Hypogonadism hypergonadotrophic

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ABSTRACT

SM, 42 years old, from Montevideo, lives in the REMAR community due to homelessness and substance use. 6 years ago in abstinence. Schooling: Complete UTU gastronomy orientation. He currently works in a bakery. Reason for consultation: Follow-up of a patient with hypogonadism receiving intramuscular Testoviron. Consultation due to the persistence of a small penis since childhood, he does not know how to specify his age. Concomitantly, it is highlighted that facial hair appears at the age of 21, maintains a low frequency of shaving and at the level of the chest, pubis and armpit it is decreased. Apocrine odor present, fine voice, preserved muscle mass.

Consultation in ASSE primary health care polyclinic in general medicine due to this symptomatology and referral to endocrinology of the aforementioned health center. Hypogonadism is diagnosed and treatment with Testoviron I.M. is started, to continue clinical, paraclinical and therapeutic controls, with the endocrinology and metabolism clinic of the hospital de clinicas.

Key Words: Hypogonadism; Testoviron; Endocrinology; Clinical; Paraclinical

INTRODUCTION

Patronymical record

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Current illness

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Today the patient receives testoviron 250 I.M every 28 days, well tolerated since August 2018. Symptoms improved, so testoviron was started. No adverse effects due to treatment, such as increased breast size, no pain at the injection site, reactions skin allergies. Denies trauma, and testicular torsion. He denies testicular cancer. No polychemotherapy, not radiotherapy, not drugs [2].

He does not recall the age at which he began having sexual intercourse, he currently refers to having them sporadically, he denies a decrease in libido, he refers to an erection and ejaculation. Had a partner, reports spontaneous abortion. A study of sterility that denies is investigated [3].

CASE PRESENTATION

Personal history

A smoker since the age of 21, he does not know how to specify the number of cigarettes. Alcoholist of the same evolution time, generally wine, daily, 1 liter. At the age of 25, he started using marijuana, cocaine, base paste. He denies having been an intravenous drug user. He abandoned problematic consumption at the age of 33 by his own decision. not diabetic Not hypertensive. Dyslipidemia in dietary hygienic treatment. Right ear hearing loss. Tuberculosis (which location? Pulmonary? Peritoneal? Adrenal?.) at the age of 36, he completed treatment with CHLA. He denies Sexually Transmitted Infections. Cholecystectomy (the indication of the cholecystectomy?) at age 28. Receives vitamin D 1000 U per day, good dairy intake, no falls, no fragility fractures [4].

Family background

He does not know them, given that at the age of 5 he goes on to live in the INAME home until he is 17 years old. From there he began to study at UTU.

RESULTS AND DISCUSSION

Physical exam

Anthropometric data: Weight 53.5 Kg, height 162 cm. BMI 20.3 kgm^2. According to the WHO classification, this BMI corresponds to normal weight. BP 110/70 mmHg.

You don't dysmorphia.

Biotype: Normoline, android distribution of fat

P and M: Lucid, sparse facial hair of androgen dependent distribution, sparse.

Chest: Both breasts are symmetrical, no tumors are palpable, no galactorrhea.

Neck: Centered visceral axis, skin without lesions, thyroid gland not seen or palpated, no lymph nodes palpated.

CV: RR of 85 cpm, well beaten noises, free rests

PP: Eupneic, mav present bilaterally, no rales.

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Abdomen: Soft, depressible, painless, no visceromegaly

Genital exam: On inspection Male genitalia external, thin skin, wrinkled, dark pigmentation, no varicocele on palpation, testes in bags, firm consistency of 4 cc each (Did you use Prader orchidometer?). Penis with dorsal vein. Erection length 7 cm approx. (reported by the patient). And which size without erection?

Confrontation visual field: Normal

Bone pole increased dorsal kyphosis, with decreased height, no bone pain.

ANALYSIS

Positive diagnosis

Given that he has a small penis, defined as one that measures 7 and 11 cm in erection, since childhood and secondary sexual characteristics of late appearance such as facial hair that appears at age 21, with low frequency of shaving, hair at the level of thorax pubis and decreased armpit, we make a clinical diagnosis of hypogonadism, which we will confirm with biochemistry [5].

Since he presents total testosterone values of 192.2 ng/dl with calculated free testosterone of 0.14, the diagnosis is confirmed (Table 1) [6].

