

# Evaluation of late-onset hypogonadism (andropause) treatment using three different formulations of injectable testosterone

Avaliação do tratamento de pacientes hipogonádicos tardios (andropausa) usando três formulações diferentes de testosterona injetável

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## ABSTRACT

**Objective:** To compare the modalities of treatment for male hypogonadism available in Brazil. **Methods:** Thirty-two men with late-onset hypogonadism (“andropause”) were followed-up in the Hospital de Guaranição de Florianópolis, in Florianópolis, south Brazil. Clinical diagnosis was established according to AMS questionnaire (positive if equal to or higher than 27 points), and laboratorial diagnosis was made through low values of total testosterone (under 300 ng/dL) and/or free calculated testosterone (under 6.5 ng/dL). Patients were randomized to three non-enteral treatment groups (Deposteron® – 11 patients; Durateston® – 11 patients; and Nebido® – 10 patients). **Results:** Clinically, Nebido® seemed to be superior when compared to Deposteron® (mean value of improvement percentage;  $p = 0.03$ ) and when compared to Durateston® (post-treatment average AMS score;  $p = 0.03$ ). According to laboratorial analysis, Nebido® showed higher testosterone levels than Deposteron® and Durateston® ( $p < 0.001$ ). **Conclusions:** All non-enteral testosterone formulas available in the Brazilian market are efficient in raising testosterone levels and in clinical improvement of hypogonadal patients. Nebido® showed both a better clinical and laboratorial effectiveness. *Arq Bras Endocrinol Metab.* 2009;53(8):989-96

## Keywords

Hypogonadism; military personnel; testosterone; treatment

## RESUMO

**Objetivo:** Comparar os tratamentos para hipogonadismo masculino disponíveis no Brasil. **Métodos:** Foram selecionados 32 homens com hipogonadismo tardio (“andropausa”) no Hospital de Guaranição de Florianópolis. O diagnóstico foi feito por meio do questionário AMS (acima de 27 pontos) e dos níveis diminuídos de testosterona total dosada (abaixo de 300 ng/dL) e/ou testosterona livre calculada (abaixo de 6,5 ng/dL). Os pacientes foram divididos em três grupos de tratamento parenteral (Deposteron® – 11 pacientes; Durateston® – 11 pacientes; Nebido® – 10 pacientes). **Resultados:** Clinicamente, o tratamento com Nebido® mostrou-se superior ao tratamento com Deposteron® (média do percentual de melhora;  $p = 0,03$ ) e ao Durateston® (média do questionário AMS pós-tratamento;  $p = 0,03$ ). Laboratorialmente, o tratamento com Nebido® mostrou níveis de testosterona superiores ao Deposteron® e Durateston® ( $p < 0,001$ ). **Conclusões:** As três formulações de testosterona parenteral existentes no mercado brasileiro são eficientes em elevar os níveis de testosterona e melhorar clinicamente pacientes hipogonádicos, sendo o Nebido® mais efetivo clínica e laboratorialmente. *Arq Bras Endocrinol Metab.* 2009;53(8):989-96.

## Descritores

Hipogonadismo; militares; testosterona; tratamento

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## INTRODUCTION

Nowadays, it is usual to refer to the decline of sexual hormone levels in males as andropause. However, this designation is inappropriate, since not all men show clinical or laboratorial changes, which is not a sudden event, but part of the aging process (1). A much more correct designation for such affection is partial androgen deficiency of the aging male (PADAM) or late-onset hypogonadism (LOH).

By the age of 40, men experience an annual decrease of 1.2% in the circulating levels of free testosterone (FT) and of 1% in albumin-bound testosterone (these two represent the bioavailable testosterone – BT). Furthermore, there is a 1.2% annual increase in sexual hormone-binding globulin (SHBG) (2,3), a highly stable testosterone carrier, which makes it unavailable for the tissues. Although total testosterone (TT) maintains its levels until 55 years old (when it begins decreasing at an annual rate of 0.4% to 0.85%) (4), it is clear that men suffer a decrease in BT after their forties.

