUTORS

TITOL DE L'ESTUDI: Metformin therapy to improve adult height prognosis in growth hormone deficient children treated with growth hormone.

Jo.....

Com a pare, mare o tutor del nen/nena:

Confirmo que:

He llegit el full d'informació que se m'ha entregat.

He pogut fer preguntes sobre l'estudi.

S'han respost les meves preguntes de manera satisfactòria.

He rebut suficient informació sobre l'estudi.

He parlat amb (nom de l'investigador/pediatra/infermer):.....

Comprendc que la participació es voluntària, i que puc retirar-me de l'estudi quan vulgui, sense que això repercuti en les cures mèdiques i sense donar explicacions.

En conseqüència,

Dono la meva conformitat perquè el meu fill/filla participem en aquest estudi.

Sí No

Permeto que les mostres siguin utilitzades en investigacions futures relacionades amb malalties de l'embaràs o el desenvolupament dels nens.

Sí No

Permeto que les mostres siguin introduïdes en el biobanc de l'hospital.

Sí No

Firma del pare/mare/tutor
del participant:

Firma del investigador:

Data: ___ / ___ / ___

Data: ___ / ___ / ___

ANNEX 5: CASE REPORT FORM

| | | |
|--|---|---|
| Hospital Dr. Josep Trueta, Av. França s/n 17007 Girona | CUADERNO DE RECOGIDA DE DATOS | Metformin therapy to improve adult height prognosis in growth hormone deficient children treated with growth hormone |
|--|---|---|

| | |
|------------------------------------|---|
| Código paciente /_/_/_/_/_/_/_/ | Fecha /_/_/_/ /_/_/_/ /_/_/_/_/_/_/ |
| | Día Mes Año |

Período Basal (0 m)

| | | | | |
|--|---|---|-----------------------------|----------------------|
| Edad cronológica | Día | Mes | Año | |
| <input type="text" value="a"/> <input type="text" value="m"/> Años | Fecha nacimiento | <input type="text"/> | <input type="text"/> | <input type="text"/> |
| Edad ósea | Peso actual | Talla actual | Velocidad crecimiento | |
| <input type="text" value="a"/> <input type="text" value="m"/> Años | <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> cm | <input type="text"/> <input type="text"/> <input type="text"/> cm | <input type="text"/> cm/año | |
| Predicción talla adulta | IMC | Cintura | | |
| <input type="text"/> <input type="text"/> <input type="text"/> cm | <input type="text"/> <input type="text"/> , <input type="text"/> <input type="text"/> Kg/m ² | <input type="text"/> <input type="text"/> cm | | |

| | |
|----------------------|---|
| Talla padre | <input type="text"/> <input type="text"/> <input type="text"/> cm |
| Talla madre | <input type="text"/> <input type="text"/> <input type="text"/> cm |
| Talla media parental | <input type="text"/> <input type="text"/> <input type="text"/> cm |

| | |
|------------------------|---|
| Estadio puberal Tanner | |
| S (seno) | <input type="text"/> <input type="text"/> |
| P (pubis) | <input type="text"/> <input type="text"/> |

| | |
|--|----------------------|
| Hospital que realizará el seguimiento: | |
| HC 1 (HUJT) | <input type="text"/> |
| HC 2 (HSJD) | <input type="text"/> |

CIMT mm

Presión Arterial / mmHg

Peso en nacer kg

| Laboratorio | Valores | Unidades |
|-----------------------------------|---------|----------|
| Hemoglobina | | |
| Glucosa | | |
| HbA1c | | |
| Creatinina | | |
| AST | | |
| ALT | | |
| Vitamina B12 | | |
| Albumina | | |
| Proteína C reactiva | | |
| Insulina | | |
| IGF-I | | |
| IGFBP3 | | |
| HOMA-IR | | |
| TSH | | |
| T4 libre | | |
| Prolactina | | |
| Anticuerpos anti-transglutaminasa | | |
| HMW-adiponectina | | |

| | | | |
|-------------------|--------------------|------------------|--|
| Peso actual (SDS) | Talla actual (SDS) | IMC actual (SDS) | |
|-------------------|--------------------|------------------|--|

Antecedentes familiares:

Antecedentes personales:

Medicamentos:

| | |
|-----------------|-----------------------|
| Código paciente | Fecha |
| / / / / / / / / | / / / / / / / / / / |
| | Día Mes Año |

Visita 6 meses

Edad cronológica Peso actual Talla actual Velocidad crecimiento

Años
 cm
 cm
 cm/año

IMC Cintura Presión arterial

, Kg/m²
 cm
 / mmHg

Peso (SDS) Talla (SDS) IMC (SDS) Cintura (SDS)

| Laboratorio | Valores | Unidades |
|---------------------|---------|----------|
| Hemoglobina | | |
| Glucosa | | |
| HbA1c | | |
| Creatinina | | |
| AST | | |
| ALT | | |
| Vitamina B12 | | |
| Proteína C reactiva | | |
| HDL-c | | |
| LDL-c | | |
| Triglicéridos | | |
| Insulina | | |
| IGF-I | | |
| IGFBP3 | | |
| HOMA-IR | | |
| HMW-adiponectina | | |

| | | |
|---------------------------|----------------------|----------------------|
| Estadio puberal Tanner | | |
| S (seno) | <input type="text"/> | <input type="text"/> |
| P (pubis) | <input type="text"/> | <input type="text"/> |

Medicamentos:

Observaciones:

| | |
|------------------------------------|---|
| Código paciente / / / / / / / / | Fecha / / / / / / / / / / Día Mes Año |
|------------------------------------|---|

Período 12 meses

Edad cronológica

Años

Presión arterial

/ mmHg CIMT mm

Edad ósea

Años

Peso actual

cm

Talla actual

cm

Velocidad crecimiento

cm/año

Predicción talla adulta

cm

IMC

Kg/m²

Cintura

cm

Peso (SDS) Talla (SDS) IMC (SDS) Cintura (SDS)

| Laboratorio | Valores | Unidades |
|---------------------|---------|----------|
| Hemoglobina | | |
| Glucosa | | |
| HbA1c | | |
| Creatinina | | |
| AST | | |
| ALT | | |
| Vitamina B12 | | |
| Proteína C reactiva | | |
| HDL-c | | |
| LDL-c | | |
| Triglicéridos | | |
| Insulina | | |
| IGF-I | | |
| IGFBP3 | | |
| HOMA-IR | | |
| HWM-adiponectina | | |

| | | |
|---------------------------|-------------------------------|-------------------------------|
| Estadio puberal Tanner | | |
| S (seno) | <input type="text" value=""/> | <input type="text" value=""/> |
| P (pubis) | <input type="text" value=""/> | <input type="text" value=""/> |

Medicamentos:

Observaciones:

| | |
|-----------------|---|
| Código paciente | Fecha |
| / / / / / / / / | / / / / / / / / / / |
| | Día Mes Año |