Table 1: Para-clinical for confirmation of the positive diagnosis.

	1. 2018	7. 2018	10. 2018 PEAK
Total Testosterone (NV 249.0 to 836.0 ng/dl)	-	192.2 ng dl	515.2 ng dl
free testosterone			
sex steroid transporter protein (VN 16.5 to 55.9 nmol/l)	-	27.7 nmol l	27.6 nmol l
Calculated Free Testosterone (VN 0.20 to 0.62 nmol l)	-	0.14 nmol l	0.42 nmol l
Calculated Bioavailable Testosterone (VN 4.36 to 14.30 nmol l)	-	3.28 nmol l	9.83 nmol l

Male hypogonadism is defined as the set of functional and psychological signs related to a lack of testicular androgens. To this clinical definition is added another one of hormonal type that consists of a decrease in circulating testosterone. Testosterone is a hormone that affects many body tissues, its effects are the appearance and maintenance of secondary sexual characteristics, such as growth of body hair with androgen dependent distribution, increased bone mass density and stimulation of peak bone mass, increased of skeletal muscle mass and strength, erythropoiesis, prostate and seminal vesicle growth, and libido stimulation. Two the clinical features of male hypogonadism depend on the age of onset, severity of testosterone deficiency, and whether or not there is a decline in one or both functions of the testis, sperm production, and testosterone production. In the adult, when testosterone deficiency occurs after puberty is complete, symptoms can include decreased energy, libido, for days to weeks. Androgen dependent body hair, muscle mass, and bone mineral density usually do not decrease significantly for several years, although profound deficiency can cause rapid decline. The development of hypogonadism prior to the onset of puberty determines small testes, less than 20 cc, and a small penis, less than 8 cm. 10

It should be noted that testosterone levels exhibit biological and assay variability. Total testosterone concentrations are affected by alterations in SHBG, and testosterone levels may be transiently suppressed by disease, certain drugs, and certain nutritional deficiencies.

Testosterone has biological and assay variability, a single measurement is not a reliable indicator of an individual's average concentration. Serum testosterone concentrations exhibit ultradian and circadian variations [7].

The ultradian variation is characterized by peaks of increased amplitude that reach approximately 240 ng dl with duration of 95 minutes, other chaotic peaks of lesser amplitude have been reported. Circadian variation consists of testosterone peaks around 8 am and has a maximum average excursion of 140 ng dl. In young men the lowest levels are recorded between 4 and 8 pm.

Classically, hypogonadism is divided into primary and secondary, depending on whether testicular function is affected primarily or secondarily to a hypothalamus pituitary alteration. Clinically, it manifests itself according to the biological moment in which testicular insufficiency occurs: prenatal, during sexual differentiation, puberty, and in adulthood when the testicle assumes the definitive production of testosterone and spermatozoa, expressed by incomplete sexual development, lack of sexual interest, reduced spontaneous erections, gynecomastia, infertility, loss of height, history of fractures to minimal trauma, hot flashes, reduced frequency of shaving. Depending on the age and intensity of the alteration in testosterone secretion and sperm production, the clinical presentation of hypogonadism varies. The diagnosis can be made in the neonatal period due to ambiguous genitalia, micropenis, cryptorchidism or hypospadias, in adolescents, due to delayed puberty, in adults, due to sexual problems, regression of sexual characteristics or infertility [8].

ETIOLOGYDIAGNOSIS

Etiology of male hypogondism Genetic

alterations in the gonadotropin receptor

- LH receptor hypofunction
- FSH receptor hypofunction
- Carbohydrate Deficient Glycoprotein Syndrome
- Mutations in the FSH and LH receptors. They are very rare. LH receptor mutations cause a female phenotype in severe forms and ambiguity at birth or micropenis and hypogonadism in adulthood in partial forms. FSH inactivating mutations predominantly affect the exocrine testis. Twenty one
- Chromosomal abnormalities
- Klinefelter syndrome,
- Down's syndrome
- Noonan syndrome

- Genetic alterations that lead to alterations in sexual differentiation.
- Genetic defects in adrenal and testicular sex steroid biosynthesis.
- Syndrome of total or partial resistance to androgens.
- anorchia,
- Chronic diseases
- Sickle cell anemia
- myotonic dystrophy
- Cystic fibrosis
- Renal insufficiency
- Spinal cord injury
- autoimmune thyroid disease
- Mellitus diabetes
- Neoplasms
- Infections:
- Idiopathic
- Chemotherapy and testicular irradiation
- Traumatism and testicular torsion, medications (Table 2).