Diagnosing LOH is really challenging, since it has no pathognomonic signs or symptoms and, for a long time, there were no cut-off points established for the laboratorial tests (5). Moreover, LOH clinical findings may be easily related to a series of other hormonal affections or even to the physiologic process of aging (1). One of its most common symptoms, erectile dysfunction, may be found in over 40% of men aged 50-80, according to the Massachusetts Male Aging Study (MMAS) (3,6).

The clinical evaluation of patients evolved when self-applied questionnaires were developed. The ADAM questionnaire, developed by the Saint Louis University, observed ten symptoms commonly found in men with low BT. The questionnaire of the Massachusetts Male Aging Study (MMAS) evaluates eight topics and may be used as a screening test for males to seek medical care (7), while the aging male symptoms (AMS) questionnaire, designed and validated in fourteen countries, can be used not only to evaluate aging symptoms, but also for hormonal treatment follow-up. The latter questionnaire consists of 17 questions, rated from 1 to 5, and defines a score in a range of 17 to 85. It is considered positive when equal to or higher than 27 (8).

As for the laboratorial findings, TT dosages not only are not enough for the diagnosis, but also can be misleading, since the reference values vary. Furthermore, men can have a normal TT level and, if associated with a high SHBG level, present a subnormal FT level.

FT levels may be established either by laboratorial tests or by an equation (Vermeulen's formula), which takes TT and SHBG levels as well as albumin levels into account. TT levels above 320 ng/dL are considered normal, while values below 200 ng/dL are considered pathological (9). TT levels between both values are controversial. According to recently published guidelines of the Journal of Clinical Endocrinology and Metabolism, the cut-off point should be established at 300 ng/dL (5). Any two FT serum dosages below 6.5 ng/dL are an indication of hypogonadism, if made with a one-month gap (10).

LOH hormone treatment requires both clinical and laboratorial criteria. Androgen replacement should only be used on patients with clinical symptoms associated with subnormal androgen serum levels (11,12). The androgen replacement therapy shows both laboratorial and clinical improvements in men (12). Its principal benefits are restoration of bone mass (13,14), improvement of sexual function (15-17), better mood and life quality (18), and improvement of carbohydrates and lipids metabolism (19-21). On the other hand, the hormone therapy presents some risks, such as exacerbation of undiagnosed prostatic disease, polycythemia, hepatotoxicity, worsening of obstructive sleep apnea (OSA) and gynecomastia (22-27). In Brazil, however, no study so far assessed the different androgen replacement therapy concerning their action and adverse effects. No androgen replacement therapy should be prescribed for patients with prostate or breast cancer history. Relative contraindications are an altered prostate-specific antigen (PSA), untreated hyperprolactinemia, OSA, and polycythemia (5).

Currently, available therapies are oral androgens, where testosterone undecanoate is the only safe testosterone ester for clinical use, since it is not hepatotoxic. Oral therapy has very little side effects and may reduce hypogonadism symptoms (28). Transdermal androgens are used as scrotal and non-scrotal patches and gels. Although patches may cause local irritation, they are easy to use and may be immediately discontinued if necessary. The gels do not have such side effect, but are more expensive (15,26,29). Parenteral testosterone esters have various presentations. In Brazil, available presentations are Durateston<sup>®</sup>, a combination of testosterone esters of different half-lives, providing longer duration of therapeutic levels; Deposteron<sup>®</sup>, a testosterone cypionate, which allows self-application and is relatively inexpensive, but causes peaks and valleys in serum testosterone levels (30); and Nebido<sup>®</sup>, a long-

acting undecanoate oil, which allows infrequent administration and shows smaller variations in testosterone serum levels, but is far more expensive.

Considering these options, the purpose of the present study was to compare both clinical and laboratory results of the different available testosterone replacement therapies in Brazil employed in patients with diagnosed LOH.

## METHODS

### Patients

The study included 50 consecutive patients attending the andrology clinic of the “Hospital de Guarnição de Florianópolis” (HGuFl) from March 2007 through March 2009. HGuFl is the Army’s reference hospital in the state of Santa Catarina, south Brazil. All patients were seen by the same physician.