Visita 18 meses

| | | | |
|--|--|---|-----------------------------|
| Edad cronológica | Peso actual | Talla actual | Velocidad crecimiento |
| <input type="text" value="a"/> <input type="text" value="m"/> Años | <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> cm | <input type="text"/> <input type="text"/> <input type="text"/> cm | <input type="text"/> cm/año |

| | | |
|---|--|--|
| IMC | Cintura | Presión arterial |
| <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Kg/m ² | <input type="text"/> <input type="text"/> cm | <input type="text"/> / <input type="text"/> mmHg |

| | | | |
|---------------------------------|----------------------------------|--------------------------------|------------------------------------|
| Peso (SDS) <input type="text"/> | Talla (SDS) <input type="text"/> | IMC (SDS) <input type="text"/> | Cintura (SDS) <input type="text"/> |
|---------------------------------|----------------------------------|--------------------------------|------------------------------------|

| Laboratorio | Valores | Unidades |
|---------------------|---------|----------|
| Hemoglobina | | |
| Glucosa | | |
| HbA1c | | |
| Creatinina | | |
| AST | | |
| ALT | | |
| Vitamina B12 | | |
| Proteína C reactiva | | |
| HDL-c | | |
| LDL-c | | |
| Triglicéridos | | |
| Insulina | | |
| IGF-I | | |
| IGFBP3 | | |
| HOMA-IR | | |
| HWM-adiponectina | | |

| | | |
|---------------------------|----------------------|----------------------|
| Estadio puberal Tanner | | |
| S (seno) | <input type="text"/> | <input type="text"/> |
| P (pubis) | <input type="text"/> | <input type="text"/> |

Medicamentos:

Observaciones:

| | |
|------------------------------------|---|
| Código paciente / / / / / / / / | Fecha / / / / / / / / / / Día Mes Año |
|------------------------------------|---|

Período 24 meses

Edad cronológica

Años

Presión arterial

/ mmHg CIMT mm

Edad ósea

Años

Peso actual

cm

Talla actual

cm

Velocidad crecimiento

cm/año

Predicción talla adulta

cm

IMC

Kg/m²

Cintura

cm

Peso (SDS) Talla (SDS) IMC (SDS) Cintura (SDS)

| Laboratorio | Valores | Unidades |
|---------------------|---------|----------|
| Hemoglobina | | |
| Glucosa | | |
| HbA1c | | |
| Creatinina | | |
| AST | | |
| ALT | | |
| Vitamina B12 | | |
| Proteína C reactiva | | |
| HDL-c | | |
| LDL-c | | |
| Triglicéridos | | |
| Insulina | | |
| IGF-I | | |
| IGFBP3 | | |
| HOMA-IR | | |
| HWM-adiponectina | | |

| | | |
|---------------------------|-------------------------------|-------------------------------|
| Estadio puberal Tanner | | |
| S (seno) | <input type="text" value=""/> | <input type="text" value=""/> |
| P (pubis) | <input type="text" value=""/> | <input type="text" value=""/> |

Medicamentos:

Observaciones:

| | |
|-----------------|---|
| Código paciente | Fecha |
| / / / / / / / / | / / / / / / / / / / |
| | <div style="display: flex; justify-content: space-around;"> Día Mes Año </div> |

Visita 30 meses

| | | | |
|--|--|---|-----------------------------|
| Edad cronológica | Peso actual | Talla actual | Velocidad crecimiento |
| <input type="text" value="a"/> <input type="text" value="m"/> Años | <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> cm | <input type="text"/> <input type="text"/> <input type="text"/> cm | <input type="text"/> cm/año |

| | | |
|---|--|--|
| IMC | Cintura | Presión arterial |
| <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Kg/m ² | <input type="text"/> <input type="text"/> cm | <input type="text"/> / <input type="text"/> mmHg |

| | | | |
|---------------------------------|----------------------------------|--------------------------------|------------------------------------|
| Peso (SDS) <input type="text"/> | Talla (SDS) <input type="text"/> | IMC (SDS) <input type="text"/> | Cintura (SDS) <input type="text"/> |
|---------------------------------|----------------------------------|--------------------------------|------------------------------------|

| Laboratorio | Valores | Unidades |
|---------------------|---------|----------|
| Hemoglobina | | |
| Glucosa | | |
| HbA1c | | |
| Creatinina | | |
| AST | | |
| ALT | | |
| Vitamina B12 | | |
| Proteína C reactiva | | |
| HDL-c | | |
| LDL-c | | |
| Triglicéridos | | |
| Insulina | | |
| IGF-I | | |
| IGFBP3 | | |
| HOMA-IR | | |
| HWM-adiponectina | | |

| | | |
|------------------------|----------------------|----------------------|
| Estadio puberal Tanner | | |
| S (seno) | <input type="text"/> | <input type="text"/> |
| P (pubis) | <input type="text"/> | <input type="text"/> |

Medicamentos:

Observaciones:

| | |
|------------------------------------|---|
| Código paciente / / / / / / / / | Fecha / / / / / / / / / / Día Mes Año |
|------------------------------------|---|

Período 36 meses

Edad cronológica

| | | |
|---|---|------|
| a | m | Años |
|---|---|------|

Presión arterial

| | | | | | |
|---|---|------|------|---|----|
| / | / | mmHg | CIMT | / | mm |
|---|---|------|------|---|----|

Edad ósea

| | | |
|---|---|------|
| a | m | Años |
|---|---|------|

Peso actual

| | | | | |
|---|---|---|---|----|
| / | / | / | / | cm |
|---|---|---|---|----|

Talla actual

| | | | |
|---|---|---|----|
| / | / | / | cm |
|---|---|---|----|

Velocidad crecimiento

| | |
|---|--------|
| / | cm/año |
|---|--------|

Predicción talla adulta

| | | | |
|---|---|---|----|
| / | / | / | cm |
|---|---|---|----|

IMC

| | | | | | |
|---|---|---|---|---|-------------------|
| / | / | / | / | / | Kg/m ² |
|---|---|---|---|---|-------------------|

Cintura

| | | |
|---|---|----|
| / | / | cm |
|---|---|----|

| | | | | | | | |
|------------|--|-------------|--|-----------|--|---------------|--|
| Peso (SDS) | | Talla (SDS) | | IMC (SDS) | | Cintura (SDS) | |
|------------|--|-------------|--|-----------|--|---------------|--|

| Laboratorio | Valores | Unidades |
|---------------------|---------|----------|
| Hemoglobina | | |
| Glucosa | | |
| HbA1c | | |
| Creatinina | | |
| AST | | |
| ALT | | |
| Vitamina B12 | | |
| Proteína C reactiva | | |
| HDL-c | | |
| LDL-c | | |
| Triglicéridos | | |
| Insulina | | |
| IGF-I | | |
| IGFBP3 | | |
| HOMA-IR | | |
| HWM-adiponectina | | |

| | | |
|---------------------------|---|---|
| Estadio puberal Tanner | | |
| S (seno) | / | / |
| P (pubis) | / | / |

Medicamentos:

Observaciones:

| | |
|-----------------|-----------------------|
| Código paciente | Fecha |
| / / / / / / / / | / / / / / / / / / / |
| | Día Mes Año |