Table 2: In the etiological evaluation of the patient's CP, LH, FSH of 07 and 10 of 2018.

LH	30.4 Mu MI	34.6 Mu MI
(VN 20 to 70 years: 1.7 to 8.6 mU/ml).		
FSH	68 mUmL	65.2 mUmL
(VN 20 to 70 years: 1.5 to 12.4 mU/ml).		

From this para-clinical, I know that it is a primary or hypergonatropic hypogonadism.

Regarding the analysis of the most likely etiology in this patient

Klinefelter syndrome is the most frequent cause of hypogonadism in men, it appears in 1:500 to 1:1000 male live newborns. Its most frequent karyotype is 47, XXY in 93% of cases, but others can be found such as: 46, XY 47, XXY 48, XXXY 48, XXYY 49, XXXXY. The mechanism by which the 47 XXY karyotype is produced is nondisjunction in the first meiotic division in one of the parents. Advanced maternal age is a risk factor for nondisjunction. It is not known why an extra X chromosome causes fertility. In these patients, testicular histology shows hyalinization of the seminiferous tubules and absence of spermatogenesis. If it is a mosaic, at puberty the testicle may have a normal size and spermatogenesis, but later degeneration and hyalinization occurs. Two in adults, the most prominent clinical manifestations consistent with KS are testes less than 4 cc in volume. They present infertility and azoospermia. Other manifestations are different degrees of androgen deficiency, eunuchoidism. Disproportionate growth, gynecomastia in 50 to 80%. Difficulty in learning occurs in 70%. Taurodontism most mosaic KS men have fewer clinical manifestations, and those with more than two X chromosomes have severe manifestations and a high incidence of intellectual disability, hypospadias, cryptorchidism, gynecomastia, and an approximately 20 fold increased risk of breast cancer, with compared to normal men. They present an increased risk of mitral valve prolapse, venous pathology of the lower limbs. The diagnosis of KS is confirmed by karyotyping, which is performed on a culture of peripheral blood lymphocytes. Occasionally, karyotyping can be performed on cultured skin fibroblasts and testicular tissue if mosaicism is suspected [9,10].

Patient karyotype

On 11.23.18 a sample is taken for karyotype, which is sent to the department of genetics according to protocol

- Cytogenetic report
- Date of reception of the sample: 23.11.18
- **Material:** Peripheral blood

20 metaphases were analyzed, which presented a single and normal chromosomal line 46 XY, without objective structural alterations with the resolution level used. In short: 46 XY.

I request the karyotype to confirm or rule out chromosomal abnormalities, and to make a differential diagnosis, the most important being Klinefelter's syndrome, who's most frequent chromosomal abnormality is 47, XXY, so I rule it out.

Anorchia was ruled out by physical examination, testes present in scrotum. About cystic fibrosis, 95% of men are not fertile, due to azoospermia due to bilateral congenital absence of the vas deferens; it may be the only manifestation of the disease with a negative sweat test. In postpubertal males, evaluation includes urogenital ultrasonography and semen analysis. Due to lack of suggestive symptoms, it is ruled out.

Neoplasms: no antecedents due to clinical history.

The infections that we can mention involved are: HIV, mumps, leprosy. He denied STIs in the anamnesis.

He has no history of chemotherapy or testicular irradiation.

Regarding trauma and testicular torsion, absence of these two situations according to the anamnesis. In the first case, the trauma generates severe damage to the seminiferous tubules and Leydig cells, and in the latter, it is the twisting of the spermatic cord itself that results in acute ischemia of the testis.

Of the drugs that can be considered a cause of hypogonadism, some are: valproic acid, finitima, corticosteroids, verapamil, anabolic steroids, spironolactone, digoxin, ketoconazole, carbamazepine. 6 Due to decreased plasma levels of testosterone or its synthesis. None is mentioned in the clinical history.

Anosmia or hyposmia suggest Kallman syndrome 10, I rule it out due to the absence of symptoms, and the paraclinical tests distance it given that I clinically and paraclinically rule out all possible etiological approaches, I conclude that the primary testicular damage could be attributed to substance use.