Every reservist must refer to a military unit on his birthday month in order to renew his official register. Patients learned about the andrology clinic of the HGuFl through a leaflet on LOH handed out to all 800 army reservists in Santa Catarina, during their annual registration renewal.

Each interested reservist made an appointment at the andrology clinic of the HGuFl. Each appointment consisted of anamnesis, physical examination and filling out of the AMS (aging male symptoms) questionnaire (8). This is a self-applied questionnaire consisting of 17 questions. Each question must be answered based on a scale from 1 to 5; thus, the total questionnaire score may sum up from 17 to 85 points.

Each patient underwent urological evaluation, including rectal examination performed at HGuFl during the previous six months.

#### Inclusion criteria

- AMS questionnaire score equal to or higher than 27 points (Brazilian Portuguese validated).
- Patients with total testosterone serum level lower than 300 ng/dL and/or calculated free testosterone (obtained by Vermeulen’s formula) lower than 6.5 ng/dL.

#### Exclusion criteria

- Patients with history of prostate or breast cancer.
- Patients with untreated hyperprolactinemia.
- Patients with prostate-specific antigen (PSA) serum dosage above 4 ng/dL.
- Patients with severe obstructive sleep apnea (OSA) syndrome.

### Study design

Patients with confirmed LOH diagnosis (positive questionnaire AND reduced testosterone serum levels) were randomized to different testosterone replacement therapies by order of service. Three commercial preparations available in Brazil, all of intramuscular administration, were used. The first randomized patient received Deposteron<sup>®</sup>, the second patient received Durateston<sup>®</sup>, and the third patient received Nebido<sup>®</sup> and so on.

- Deposteron<sup>®</sup> 200 mg (testosterone cypionate 200 mg): one dose every 4 weeks; 11 patients.
- Durateston<sup>®</sup> 250 mg (testosterone propionate 30 mg + testosterone phenylpropionate 60 mg + testosterone isocaproate 60 mg + testosterone decanoate 100 mg): one dose every 4 weeks; 11 patients.
- Nebido<sup>®</sup> 1,000 mg (testosterone undecanoate 1,000 mg): to begin with, one dose every 6 weeks; later, one dose every 12 weeks; 10 patients.

Two weeks after the second set of laboratory tests following treatment, all patients were referred to a second medical appointment and once again filled out the AMS questionnaire.

### Biological samples

After a 10 to 12-hour fasting period, peripheral blood samples were acquired at 8 a.m. from each patient. A 10-mL blood sample was taken by venous puncture, using a BD Vacutainer<sup>®</sup>. Laboratory dosages were made by automatic enzyme chemiluminescence method processed in an Immulite analyzer (Diagnostic Products Corporation – DPC). Each specific hormone used a specific testing kit, all of the same brand (Immulite<sup>®</sup> prolactin, Immulite<sup>®</sup> estradiol, Immulite<sup>®</sup> total testosterone, Immulite<sup>®</sup> SHBG, Immulite<sup>®</sup> FSH, Immulite<sup>®</sup> LH, Immulite<sup>®</sup> PSA).

Biochemical assays were conducted at the clinical laboratory of the HGuFl.

All patients provided two blood samples. The first sample was taken for laboratorial diagnosis of LOH (before any treatment whatsoever). If the results were altered, the testing was repeated. The second sample was collected after the treatment had begun, according to following periodicity:

Patients receiving Deposteron<sup>®</sup> or Durateston<sup>®</sup> had the second blood test 14 days after the fourth dose of the hormone replacement therapy (week 14);

Patients receiving Nebido<sup>®</sup> had the second blood test 6 weeks after the second dose of hormone replacement therapy (week 12).

## Variables studied

Clinical, anthropometric, and laboratorial data (Table 1) were collected, including age, weight, height, and body mass index (BMI).

Hormonal dosages were total testosterone, calculated free testosterone (CFT) according to Vermeulen's formula (<http://www.issam.ch/freetesto.htm>), SHBG, LH, FSH, estradiol and prolactin, a complete blood count and PSA.