Visita 42 meses

| | | | |
|--|--|---|-----------------------------|
| Edad cronológica | Peso actual | Talla actual | Velocidad crecimiento |
| <input type="text" value="a"/> <input type="text" value="m"/> Años | <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> cm | <input type="text"/> <input type="text"/> <input type="text"/> cm | <input type="text"/> cm/año |

| | | |
|---|--|--|
| IMC | Cintura | Presión arterial |
| <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Kg/m ² | <input type="text"/> <input type="text"/> cm | <input type="text"/> / <input type="text"/> mmHg |

| | | | |
|---------------------------------|----------------------------------|--------------------------------|------------------------------------|
| Peso (SDS) <input type="text"/> | Talla (SDS) <input type="text"/> | IMC (SDS) <input type="text"/> | Cintura (SDS) <input type="text"/> |
|---------------------------------|----------------------------------|--------------------------------|------------------------------------|

| Laboratorio | Valores | Unidades |
|---------------------|---------|----------|
| Hemoglobina | | |
| Glucosa | | |
| HbA1c | | |
| Creatinina | | |
| AST | | |
| ALT | | |
| Vitamina B12 | | |
| Proteína C reactiva | | |
| HDL-c | | |
| LDL-c | | |
| Triglicéridos | | |
| Insulina | | |
| IGF-I | | |
| IGFBP3 | | |
| HOMA-IR | | |
| HWM-adiponectina | | |

| | | |
|---------------------------|----------------------|----------------------|
| Estadio puberal Tanner | | |
| S (seno) | <input type="text"/> | <input type="text"/> |
| P (pubis) | <input type="text"/> | <input type="text"/> |

Medicamentos:

Observaciones:

| | |
|------------------------------------|---|
| Código paciente / / / / / / / / | Fecha / / / / / / / / / / Día Mes Año |
|------------------------------------|---|

Período 48 meses

Edad cronológica

Años

Presión arterial

/ mmHg CIMT mm

Edad ósea

Años

Peso actual

cm

Talla actual

cm

Velocidad crecimiento

cm/año

Predicción talla adulta

cm

IMC

Kg/m²

Cintura

cm

Peso (SDS) Talla (SDS) IMC (SDS) Cintura (SDS)

| Laboratorio | Valores | Unidades |
|---------------------|---------|----------|
| Hemoglobina | | |
| Glucosa | | |
| HbA1c | | |
| Creatinina | | |
| AST | | |
| ALT | | |
| Vitamina B12 | | |
| Proteína C reactiva | | |
| HDL-c | | |
| LDL-c | | |
| Triglicéridos | | |
| Insulina | | |
| IGF-I | | |
| IGFBP3 | | |
| HOMA-IR | | |
| HWM-adiponectina | | |

| | | |
|---------------------------|-------------------------------|-------------------------------|
| Estadio puberal Tanner | | |
| S (seno) | <input type="text" value=""/> | <input type="text" value=""/> |
| P (pubis) | <input type="text" value=""/> | <input type="text" value=""/> |

Medicamentos:

Observaciones:

ANNEX 6: SIDE-EFFECTS DATASHEET

| | | |
|--|--|---|
| Hospital Dr. Josep Trueta, Av. França s/n 17007 Girona | HOJA DE RECOGIDA DE EFECTOS ADVERSOS | Metformin therapy to improve adult height prognosis in growth hormone deficient children treated with growth hormone |
|--|--|---|

| | |
|---------------------|---|
| Código paciente | Fecha |
| / / / / / / / / / / | / / / / / / / / / / |
| | Día Mes Año |

Responsable de la recogida de datos:

Firma:

Nombre: _____

Apellidos: _____

Señale con una cruz si la paciente ha sufrido alguno de los siguientes signos/síntomas, relacionados con posibles efectos adversos debidos al tratamiento en estudio metformina:

| SIGNO / SINTOMA | |
|----------------------|--|
| Náuseas | |
| Vómitos | |
| Diarreas | |
| Dolor abdominal | |
| Pérdida de apetito | |
| Alteración del sabor | |
| Eritema | |
| Prurito | |
| Urticaria | |
| Disnea | |
| Hipotermia | |
| Coma | |
| Otros | |

Descripción detallada del evento:

ANNEX 7: METFORMIN DATASHEET



FICHA TÉCNICA

1. NOMBRE DEL MEDICAMENTO

Dianben 850 mg comprimidos recubiertos con película

2. COMPOSICIÓN CUALITATIVA Y CUANTITATIVA

Cada comprimido recubierto con película contiene 850 mg de hidrocloreuro de metformina correspondientes a 662,9 mg de metformina base.

Para consultar la lista completa de excipientes, ver sección 6.1.

3. FORMA FARMACÉUTICA

Comprimido recubierto con película.

Comprimidos recubiertos con película blancos, circulares y biconvexos.

4. DATOS CLÍNICOS

4.1 Indicaciones terapéuticas

Tratamiento de la diabetes mellitus tipo 2, especialmente en pacientes con sobrepeso, cuando la dieta prescrita y el ejercicio por sí solos no sean suficientes para un control glucémico adecuado.

- En adultos, Dianben puede utilizarse en monoterapia o en combinación con otros antidiabéticos orales, o con insulina.
- En niños a partir de 10 años de edad y adolescentes, Dianben puede utilizarse en monoterapia o en combinación con insulina.

Se ha demostrado una reducción de las complicaciones relacionadas con la diabetes en pacientes adultos diabéticos tipo 2 con sobrepeso tratados con metformina como tratamiento de primera línea tras el fracaso de la dieta (ver sección 5.1).

4.2 Posología y forma de administración

Posología

Adultos:

Monoterapia y combinación con otros antidiabéticos orales:

La dosis inicial habitual es 500 mg u 850 mg de hidrocloreuro de metformina 2 ó 3 veces al día administrados durante o después de las comidas.

Tras 10-15 días, la posología debería ajustarse en función de los niveles de glucosa en sangre. Un aumento lento de la dosis puede mejorar la tolerancia gastrointestinal.

La dosis máxima recomendada es de 3 g de hidrocloreuro de metformina al día, administrados en 3 tomas.

Si se pretende administrar Dianben en sustitución de otro antidiabético oral: suspender la terapia anterior e iniciar la terapia con metformina a la posología indicada anteriormente.

Combinación con insulina:

La metformina y la insulina pueden ser utilizadas en terapia combinada para lograr un mejor control de la glucosa en sangre. El hidrocloreto de metformina se administra a la dosis inicial habitual de 500 mg u 850 mg 2 ó 3 veces al día, mientras que la posología de insulina se ajusta en función de los niveles de glucosa en sangre.

Pacientes de edad avanzada:

Debido a la posible reducción de la función renal en personas de edad avanzada, la posología de metformina debe ajustarse según la función renal. Es necesaria una evaluación regular de la función renal (ver sección 4.4).