A review of 18 studies 7 shows that smokers are 1.5 times more likely to suffer from erectile dysfunction than non-smokers. Physiological effects of marijuana in men include decreased secretion of sex hormones, with decreased secretion of testosterone and decreased number and motility of sperm, and the presence of increased numbers of abnormal sperm. It also decreases sexual desire and causes erectile dysfunction [11-15].

Etiopathogenic and physiopathological diagnosis

Opioids and cocaine are considered the main drugs of abuse, both with a potential effect on the hypothalamus pituitary adrenal and gonadal axes. The consequences of the changes are not clear. Affecting mood, stress, cognitive status, and energy, or enhancing depression [16].

Illegal drug use can be a major cause of infertility and includes the use of anabolic steroids, marijuana, narcotic opioids, cocaine, and methamphetamine. They have been reported to have adverse effects on the hypothalamic pituitary testicular axis, spermatogenesis, and testicular structure. Our patient reports consumption of marijuana and cocaine in the past, about these drugs of abuse, data from the national survey of drug.

Use and Health (NSDUH) of the United States are known, which reports strong evidence of drug use among those men who consult for infertility. Among men in the age groups 26 to 34 years, 35 to 49 years, and 50 years and older, past drug use was 24.6%, 14.5%, and 7.8%, respectively [17].

Regarding marijuana, studies conclude that the component delta 9-tetrahydrocannabinol, THC, negatively affects male reproductive physiology. Alterations in the hypothalamic pituitary testicular axis are observed, obtaining low levels of LH. When testosterone levels are investigated in chronic and exclusively marijuana smokers, the findings are compatible with low levels of it, and that they are dose dependent on consumption. Kolodny et al found that they have oligospermia, with decreased LH levels, which in turn decreases testosterone and spermatogenesis [18].

With regard to cocaine, the lack of prospective studies stands out. Bracken et al, in 1990, reported some interesting results, intervening on patients attending a Yale fertility clinic. Men with sperm counts less than 20 million per milliliter had used cocaine in the previous 2 years than those who did not. The bibliography consulted showed that acute exposure to cocaine is associated with dysregulation of the gonadal axis, with increases in LH of uncertain significance.

Paraclinical to assess the repercussions of hypogonadism or lesion association on 8.24.2018.

Bone densitometry

Vertebral Column L_1 L_4 Z 0.5. T-score: -0.5

Femoral neck Z-1,2. T-score: -2.1

Made with 42 years, The Z score is reported, which expresses the difference between the BMD values of the patient with a pattern of the same age and sex group, and which has the utility that it should be the pattern used in men under 50 years of age. The ISCD recommends a Z score of ≤-2.0 is defined as below the expected range for age and a Z score ≥-2.0 within the expected range for age. In patients with hypogonadism, both the Z and the T score are assessed, In this case it is normal (Table 3).

Table 3: Paraclinic for lesional associations.

TSH VN 0.27 to 4.20 Uui ML	5.68 Uui ML	2.62 Uui ML
FT_4 NV 0.93 to 1.70 ng dl	1.40 ng dl	1.21 ng dl
Normal PSA less than or equal to 4		0.26 ng ml
blood glucose	0.86 mg dl	
Creatininemia	0.53 mg dl	
glomerular filtration	Greater than 60 thousand min	
Vitamin D		29 ng ml
TGO	29 IU L	
TGP	29 IU L	
Cabbage Total	236 mg/dl	
HDL	63 mg/dl	
TGD	99 mg/dl	
red blood cells		4.83
Hb		12.7
PLT		266
LEU		5.37

The association of lesions with other comorbidities and hypergonadotropic hypogonadism is well known.

- Neoplastic prostatic pathology, for which PSA must be requested at the beginning of the substitution treatment that we will explain in the treatment item.
- Decreased bone mineral density. It is essential to know if you have had falls, fractures, use of corticosteroids in prolonged treatments. The patient has vitamin D insufficiency, we ask for dosage and he supplements with 2000 IU daily. Request bone densitometry.
- Anemia, for which we requested a complete blood count.
- Presents dyslipidemia in hygienic dietary treatment, a control lipid profile is requested
- Assessment of the thyroid pole, with thyroid profile.

Treatment

It is aimed at correcting androgen deficiency, development of secondary sexual characteristics, muscle mass and strength, energy and motivation. With low total or free testosterone levels, they should receive testosterone replacement.