Seven patients had normal levels of testosterone. Eleven patients were excluded from the study, as follows:

- OSA: 1 patient.
- Untreated hyperprolactinemia: 3 patients.
- History of prostate cancer: 3 patients.
- PSA above cut-off point (4 ng/dL): 4 patients.

## Statistical analysis

First, a univariate analysis was conducted to find the association level between the dependent variable (treatment) and the independent variables. At this phase, the independent variables studied were age, BMI, first AMS questionnaire and the following pre-treatment lab tests: total testosterone (TT), calculated free testosterone (CFT), sex hormone-binding globulin (SHBG), LH, FSH, PSA, hematocrit, and hemoglobin. One-way ANOVA was used to determine 'p' values, which was similar in all groups.

The post-treatment univariate analysis evaluated the association level between the dependent variable (treatment) and the independent clinical variables (second AMS questionnaire scoring and improvement percentile between the questionnaires) and laboratorial (TT, CFT, PSA, Ht, and Hb). The 'p' values were determined by one-way ANOVA.

Statistical analyses were performed with the SPSS 12.0 software (Chicago, USA).

## Ethical aspects

A written informed consent was obtained from each patient for the blood samples, according to the protocol approved by the Ethics Committee. The acquisition of medication could be subsidized by FUSEX (Fundo de Saúde do Exército).

## RESULTS

Table 1 shows clinical, laboratorial and demographic variables of the 32 hypogonadal patients studied. The mean age was  $59.9 \pm 8.0$  years. Men showed to be overweight, with a mean BMI of  $28.1 \text{ kg/m}^2$ . Average gonadotropin levels were normal: LH =  $3.4 \pm 1.5 \text{ mUI/mL}$  and FSH =  $5.6 \pm 4.0 \text{ mUI/mL}$ . Median serum total testosterone levels at baseline indicated a mildly hypogonadal state in all three groups (all groups =  $287.2 \pm 35.6$ ; group A =  $291.1 \pm 33.1$ ; group B =

**Table 1.** Clinical and laboratorial variables of late-onset hypogonadism patients before treatment

Variable mean ( $\pm$ SD)	Treatment				P <sup>a</sup>
	All Patients n = 32	Deposteron® n = 11 (34.4%)	Durateston® n = 11 (34.4%)	Nebido® n = 10 (31.2%)	
Age (years)	59.9 (8.0)	59.6 (7.1)	60.4 (8.8)	59.6 (8.9)	0.96
Body mass index (kg/m <sup>2</sup> )	28.1 (3.0)	27.7 (2.8)	28.3 (2.4)	28.2 (3.9)	0.87
Total testosterone (ng/dL)	287.2 (35.6)	291.1 (33.1)	284.8 (44.0)	285.7 (31.2)	0.91
Calculated free testosterone (ng/dL)	5.8 (0.6)	6.0 (0.4)	5.8 (0.7)	5.7 (0.7)	0.35
Bioavailable testosterone (ng/dL)	136.8 (14.8)	141.7 (9.3)	135.6 (16.7)	132.6 (17.3)	0.37
SHBG (nmol/L)	31.2 (7.4)	30.0 (5.7)	30.2 (5.4)	33.4 (10.4)	0.52
LH (mUI/mL)	3.4 (1.5)	3.7 (1.6)	3.0 (1.4)	3.7 (1.4)	0.42
FSH (mUI/mL)	5.6 (4.0)	5.4 (2.7)	6.4 (6.1)	4.9 (1.9)	0.69
Estradiol (ng/dL)	2.7 (0.8)	2.9 (0.9)	2.5 (0.9)	2.5 (0.6)	0.39
Prostate specific antigen (ng/dL)	1.2 (0.8)	1.1 (0.7)	1.1 (0.7)	1.4 (1.1)	0.60
Hematocrit (%)	43.0 (2.8)	42.8 (2.7)	42.1 (3.2)	44.2 (2.2)	0.46
Hemoglobin (g/dL)	14.3 (1.1)	14.0 (0.9)	14.3 (1.2)	14.6 (1.1)	0.62
AMS questionnaire	37.6 (8.0)	36.7 (5.9)	40.5 (8.0)	35.3 (9.5)	0.31

SHBG: sex hormone-binding globulin; LH: luteinizing hormone; FSH: follicle-stimulating hormone; AMS: aging male symptoms.