Niños y adolescentes:

Monoterapia y combinación con insulina

- Dianben puede utilizarse en niños a partir de 10 años de edad y adolescentes.
- La dosis inicial habitual es de 500 mg u 850 mg de hidrocloreto de metformina una vez al día, administrada durante o después de las comidas.

Tras 10-15 días, la dosis debería ajustarse la dosis en función de los valores de glucosa en sangre. Un aumento lento de la dosis puede mejorar la tolerabilidad gastrointestinal. La dosis máxima recomendada de hidrocloreto de metformina es de 2 g al día, administrados en 2 ó 3 tomas.

4.3 Contraindicaciones

- Hipersensibilidad a la metformina o a alguno de los excipientes.
- Cetoacidosis diabética, precoma diabético.
- Insuficiencia o disfunción renal (aclaramiento de creatinina < 60 ml/min).
- Situaciones agudas con potencial para alterar la función renal tales como: deshidratación, infección grave, shock.
- Enfermedad aguda o crónica que puede provocar hipoxia tisular como: insuficiencia cardiaca o respiratoria, infarto de miocardio reciente, shock.
- Insuficiencia hepática, intoxicación alcohólica aguda, alcoholismo.

4.4 Advertencias y precauciones especiales de empleo

Acidosis láctica:

La acidosis láctica es una complicación metabólica rara pero grave (alta mortalidad en ausencia de un tratamiento precoz) que puede aparecer por acumulación de metformina. Los casos descritos de acidosis láctica en pacientes tratados con metformina han ocurrido principalmente en pacientes diabéticos con una insuficiencia renal marcada. La incidencia de la acidosis láctica puede y debe reducirse evaluando también otros factores de riesgo asociados como una diabetes mal controlada, cetosis, ayuno prolongado, consumo excesivo de alcohol, insuficiencia hepática y cualquier estado asociado con la hipoxia.

Diagnóstico:

Debe tenerse en cuenta el riesgo de acidosis láctica en caso de signos inespecíficos como calambres musculares con trastornos digestivos como dolor abdominal y astenia grave.

Esto puede ir seguido de disnea acidótica, dolor abdominal, hipotermia y coma. Los resultados diagnósticos de laboratorio incluyen la reducción del pH sanguíneo, unos niveles de lactato en plasma superiores a 5 mmol/l, y un incremento del desequilibrio aniónico (anión gap) y de la relación lactato/piruvato. Si hay sospecha de acidosis metabólica, debe interrumpirse el tratamiento con metformina y el paciente debería ser hospitalizado inmediatamente (ver sección 4.9).

Función renal:

Debido a que la metformina se elimina por el riñón, el aclaramiento de creatinina (éste puede estimarse a partir de los niveles de creatinina en suero utilizando la fórmula Cockcroft-Gault) debe determinarse antes de iniciarse el tratamiento y regularmente desde su inicio:

- al menos una vez al año en pacientes con función renal normal,
- al menos de dos a cuatro veces al año en pacientes con un aclaramiento de creatinina próximo al límite inferior del valor normal y en pacientes de edad avanzada.

En pacientes de edad avanzada, la función renal disminuida es frecuente y asintomática. Debe tenerse especial cuidado en situaciones en las que la función renal pueda estar afectada, por ejemplo, al iniciar un tratamiento antihipertensor o un tratamiento diurético y al iniciar un tratamiento con medicamentos antiinflamatorios no esteroideos (AINEs).

Administración de medios de contraste yodados:

La administración intravascular de medios de contraste yodados en exploraciones radiológicas puede desembocar en un fallo renal. Esto puede dar lugar a acumulación de metformina e inducir acidosis láctica. Debe suspenderse el tratamiento con metformina antes o en el momento de la exploración y no reanudarlo hasta pasadas 48 horas, y sólo tras haber re-evaluado la función renal y comprobar que es normal (ver sección 4.5).

Cirugía:

El tratamiento con metformina debe interrumpirse 48 horas antes de una intervención quirúrgica programada con anestesia general, raquídea o peridural. El tratamiento puede reiniciarse no antes de 48 horas después de la intervención quirúrgica o tras la reanudación de la alimentación oral, y sólo si la función renal se ha restablecido.

Niños y adolescentes:

El diagnóstico de diabetes mellitus tipo 2 debe ser confirmado antes de iniciar el tratamiento con metformina.

Durante los ensayos clínicos controlados de un año de duración no se han detectado efectos de la metformina en el crecimiento o en la pubertad pero no se dispone de información a largo plazo sobre estos casos específicos. Por consiguiente, se recomienda un seguimiento cuidadoso de los efectos de la metformina en estos parámetros en niños tratados con metformina, especialmente en niños de edades comprendidas entre 10 y 12 años.

Niños entre 10 y 12 años de edad:

Solamente 15 individuos con edades comprendidas entre 10 y 12 años fueron incluidos en los estudios clínicos controlados llevados a cabo en niños y adolescentes. Aunque la eficacia y seguridad de la metformina en estos niños no difirieron de la eficacia y seguridad en niños mayores y adolescentes, se recomienda especial precaución al prescribirla a niños con edades comprendidas entre 10 y 12 años.

Otras precauciones:

Todos los pacientes deben continuar su dieta con una distribución regular de la ingesta de carbohidratos durante el día. Los pacientes con sobrepeso deben continuar con su dieta hipocalórica.

Deberán realizarse regularmente las pruebas de laboratorio habituales para el control de la diabetes.

La metformina no provoca por sí sola hipoglucemia; no obstante, se recomienda precaución cuando se utiliza en combinación con insulina u otros antidiabéticos orales (ej. sulfonilureas o meglitinidas).

4.5 Interacción con otros medicamentos y otras formas de interacción

No se recomienda el uso concomitante con:

Alcohol:

La intoxicación alcohólica aguda se asocia a un aumento del riesgo de acidosis láctica, especialmente en caso de: ayuno o desnutrición, insuficiencia hepática.

Evitar el consumo de alcohol y medicamentos que contengan alcohol.

Medios de contraste yodados:

La administración intravascular de medios de contraste yodados puede producir un fallo renal que desemboque en la acumulación de metformina y en un riesgo mayor de acidosis láctica.

El tratamiento con metformina debe suspenderse antes o en el momento de la exploración y no reanudarse hasta pasadas 48 horas y sólo tras haber re-evaluado la función renal y haber comprobado que es normal (ver sección 4.4).

Combinaciones que requieren precauciones de empleo:

Medicamentos con actividad hiperglucémica intrínseca (ej. glucocorticoides (vías sistémica y local) y simpaticomiméticos):

Puede requerirse realizar un control más frecuente de la glucosa en sangre, especialmente al principio del tratamiento. Si es necesario, ajustar la posología de la metformina durante la terapia con el respectivo medicamento y tras su suspensión.

Diuréticos, especialmente diuréticos de asa:

Pueden incrementar el riesgo de acidosis láctica debido a su potencial para disminuir la función renal.

4.6 Fertilidad, embarazo y lactancia

Embarazo

La diabetes no controlada durante el embarazo (gestacional o permanente) se asocia a un mayor riesgo de anomalías congénitas y mortalidad perinatal.