Symptoms and signs of androgen deficiency should be evaluated before the start of testosterone treatment, 3 to 6 months after the start, and yearly thereafter. After 3 to 6 months, most patients experience improvements in libido, sexual function and activity, energy, vitality, motivation, and sense of humor. Increases in body hair growth, muscle mass and strength, and bone mineral density occur progressively over months to years of testosterone therapy. The patient has expressed in the consultations as in the telephone interview that, since he started treatment in August 2018, he has not noticed the aforementioned changes, until now with the same dose.

A parenteral formulation of testosterone esters is used, such as testosterone enanthate I.M which, in adults, its dosage is 150 to 200 mg I.M. every 2 weeks. Its advantage is widespread use, low cost if the patient self-administers it, and flexibility in dosage. Cons, I.M management, discomfort. Symptomatic fluctuation of testosterone levels, which may be supraphysiological after injection to low normal or low prior to administration.

- It is a long acting testosterone ester, whose route of administration is I.M. Effective, safe, practical preparations and not very expensive.

- Following I.M administration, testosterone esters are released from the vehicle within muscle tissue, resulting in a high peak serum testosterone with extended release duration.
- The starting dose is 150 to 200 mg I.M every 2 weeks. Following administration, serum levels rise above the normal range for 1 to 3 days and then gradually decline over 2 weeks to or below the normal range. These extreme changes in nadir testosterone levels can cause fluctuations in energy, mood, and libido, which can be resolved by lowering the dose interval to 10 days, and to 150 mg.
- The patient received 250 mg of I.M testosterone enanthate, which he has received correctly, every 28 days, going to the polyclinic, being administered by nursing staff.

Risks and adverse effects

Contraindications and precautions: Contraindicated in metastatic prostate cancer, since the administration of testosterone can stimulate the growth of this androgen dependent neoplasm, worsens bone pain and compression of the spine. A digital rectal exam and prior PSA should always be performed, since, on evaluation, if any of the following, such as a physical exam that reveals nodules or induration, or PSA values consistently elevated greater than 4 ng dl.

Breast cancer, exceptional, is also a contraindication, since the conversion of testosterone to estradiol can stimulate ER positive breast cancer.

Relative contraindications

- Untreated sleep apnea
- Hematocrit in the high normal range, e.g. greater than 50 or near the level, given testosterone induced stimulation of erythropoiesis, results in erythrocytosis, and potentially hyperviscosity and vascular complications.
- Edema due to retention

Lower urinary tract symptoms due to benign prostatic hypertrophy, in men with a score greater than 19.

The patient refers and the examination shows that the treatment is not effective, although to date, it is free of adverse effects.

Follow Up para-clinic

Given that he has a cause of hypergonatropic hypogonadism that caused irreversible damage to gonadal tissue, although he has good adherence to treatment with testosterone enanthate IM every 28 days, and understands the importance of attending controls, he is not able to attend the laboratory on the dates agreed for the testosterone extractions, which makes it difficult to monitor them in the polyclinic due to the length of the consultations, in order to be able to objectify the evolutionary clinical changes.

Clinical response to testoviron treatment and serum testosterone levels are used to monitor therapy. Symptoms and signs of androgen deficiency are monitored prior to initiation of treatment, then 3 to 6 months after initiation, and yearly. It is expected that at 3 to 6 months, most men with hypogonadism experience improvements in libido, sexual activity and function, energy, vitality, motivation and mood, characteristics that did not improve in the patient analyzed. Serum testosterone concentrations are monitored to avoid under or over replacement. Testosterone concentrations should be measured at 3 to 6 months of treatment, between 2 injections. Serum Testosterone can be measured at the nadir of an interval, that is, before the next administration, or at the peak, midpoint between 2 administrations, it is expected to find low normal levels of testosterone and high normal levels, respectively.

CONCLUSION

Immediate vital prognosis

In the immediate term it is good, there is no condition that increases mortality.