<sup>a</sup> One-way ANOVA test.

284.8 ± 44.0; group C = 285.7 ± 31.2 ng/dL). Average PSA levels (1.2 ± 0.8 ng/dL), hematocrit (43.0 ± 2.8%), and hemoglobin (14.3 ± 1.1 g/dL) at baseline were normal. All three groups were paired in every studied variable.

Table 2 shows clinical response to treatment, measured by the average score of the AMS questionnaire and by the improvement percentage on the questionnaire before and after treatment. The decrease of libido was present in all patients.

Analysis of the second questionnaire's mean scores showed that Nebido® scored lower (23.8) in comparison to the three therapeutic options, being statistically significant when compared with Durateston® (29.6 – p = 0.03).

When evaluating the improvement percentage between the first and the second questionnaires, Nebido® showed better results (34.3%) among the three treatment groups, being statistically significant when compared to Deposteron® (23.1% – p = 0.03).

Table 3 shows the laboratorial response to treatment, measured by the mean testosterone levels (TT, CFT, and DFT) and the influence of therapy on the hematocrit, hemoglobin, and PSA levels.

The laboratorial improvement analysis showed that Nebido® seemed to be significantly superior (p < 0.001) to other options in all parameters analyzed (TT, FCT and DFT). On the other hand, there was no significant increase in hematocrit (p = 0.28), hemoglobin (p = 0.32) and PSA (p = 0.72).

**Table 2.** Second AMS questionnaire analysis according to treatment

Variable Mean (± SD)	Treatment			P
	Deposteron® n = 11	Durateston® n = 11	Nebido® n = 10	
Q2 score				
Time after the initiation of treatment	16 weeks 28.2 (4.8)	16 weeks 29.6 (6.4)	14 weeks 23.8 (6.3)	0.03 <sup>a</sup> 0.11 <sup>b</sup> 1.00 <sup>c</sup>
Improvement % between Q1 and Q2	23.1 (8.0)	26.9 (5.7)	34.3 (6.9)	0.06 <sup>a</sup> 0.03 <sup>b</sup> 0.60 <sup>c</sup>

Q1: First AMS (aging male symptoms) questionnaire; Q2: second AMS questionnaire.

<sup>a</sup> Treatment Nebido® versus Treatment Durateston®.

<sup>b</sup> Treatment Nebido® versus Treatment Deposteron®.

<sup>c</sup> Treatment Durateston® versus Treatment Deposteron®.

**Table 3.** Laboratorial tests variation between first and second samples, according to treatment

Variable Mean (± SD)	Treatment			P
	Deposteron® n = 11	Durateston® n = 11	Nebido® n = 10	
Testosterone total (ng/dL)	396.4 (46.3)	407.3 (80.9)	603.6 (55.6)	< 0.001 <sup>a</sup> < 0.001 <sup>b</sup> 1.00 <sup>c</sup>
Calculated free testosterone (ng/dL)	10.2 (1.4)	9.8 (1.0)	15.1 (1.9)	< 0.001 <sup>a</sup> < 0.001 <sup>b</sup> 1.00 <sup>c</sup>
Bioavailable testosterone (ng/dL)	238.7 (33.0)	230.8 (23.7)	353.4 (43.6)	< 0.001 <sup>a</sup> < 0.001 <sup>b</sup> 1.00 <sup>c</sup>
Prostate specific antigen (ng/dL)	1.4 (0.9)	1.3 (0.7)	1.6 (1.1)	0.72
Hematocrit (%)	44.9 (1.6)	46.0 (3.6)	46.8 (2.5)	0.28
Hemoglobin (g/dL)	14.9 (0.6)	15.4 (1.1)	15.5 (0.9)	0.32

<sup>a</sup> Treatment Nebido® versus Treatment Durateston®.