La información limitada sobre el uso de metformina en mujeres embarazadas no indica un mayor riesgo de anomalías congénitas. Los estudios en animales no muestran efectos dañinos sobre el embarazo, el desarrollo embrionario o fetal, el parto o el desarrollo postnatal (ver la sección 5.3).

Cuando la paciente planifique quedarse embarazada y durante el embarazo, se recomienda que la diabetes no se trate con metformina, sino con insulina para mantener los niveles de glucosa en sangre lo más próximos posible a los valores normales con el fin de reducir el riesgo de malformaciones fetales.

Lactancia

La metformina se excreta en la leche materna. No se han observado efectos adversos en los recién nacidos/bebés con lactancia materna. Sin embargo, dado que la información disponible es limitada, la lactancia materna no se recomienda durante el tratamiento con metformina. La decisión de retirar la lactancia materna debe tomarse teniendo en cuenta los beneficios de la lactancia y el riesgo potencial de los efectos adversos en el niño.

Fertilidad

La fertilidad de ratas machos y hembras no se vio afectada por la metformina cuando ésta se administró a dosis tan altas como 600 mg/Kg/día, que es aproximadamente tres veces la dosis máxima diaria recomendada en humanos basándose en la comparación de la superficie corporal.

4.7 Efectos sobre la capacidad para conducir y utilizar máquinas

La metformina en monoterapia no provoca hipoglucemia y por tanto no produce efectos en la capacidad para conducir o utilizar máquinas.

No obstante, se debe advertir al paciente de los riesgos de aparición de hipoglucemia cuando la metformina se utiliza en combinación con otros antidiabéticos (ej. sulfonilureas o meglitinidas).

4.8 Reacciones adversas

Durante el inicio del tratamiento, las reacciones adversas más frecuentes son náuseas, vómitos, diarrea, dolor abdominal o pérdida de apetito, que se resuelven espontáneamente en la mayoría de los casos. Para prevenirlos, se recomienda tomar metformina en 2 ó 3 tomas al día e incrementar la dosis lentamente.

Durante el tratamiento con metformina pueden ocurrir las siguientes reacciones adversas. Las frecuencias se definen de la siguiente forma: muy frecuentes $\geq 1/10$; frecuentes $\geq 1/100$ a $<1/10$; poco frecuentes $\geq 1/1.000$ a $<1/100$; raras $\geq 1/10.000$ a $<1/1.000$; muy raras $<1/10.000$.

Las reacciones adversas se enumeran en orden decreciente de gravedad dentro de cada intervalo de frecuencia.

Trastornos del metabolismo y nutrición:

Muy raras:

Acidosis láctica (ver sección 4.4).

El uso de metformina durante periodos largos reduce la absorción y los niveles en suero de la vitamina B12. Se recomienda considerar esta etiología en pacientes que presenten anemia megaloblástica.

Trastornos del sistema nervioso:

Frecuentes: alteraciones del gusto.

Trastornos gastrointestinales:

Muy frecuentes: Trastornos gastrointestinales como náuseas, vómitos, diarreas, dolor abdominal y pérdida de apetito. Estos trastornos aparecen con mayor frecuencia durante el inicio del tratamiento y desaparecen espontáneamente en la mayoría de los casos. Para prevenirlos se recomienda administrar metformina en 2 ó 3 tomas al día, durante o después de las comidas. Un incremento lento de la dosis también contribuye a mejorar la tolerabilidad gastrointestinal.

Trastornos hepatobiliares:

Muy raras: Se han descrito casos aislados de alteración de las pruebas de la función hepática o hepatitis, que se resuelven al retirar el tratamiento con metformina.

Trastornos de la piel y del tejido subcutáneo:

Muy raras: reacciones cutáneas tales como eritema, prurito, urticaria.

Población pediátrica

En datos publicados, datos post-comercialización y en estudios clínicos controlados en una población pediátrica limitada con edades comprendidas entre 10-16 años y tratados durante 1 año, las reacciones adversas comunicadas fueron similares en naturaleza y gravedad a las observadas en adultos.

4.9 Sobredosis

No se ha observado hipoglucemia con dosis de hidrocloreto de metformina hasta 85 g, aunque en estas condiciones ha aparecido acidosis láctica. Una gran sobredosis de metformina o riesgos concomitantes pueden desembocar en acidosis láctica. La acidosis láctica es una urgencia médica y debe ser tratada en un hospital. El método más eficaz para eliminar los lactatos y la metformina es mediante hemodiálisis.

5. PROPIEDADES FARMACOLÓGICAS

5.1 Propiedades farmacodinámicas

Grupo farmacoterapéutico: Fármacos hipoglucemiantes orales. Biguanida, código ATC: A10BA02.

La metformina es una biguanida con efectos antihiperoglucemiantes, que reduce la glucosa en plasma postprandial y basal. No estimula la secreción de insulina, por lo que no provoca hipoglucemia.

La metformina actúa por medio de 3 mecanismos:

- (1) reducción de la producción hepática de glucosa mediante la inhibición de la gluconeogénesis y la glucogenólisis.
- (2) en el músculo, incrementando la sensibilidad a la insulina, mejorando la captación de glucosa periférica y su utilización.
- (3) y retraso de la absorción intestinal de la glucosa.

La metformina estimula la síntesis intracelular del glucógeno actuando sobre la glucógeno sintetasa.

La metformina incrementa la capacidad de transporte de todos los tipos de transportadores de membrana de glucosa (GLUT) conocidos hasta hoy.

En estudios clínicos, el uso de metformina se asoció a un mantenimiento del peso corporal o una ligera disminución del mismo.

En humanos, independientemente de su acción sobre la glucemia, la metformina presenta efectos favorables sobre el metabolismo lipídico. Este hecho se ha demostrado con dosis terapéuticas en estudios clínicos controlados a medio o largo plazo: la metformina reduce el colesterol total, el colesterol LDL y los niveles de triglicéridos.

Eficacia clínica:

El estudio prospectivo aleatorizado (UKPDS) ha establecido el beneficio a largo plazo de un control intensivo de la glucemia en sangre en pacientes adultos con diabetes tipo 2.

El análisis de los resultados de los pacientes con sobrepeso tratados con metformina tras el fracaso de la dieta sola, muestra:

- una reducción significativa del riesgo absoluto de complicaciones relacionadas con la diabetes en el grupo de metformina (29,8 casos/ 1.000 pacientes-año) frente la dieta sola (43,3 casos/ 1.000 pacientes-año), $p=0,0023$, y frente a los grupos de sulfonilureas combinadas y monoterapia de insulina (40,1 casos/ 1.000 pacientes-año), $p=0,0034$;

- una reducción significativa del riesgo absoluto de mortalidad relacionada con la diabetes: metformina 7,5 casos/1.000 pacientes-año, la dieta sola 12,7 sucesos/ 1.000 pacientes-año, $p=0,017$;

- una reducción significativa del riesgo absoluto de mortalidad global: metformina 13,5 casos/ 1.000 pacientes-año, frente a la dieta sola: 20,6 casos/ 1.000 pacientes-año ($p=0,011$), y frente a los grupos de sulfonilureas combinadas y monoterapia de insulina 18,9 casos/ 1.000 pacientes-año ($p=0,021$);

- una reducción significativa del riesgo absoluto de infarto de miocardio: metformina 11 casos/ 1.000 pacientes-año, sólo dieta 18 casos/ 1.000 pacientes-año ($p=0,01$)

No se han demostrado beneficios con respecto al resultado clínico cuando la metformina se utiliza como terapia de segunda línea, en combinación con una sulfonilurea.