Distant vital prognosis: Hypogonadism determines a higher cardiovascular risk. Low levels of testosterone are associated with diabetes mellitus, kidney failure, high blood pressure, and dyslipidemia. Testosterone correlates positively with HDL cholesterol levels and negatively with LDL cholesterol levels and pro-inflammatory state. Epidemiological studies have shown that low testosterone levels are associated with atherosclerosis, coronary and cardiovascular disease. A profile of metabolic syndrome, insulin resistance, diabetes mellitus, high BMI is described. Visceral fat present in central obesity, which includes omental, mesenteric and retroperitoneal tissue, is currently recognized as the most prevalent manifestation of MS, identified as an increased abdominal perimeter and is the one most associated with type 2 diabetes and cardiovascular risk factors. The amount of visceral adipose tissue is inversely associated with plasma testosterone levels. Prospective epidemiological studies show that both hypogonadism is a predictor of an increased risk of developing MS and DM_2, and that the presence of MS is a risk factor for developing hypogonadism. A pathophysiological explanation for the decrease in androgens secondary to obesity would be that adipose tissue expresses numerous enzymes capable of modifying steroids, such as aromatase, which catalyzes the conversion of testosterone to estradiol and androstenedione to estrone.

New research further suggests that aldoketoreductase 1C family enzymes are highly active in visceral and subcutaneous fat tissue and can inactivate dihydrotestosterone (DHT), the most potent androgen, especially in mature adipocytes. These studies support the hypothesis that the greater the total body fat, the greater the conversion of androgens to estrogens and the greater the inactivation of DHT, which would favor the development of hypogonadism described in obese subjects.

Although central male obesity is associated with low total testosterone, the degree of obesity, measured by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI), is inversely associated with levels of hepatic sex Steroid Binding Globulin (SHBG), which is at least partially explained by insulin resistance that decreases SHBG 2. The coexistence of low values of both testosterone and SHBG would explain why free testosterone remains in the low normal range and why only a fraction of obese men present symptoms or categorical signs of hypogonadism.

Functional prognosis: compromised in the reproductive and eventually in the risk of having bone fractures.

With regard to reproduction: infertility is defined as, after a year of intercourse without taking protective measures, no pregnancy is achieved, it affects approximately 15% of couples. The importance of the male factor as a cause of infertility can reach 50% of all consultations. Primary testicular failure and other endocrine disturbances may be possible etiologies.

In the study by Enzo Devoto et al. on endocrine causes of factors that contribute to male infertility, he found gonadotoxins as testicular causal factors in fourth place, agents in which contact may be due to iatrogeny, drug abuse, environmental or occupational toxins, the latter could be suspected in 3 patients; one in contact with pesticides and two that manipulated estrogens. In the 3 cases, the exposure lasted for years, without respecting protection measures. Alcohol was the most frequent gonadotoxin, followed by cancer therapies; of 8 alcoholic patients, 2 normalized the spermiogram, post antialcoholic therapy this study and more than 6 months of abstinence. The 7 patients who correspond to testicular alteration due to chemotherapy and radiotherapy, consulted in the last 5 years of the period of this study.

We also highlight the increased risk of fractures. He now has a normal DXA. A head if it is not replaced with testosterone, if it can alter and greater than the decline in testosterone levels, there is a decrease in muscle strength, given the low physical activity, decreased bone mineral density and high risk of osteoporosis and fractures. The correlation between bone mineral density and the role of testosterone is not entirely clear. A number of observational studies have been conducted on the potential risk of osteoporotic fracture in men. One of them is the largest, osteoporotic fractures in men study MrOS. This study followed a large cohort of men, average age 65 years, for an average of 4.5 years. The first results showed that testosterone levels are positively related to BMD of the hip and fist, but of the lumbar spine. Low testosterone levels were associated with an

increased risk of fracture. Testosterone has a clear effect on bone, by stimulating osteoblasts and maintaining osteocytes to prevent loss of trabecular bone. It has an indirect effect by aromatization of estrogens *via* aromatase.

Summary

- Young adult, 42 years old, male
- Former user of drugs of abuse, in abstinence for 7 years.
- With a history of tuberculosis
- Derived from ASSE peripheral polyclinic, due to primary hypogonadism, given by low testosterone levels and high LH and FSH levels, which started treatment with Testosterone Enanthant 250 mg IM, in August 2018, every 28 days, which complies, although he does not attend the dates agreed for biochemical follow up.
- After ruling out the main causes of hypergonadotrophic hypogonadism, clinical and paraclinical, congenital and acquired, with Klinefelter syndrome being the most important, it is concluded that substance use is the etiological diagnosis.

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