<sup>b</sup> Treatment Nebido® versus Treatment Deposteron®.

<sup>c</sup> Treatment Durateston® versus Treatment Deposteron®.

## DISCUSSION

Testosterone levels decline by 1% to 2% per year from the peak levels achieved in young adulthood, and 20% of men older than 60 have levels below the normal range or young men. Spontaneous and experimentally-induced androgen deficiency is associated with a decreased frequency of sexual thoughts and fantasies, night time erections, and libido (5). Potential risks of treatment include local effects on the prostate, promotion of growth of occult prostate cancer cells, and prostatic hypertrophy. Other systemic effects include fluid retention, sleep apnea, gynecomastia, polycythemia, and increased risk of cardiovascular disease (5).

There are several preparations of testosterone throughout the world. Although elevations in liver function tests and abnormalities at liver scan and biopsy are relatively common in patients receiving oral testosterone, these preparations are still prescript in the United States. There are preparations designed for skin application which employs a testosterone containing patch applied directly to the testicle. Another patch can be placed on any area of skin on the body which is free of hair. The adhesive on the patch occasionally causes a skin rash, and the patch itself is cumbersome. There is testosterone gel product. The gel is rubbed directly into the skin every day without the need for a patch. Many men find this the easiest and least irritating of the transdermal preparations of testosterone (1,5).

In Brazil, LOH treatment is restricted to parenteral testosterone esters formulas. There is a significant difference in treatment costs and pharmacokinetic properties of each formula (1). Enanthate and cypionate esters for i.m. injections were developed in the 1950's. These intramuscular injections of 200 to 250 mg must be administered every 2 or 4 weeks to achieve serum testosterone levels above the lower limit of normal (31). Recently, injectable testosterone undecanoate (Nebido®) has become available in Europe and in south America (including Brazil). After a recommended loading dose in the form of an initial six-week interval, injectable testosterone undecanoate is the first intramuscular agent that can be taken every three months (12 weeks) (32).

LOH diagnosis is based both on clinical and laboratorial aspects of hypogonadism (33). Clinical questionnaires, such as AMS, can be used both for diagnosis and for therapy follow-up (34). The symptom that best

correlated with late-onset hypogonadism is low libido (35,36), present in all patients.

Results indicate that Nebido® was superior in both clinical and laboratorial findings when compared to the two other formulations studied. Parenteral testosterone undecanoate provided patients with higher testosterone serum (total, free and bioavailable) levels during the mid-treatment period. It also seemed to show greater improvement in clinical response, according to the results of the AMS questionnaire.

Testosterone therapy may cause polycythemia when used at above-physiological doses (37). In spite of higher testosterone serum levels, patients treated with Nebido® showed similar hematocrit/hemoglobin serum levels when compared to the other treatment groups. The long-acting nature of this preparation permits 12-weekly administrations of injections to maintain physiological levels of serum testosterone, without peaks above normal.

It is well established that testosterone therapy has no effect on the development of prostate cancer (5,25,38). However, there is testosterone peripheral conversion in dihydrotestosterone (DHT), which may stimulate prostate cells. Continuous monitoring of PSA is necessary during testosterone therapy in patients with LOH (39). The study showed that all three therapeutic options slightly raised PSA levels (1.2 ng/dL against 1.4 ng/dL), with no statistically significant difference among the three groups and without reaching PSA levels above 4.0 ng/dL during treatment period. No clinically significant pathological findings of the prostate were observed during treatment with testosterone in this study.

## CONCLUSIONS

The study showed that all three testosterone therapeutic options available on the Brazilian market are effective in raising testosterone serum levels and in clinical improvement of hypogonadal patients. Although it has a higher cost, testosterone undecanoate showed higher clinical and laboratorial effectiveness, when compared to other treatment formulas. The therapeutic options studied showed to be safe in non-significant raising hematocrit, hemoglobin and PSA levels.

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