En diabetes del tipo 1, se ha utilizado la combinación de metformina e insulina en pacientes seleccionados, pero no se han establecido formalmente los beneficios clínicos de esta combinación.

Población pediátrica

Los estudios clínicos controlados llevados a cabo en una población pediátrica limitada de edades comprendidas entre los 10 y los 16 años tratados durante 1 año, mostraron una respuesta al control glucémico parecida a la observada en adultos.

5.2 Propiedades farmacocinéticas

Absorción

Tras la administración por vía oral de un comprimido de hidrocloreuro de metformina, la concentración plasmática máxima (C_{max}) se alcanza aproximadamente en 2,5 horas (t_{max}). La biodisponibilidad absoluta de un comprimido de 500 u 850 mg de hidrocloreuro de metformina es aproximadamente del 50 al 60 % en sujetos sanos. Tras una dosis oral, la fracción no absorbida recuperada en las heces fue del 20-30 %.

Tras la administración oral, la absorción de la metformina es saturable e incompleta. Esto sugiere que la farmacocinética de la absorción de la metformina es no lineal.

Con las dosis y las posologías recomendadas de metformina, las concentraciones plasmáticas en estado estacionario se alcanzan entre las 24 y 48 horas y generalmente son inferiores a 1 microgramo/ml. En los ensayos clínicos controlados, los niveles plasmáticos máximos de metformina (C_{max}) no excedieron los 5 microgramos/ml, incluso con dosis máximas.

Los alimentos reducen y retrasan ligeramente la absorción de metformina. Tras la administración oral de un comprimido de 850 mg, se observa una disminución del pico de concentración plasmática del 40 %, una disminución del 25 % del AUC (área bajo la curva) y una prolongación de 35 minutos en el tiempo hasta alcanzar el pico de concentración plasmática. No se conoce la importancia clínica de estas observaciones.

Distribución

La fijación a las proteínas plasmáticas es despreciable. La metformina se difunde por los eritrocitos. El pico sanguíneo es menor que el pico plasmático y aparece aproximadamente al mismo tiempo. Los glóbulos

rojos representan probablemente un compartimento secundario de distribución. El volumen medio de distribución (Vd) osciló entre 63 y 276 l.

Metabolismo:

La metformina se excreta inalterada en la orina. No se han identificado metabolitos en humanos.

Eliminación

El aclaramiento renal de la metformina es > 400 ml/min, lo que indica que la metformina se elimina por filtración glomerular y por secreción tubular. Tras una dosis oral, la vida media aparente de eliminación total es de aproximadamente 6,5 horas.

En caso de que la función renal esté alterada, el aclaramiento renal disminuye proporcionalmente al de creatinina, con lo que se prolonga la vida media de eliminación, dando lugar a un aumento de los niveles de metformina en plasma.

Población pediátrica:

Estudio a dosis única: Tras una dosis única de hidrocloreto de metformina de 500 mg, la población pediátrica ha mostrado un perfil farmacocinético similar al observado en adultos sanos.

Estudio a dosis múltiples: La información se limita a un estudio. Tras dosis repetidas de 500 mg, dos veces al día durante 7 días en pacientes pediátricos, la concentración plasmática máxima (C_{max}) y la exposición sistémica (AUC_{0-t}) se redujeron aproximadamente un 33% y un 40% respectivamente en comparación a los pacientes diabéticos adultos que recibieron dosis repetidas de 500 mg, dos veces al día durante 14 días. Dado que la dosis se ajusta individualmente según un control glucémico, este hecho posee una relevancia clínica limitada.

5.3 Datos preclínicos sobre seguridad

Los datos de los estudios preclínicos no muestran riesgos especiales para los seres humanos según los estudios convencionales de seguridad, farmacología, toxicidad a dosis repetidas, genotoxicidad, potencial carcinogénico y toxicidad para la reproducción.

6 . DATOS FARMACÉUTICOS

6.1 Lista de excipientes

Núcleo del comprimido

Povidona K 30

Estearato de magnesio

Recubrimiento pelicular

Hipromelosa

6.2 Incompatibilidades

No aplicable.

6.3 Periodo de validez

5 años.

6.4 Precauciones especiales de conservación

No requiere condiciones especiales de conservación.

6.5 Naturaleza y contenido del envase

Blisteres (PVC-aluminio) con 1 (x100), 8, 9, 10, 14, 20, 21, 30, 40, 50, 56, 60, 84, 90, 100, 120, 300, 600 ó 1000 comprimidos.

Frascos de plástico (polietileno de alta densidad) con tapón a prueba de niños (polipropileno) con 30, 60, 200, 300, ó 600 comprimidos.

Puede que solamente estén comercializados algunos tamaños de envases.

6.6 Precauciones especiales de eliminación

La eliminación del medicamento no utilizado y de todos los materiales que hayan estado en contacto con él, se realizará de acuerdo con la normativa local.

7. TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACIÓN

Merck Santé s.a.s.
37 rue Saint Romain
69008 Lyon
Francia

8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN

55.211

9. FECHA DE LA PRIMERA AUTORIZACIÓN/ RENOVACIÓN DE LA AUTORIZACIÓN

Fecha de la primera autorización: Enero 1982

Fecha de la última revalidación: Enero 2008

10. FECHA DE LA REVISIÓN DEL TEXTO

Octubre 2010

ANNEX 8: HELSINKI DECLARATION



Declaración de Helsinki de la AMM - Principios éticos para las investigaciones médicas en seres humanos

Adoptada por la
18ª Asamblea Médica Mundial, Helsinki, Finlandia, junio 1964
y enmendada por la
29ª Asamblea Médica Mundial, Tokio, Japón, octubre 1975
35ª Asamblea Médica Mundial, Venecia, Italia, octubre 1983
41ª Asamblea Médica Mundial, Hong Kong, septiembre 1989
48ª Asamblea General Somerset West, Sudáfrica, octubre 1996
52ª Asamblea General, Edimburgo, Escocia, octubre 2000
Nota de Clarificación, agregada por la Asamblea General de la AMM, Washington 2002
Nota de Clarificación, agregada por la Asamblea General de la AMM, Tokio 2004
59ª Asamblea General, Seúl, Corea, octubre 2008
64ª Asamblea General, Fortaleza, Brasil, octubre 2013

Introducción

1. La Asociación Médica Mundial (AMM) ha promulgado la Declaración de Helsinki como una propuesta de principios éticos para investigación médica en seres humanos, incluida la investigación del material humano y de información identificables.

