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ORIGINAL ARTICLE

Natural course of hypogonadism diagnosed during hospitalization in aged male patients

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Abstract Our aim was to assess short-term natural course of hypogonadism diagnosed during hospitalization for acute disease in aged male patients after discharge. A group of 43 hypogonadal males, aged 86.7 ± 5.7 year, was studied. Serum concentrations of testosterone (T) and gonadotropins (follicle-stimulating hormone, FSH, and luteinizing hormone, LH) were measured in every patient both at admission and one month after discharge. Mean serum T at entry was 115.4 ± 48.0 ng/dl. Hypogonadism was hyper-, hypo-, and normogonadotropic in 20 (46.5 %), 20 (46.5 %), and 3 (7.0 %) patients, respectively. One month after discharge serum T concentrations increased significantly (230.9 ± 135.6 ng/dl, $p < 0.001$). At this point, more than half of the patients ($n = 27$, 62.8 %) showed normal serum T concentrations. Both gonadotropins, FSH ($p < 0.001$), and LH ($p = 0.04$) also increased one month after discharge. Approximately, half of the patients (13, 48.1 %) who normalized serum T concentrations also showed normal serum gonadotropin concentrations. Patients who normalized their serum T concentrations one month after discharge showed significantly higher baseline values of T (134.7 ± 33.9 ng/dl) than those who persisted with hypogonadism ($n = 16$, 32.7 %; 82.8 ± 51.6 ng/dl, $p < 0.001$). Lastly, serum T was the only independent predictor for achieving eugonadal status (OR 1.030; CI 95 %, 1.010–1.050; $p < 0.001$). In conclusion, about 63 % of aged patients hospitalized for acute illness with hypogonadism discovered during hospitalization spontaneously normalize their serum T concentrations one month after discharge. Serum gonadotropin concentrations also increased after discharge. Serum T levels at admission was an independent predictor for the normalization of serum T concentrations.

Keywords Testosterone · Elderly · Hypogonadism · Gonadotropins · Spontaneous recovery

Introduction

Hypogonadism in the aged male can be either due to primary testicular failure or secondary to a hypothalamic-pituitary failure. Several factors both at hypothalamic-pituitary (loss of circadian rhythm of testosterone (T), decreased frequency and amplitude of luteinizing hormone (LH) pulses, decrease LH bioactivity, and decreased hypothalamic-pituitary threshold to the inhibitory action androgens) and testicular (decreased amount Leydig cell, decreased response of Leydig cells to human chorionic gonadotropin, alterations in steroidogenesis enzymes, and alterations of arterial vascularization of the testis) levels are involved in the male hypogonadism associated with advanced age. Moreover, the increase in sex hormone binding globulin (SHBG), associated to age is followed by a decrease in the absolute concentration of free T [1]. Lastly, it has been postulated a role of oxidative stress on the ageing of the endocrine system and the induction of age-related endocrine diseases [2].

Gonadal hypofunction in men is a common endocrine disturbance. Hypogonadism has been reported to be present

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in about 6–9.5 % of community-dwelling men aged 40–70 years increasing to 15–30 % in some pathological situations such as diabetes or obesity [3]. Moreover, due to the fact that gonadal function declines gradually with age in men, T deficiency is more prevalent in the elderly ranging from 30 to 50 % [4–11]. This prevalence increases even more than 50 % in aged male patients hospitalized for acute illness [12].

An association between low T levels and morbidity in elderly men has been reported [9, 13, 14]. Reduction in circulating T level is a predictor of deterioration of functional capacity over time negatively influencing on muscle mass, strength, and bone mass [15, 16]. On the other hand, several studies have shown a relationship between low T levels and cardiovascular and overall mortality in elderly men [17–21]. It has been also reported that hypogonadism is clearly associated to mortality during hospital stay in the elderly and low serum T concentrations is a main predictor for mortality during hospitalization for an acute disease in this population [12].