La Declaración debe ser considerada como un todo y un párrafo debe ser aplicado con consideración de todos los otros párrafos pertinentes.

2. Conforme al mandato de la AMM, la Declaración está destinada principalmente a los médicos. La AMM insta a otros involucrados en la investigación médica en seres humanos a adoptar estos principios.

Principios generales

3. La Declaración de Ginebra de la Asociación Médica Mundial vincula al médico con la fórmula "velar solícitamente y ante todo por la salud de mi paciente", y el Código Internacional de Ética Médica afirma que: "El médico debe considerar lo mejor para el paciente cuando preste atención médica".
4. El deber del médico es promover y velar por la salud, bienestar y derechos de los pacientes, incluidos los que participan en investigación médica. Los conocimientos y la conciencia del médico han de subordinarse al cumplimiento de ese deber.
5. El progreso de la medicina se basa en la investigación que, en último término, debe incluir estudios en seres humanos.
6. El propósito principal de la investigación médica en seres humanos es comprender las causas, evolución y efectos de las enfermedades y mejorar las intervenciones preventivas, diagnósticas y terapéuticas (métodos, procedimientos y tratamientos). Incluso, las mejores intervenciones probadas deben ser evaluadas continuamente a través de la investigación para que sean seguras, eficaces, efectivas, accesibles y de calidad.
7. La investigación médica está sujeta a normas éticas que sirven para promover y asegurar el respeto a todos los seres humanos y para proteger su salud y sus derechos individuales.
8. Aunque el objetivo principal de la investigación médica es generar nuevos conocimientos, este objetivo nunca debe tener primacía sobre los derechos y los intereses de la persona que participa en la investigación.
9. En la investigación médica, es deber del médico proteger la vida, la salud, la dignidad, la integridad, el derecho a la autodeterminación, la intimidad y la confidencialidad de la información personal de las personas que participan en investigación. La responsabilidad de la protección de las personas que toman parte en la investigación debe recaer siempre en un médico u otro profesional de la salud y nunca en los participantes en la investigación, aunque hayan otorgado su consentimiento.
10. Los médicos deben considerar las normas y estándares éticos, legales y jurídicos para la investigación en seres humanos en sus propios países, al igual que las normas y estándares internacionales vigentes. No se debe permitir que un requisito ético, legal o jurídico nacional o internacional disminuya o elimine cualquiera medida de protección para las personas que participan en la investigación establecida en esta

Declaración.

11. La investigación médica debe realizarse de manera que reduzca al mínimo el posible daño al medio ambiente.
12. La investigación médica en seres humanos debe ser llevada a cabo sólo por personas con la educación, formación y calificaciones científicas y éticas apropiadas. La investigación en pacientes o voluntarios sanos necesita la supervisión de un médico u otro profesional de la salud competente y calificado apropiadamente.
13. Los grupos que están subrepresentados en la investigación médica deben tener un acceso apropiado a la participación en la investigación.
14. El médico que combina la investigación médica con la atención médica debe involucrar a sus pacientes en la investigación sólo en la medida en que esto acredite un justificado valor potencial preventivo, diagnóstico o terapéutico y si el médico tiene buenas razones para creer que la participación en el estudio no afectará de manera adversa la salud de los pacientes que toman parte en la investigación.
15. Se debe asegurar compensación y tratamiento apropiados para las personas que son dañadas durante su participación en la investigación.

Riesgos, Costos y Beneficios

16. En la práctica de la medicina y de la investigación médica, la mayoría de las intervenciones implican algunos riesgos y costos.

La investigación médica en seres humanos sólo debe realizarse cuando la importancia de su objetivo es mayor que el riesgo y los costos para la persona que participa en la investigación.

17. Toda investigación médica en seres humanos debe ser precedido de una cuidadosa comparación de los riesgos y los costos para las personas y los grupos que participan en la investigación, en comparación con los beneficios previsibles para ellos y para otras personas o grupos afectados por la enfermedad que se investiga.

Se deben implementar medidas para reducir al mínimo los riesgos. Los riesgos deben ser monitoreados, evaluados y documentados continuamente por el investigador.

18. Los médicos no deben involucrarse en estudios de investigación en seres

humanos a menos de que estén seguros de que los riesgos han sido adecuadamente evaluados y de que es posible hacerles frente de manera satisfactoria.

Cuando los riesgos que implican son más importantes que los beneficios esperados o si existen pruebas concluyentes de resultados definitivos, los médicos deben evaluar si continúan, modifican o suspenden inmediatamente el estudio.

Grupos y personas vulnerables

19. Algunos grupos y personas sometidas a la investigación son particularmente vulnerables y pueden tener más posibilidades de sufrir abusos o daño adicional.

Todos los grupos y personas vulnerables deben recibir protección específica.

20. La investigación médica en un grupo vulnerable sólo se justifica si la investigación responde a las necesidades o prioridades de salud de este grupo y la investigación no puede realizarse en un grupo no vulnerable. Además, este grupo podrá beneficiarse de los conocimientos, prácticas o intervenciones derivadas de la investigación.

Requisitos científicos y protocolos de investigación

21. La investigación médica en seres humanos debe conformarse con los principios científicos generalmente aceptados y debe apoyarse en un profundo conocimiento de la bibliografía científica, en otras fuentes de información pertinentes, así como en experimentos de laboratorio correctamente realizados y en animales, cuando sea oportuno. Se debe cuidar también del bienestar de los animales utilizados en los experimentos.

22. El proyecto y el método de todo estudio en seres humanos deben describirse claramente y ser justificados en un protocolo de investigación.

El protocolo debe hacer referencia siempre a las consideraciones éticas que fueran del caso y debe indicar cómo se han considerado los principios enunciados en esta Declaración. El protocolo debe incluir información sobre financiamiento, patrocinadores, afiliaciones institucionales, posibles conflictos de interés e incentivos para las personas del estudio y la información sobre las estipulaciones para tratar o compensar a las personas que han sufrido daños como consecuencia de su participación en la investigación.

En los ensayos clínicos, el protocolo también debe describir los arreglos

apropiados para las estipulaciones después del ensayo.

Comités de ética de investigación

23. El protocolo de la investigación debe enviarse, para consideración, comentario, consejo y aprobación al comité de ética de investigación pertinente antes de comenzar el estudio. Este comité debe ser transparente en su funcionamiento, debe ser independiente del investigador, del patrocinador o de cualquier otro tipo de influencia indebida y debe estar debidamente calificado. El comité debe considerar las leyes y reglamentos vigentes en el país donde se realiza la investigación, como también las normas internacionales vigentes, pero no se debe permitir que éstas disminuyan o eliminen ninguna de las protecciones para las personas que participan en la investigación establecidas en esta Declaración.

El comité tiene el derecho de controlar los ensayos en curso. El investigador tiene la obligación de proporcionar información del control al comité, en especial sobre todo incidente adverso grave. No se debe hacer ninguna enmienda en el protocolo sin la consideración y aprobación del comité. Después que termine el estudio, los investigadores deben presentar un informe final al comité con un resumen de los resultados y conclusiones del estudio.

Privacidad y confidencialidad

24. Deben tomarse toda clase de precauciones para resguardar la intimidad de la persona que participa en la investigación y la confidencialidad de su información personal.

Consentimiento informado

25. La participación de personas capaces de dar su consentimiento informado en la investigación médica debe ser voluntaria. Aunque puede ser apropiado consultar a familiares o líderes de la comunidad, ninguna persona capaz de dar su consentimiento informado debe ser incluida en un estudio, a menos que ella acepte libremente.

26. En la investigación médica en seres humanos capaces de dar su consentimiento informado, cada participante potencial debe recibir información adecuada acerca de los objetivos, métodos, fuentes de financiamiento, posibles conflictos de intereses, afiliaciones institucionales del investigador, beneficios calculados, riesgos previsibles e incomodidades derivadas del experimento, estipulaciones post estudio y todo otro aspecto pertinente de la investigación. El

participante potencial debe ser informado del derecho de participar o no en la investigación y de retirar su consentimiento en cualquier momento, sin exponerse a represalias. Se debe prestar especial atención a las necesidades específicas de información de cada participante potencial, como también a los métodos utilizados para entregar la información.

Después de asegurarse de que el individuo ha comprendido la información, el médico u otra persona calificada apropiadamente debe pedir entonces, preferiblemente por escrito, el consentimiento informado y voluntario de la persona. Si el consentimiento no se puede otorgar por escrito, el proceso para lograrlo debe ser documentado y atestado formalmente.

Todas las personas que participan en la investigación médica deben tener la opción de ser informadas sobre los resultados generales del estudio.

27. Al pedir el consentimiento informado para la participación en la investigación, el médico debe poner especial cuidado cuando el participante potencial está vinculado con él por una relación de dependencia o si consiente bajo presión. En una situación así, el consentimiento informado debe ser pedido por una persona calificada adecuadamente y que nada tenga que ver con aquella relación.

28. Cuando el participante potencial sea incapaz de dar su consentimiento informado, el médico debe pedir el consentimiento informado del representante legal. Estas personas no deben ser incluidas en la investigación que no tenga posibilidades de beneficio para ellas, a menos que ésta tenga como objetivo promover la salud del grupo representado por el participante potencial y esta investigación no puede realizarse en personas capaces de dar su consentimiento informado y la investigación implica sólo un riesgo y costo mínimos.

29. Si un participante potencial que toma parte en la investigación considerado incapaz de dar su consentimiento informado es capaz de dar su asentimiento a participar o no en la investigación, el médico debe pedirlo, además del consentimiento del representante legal. El desacuerdo del participante potencial debe ser respetado.

30. La investigación en individuos que no son capaces física o mentalmente de otorgar consentimiento, por ejemplo los pacientes inconscientes, se puede realizar sólo si la condición física/mental que impide otorgar el consentimiento informado es una característica necesaria del grupo investigado. En estas circunstancias, el médico debe pedir el consentimiento informado al representante legal. Si dicho representante no está disponible y si no se puede retrasar la investigación, el estudio puede llevarse

a cabo sin consentimiento informado, siempre que las razones específicas para incluir a individuos con una enfermedad que no les permite otorgar consentimiento informado hayan sido estipuladas en el protocolo de la investigación y el estudio haya sido aprobado por un comité de ética de investigación. El consentimiento para mantenerse en la investigación debe obtenerse a la brevedad posible del individuo o de un representante legal.

31. El médico debe informar cabalmente al paciente los aspectos de la atención que tienen relación con la investigación. La negativa del paciente a participar en una investigación o su decisión de retirarse nunca debe afectar de manera adversa la relación médico-paciente.

32. Para la investigación médica en que se utilice material o datos humanos identificables, como la investigación sobre material o datos contenidos en biobancos o depósitos similares, el médico debe pedir el consentimiento informado para la recolección, almacenamiento y reutilización. Podrá haber situaciones excepcionales en las que será imposible o impracticable obtener el consentimiento para dicha investigación. En esta situación, la investigación sólo puede ser realizada después de ser considerada y aprobada por un comité de ética de investigación.

Uso del placebo

33. Los posibles beneficios, riesgos, costos y eficacia de toda intervención nueva deben ser evaluados mediante su comparación con las mejores intervenciones probadas, excepto en las siguientes circunstancias:

 Cuando no existe una intervención probada, el uso de un placebo, o ninguna intervención, es aceptable; o

 cuando por razones metodológicas científicamente sólidas y convincentes, sea necesario para determinar la eficacia y la seguridad de una intervención el uso de cualquier intervención menos eficaz que la mejor probada, el uso de un placebo o ninguna intervención.

 Los pacientes que reciben cualquier intervención menos eficaz que la mejor probada, el placebo o ninguna intervención, no correrán riesgos adicionales de daño grave o irreversible como consecuencia de no recibir la mejor intervención probada.

 Se debe tener muchísimo cuidado para evitar abusar de esta opción.

Estipulaciones post ensayo

34. Antes del ensayo clínico, los auspiciadores, investigadores y los gobiernos de los países anfitriones deben prever el acceso post ensayo a todos los participantes que todavía necesitan una intervención que ha sido identificada como beneficiosa en el ensayo. Esta información también se debe proporcionar a los participantes durante el proceso del consentimiento informado.

Inscripción y publicación de la investigación y difusión de resultados

35. Todo estudio de investigación con seres humanos debe ser inscrito en una base de datos disponible al público antes de aceptar a la primera persona.

36. Los investigadores, autores, auspiciadores, directores y editores todos tienen obligaciones éticas con respecto a la publicación y difusión de los resultados de su investigación. Los investigadores tienen el deber de tener a la disposición del público los resultados de su investigación en seres humanos y son responsables de la integridad y exactitud de sus informes. Todas las partes deben aceptar las normas éticas de entrega de información. Se deben publicar tanto los resultados negativos e inconclusos como los positivos o de lo contrario deben estar a la disposición del público. En la publicación se debe citar la fuente de financiamiento, afiliaciones institucionales y conflictos de intereses. Los informes sobre investigaciones que no se ciñan a los principios descritos en esta Declaración no deben ser aceptados para su publicación.

Intervenciones no probadas en la práctica clínica

37. Cuando en la atención de un enfermo las intervenciones probadas no existen u otras intervenciones conocidas han resultado ineficaces, el médico, después de pedir consejo de experto, con el consentimiento informado del paciente o de un representante legal autorizado, puede permitirse usar intervenciones no comprobadas, si, a su juicio, ello da alguna esperanza de salvar la vida, restituir la salud o aliviar el sufrimiento. Tales intervenciones deben ser investigadas posteriormente a fin de evaluar su seguridad y eficacia. En todos los casos, esa información nueva debe ser registrada y, cuando sea oportuno, puesta a disposición del público.

****Los párrafos 26, 27, 28 y 29 han sido revisados editorialmente por el Secretariado de la AMM el 5 de mayo de 2015.***