Given the association between low serum T concentrations and morbidity and mortality, it would be important to know the natural course of hypogonadism discovered during the hospitalization for an acute disease in aged male patients. To our knowledge, this fact has not been evaluated so far. Therefore, the aim of the present study has been to assess short-term spontaneous evolution of gonadal hypofunction after discharge in aged hospitalized patients and establish whether there is any clinical or analytical parameter that could be related to the normalization of gonadal function in these patients.

Patients and methods

Patients

A prospective study in a group of men older than 65 years hospitalized for an acute disease and diagnosed of hypogonadism during hospitalization was carried out. There was no patient with prostate cancer or chronically treated with androgen deprivation therapy or T preparations throughout the entire study. Patients were recruited from a previous cross-sectional study [12] that assessed the prevalence of hypogonadism in aged hospitalized male patients. From the 150 patients included in our initial study, hypogonadism was found in 80 patients (53.3 %). Of these, 12 patients died during hospitalization and 5 had been diagnosed of prostate cancer and were undergoing androgen deprivation therapy. Twenty patients did not attend their planned medical visits after discharge for unknown reasons. Therefore, a group of 43 hypogonadal aged males was finally studied. All subjects gave their informed consent to participate in the study which was approved by our local ethical committee.

Study design

Gonadal function was assessed on two separate occasions, immediately after admission and again one month after hospital discharge. Gonadal function was evaluated by measuring serum concentrations of gonadotropins (follicle-stimulating hormone, FSH and LH) and T. Bioavailable (BioT) and free T (FT) were calculated based on the values of T, SHBG, and albumin, as previously described [22]. Other serum hormones analyzed were estradiol (E2) and prolactin (PRL).

Hormone assays

Fasting samples of venous blood were obtained from an antecubital vein between 08:30 and 09:00 h in the first day of admission and one month after discharge for quantification. Serum FSH, LH, PRL, E2, and T were measured by a chemiluminescence immunoassay (ADVIA Centaur XP analyzer, Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA). The sensitivity (S) of the assay for these hormones was 0.3, 0.07 mU/ml, 0.3 ng/ml, 10 pg/ml, and 10 ng/dl, respectively. Normal ranges (NR) for adult males were: FSH 1.4–18.1 mU/ml; LH 1.5–9.3 mU/ml; PRL 2.1–17.7 ng/ml; E2 11.6–41.2 pg/ml; and T 240–820 ng/dl. SHBG was quantified by a chemiluminescent immunometric assay (Immulite 2000 analyzer, Siemens Medical Solutions Diagnostics, Llanberis, Gwynedd, UK) and the NR and S were 10–57 and 0.02 nmol/l, respectively.

Criteria for diagnosis

Patients were classified in eugonadal and hypogonadal (hyper-, normo-, or hypogonadotropic) depending on the values of serum T and gonadotropins (FSH and LH). In this elderly population, patients were considered eugonadal when serum T concentrations were $\geq$200 ng/dl regardless of the gonadotropins levels. The diagnostic criteria for hypogonadism (serum T concentrations <200 ng/dl) was arbitrarily chosen taking into consideration the advanced age of the patients and the presence of an associated acute illness. The diagnosis of primary hypogonadism (hypergonadotropic) was established when patients simultaneously showed serum T concentrations <200 ng/dl and FSH and LH concentrations exceeding the upper limit of the normal reference range for these hormones (>18.1 mU/ml for FSH and >9.3 mU/ml for LH). Central or secondary hypogonadism (normo or hypogonadotropic) was considered when reduced serum T concentrations (<200 ng/dl)

and normal or decreased gonadotropins levels (≤18.1 mU/ml for FSH and ≤9.3 mU/ml for LH) were found.

Statistical analysis

Quantitative variables are expressed as mean ± SD for normally distributed data and as median (interquartile range) for nonparametric data. Adjustment to normal distribution was tested by the Kolmogorov test. Categorical variables are described as percentages. For comparisons of means between two or more groups of subjects, the Student *t* test or ANOVA test, were used respectively for normally distributed data, and the Mann–Whitney test or Kruskal–Wallis test were employed, respectively, for nonparametric data. For comparisons of variables before and after discharge, paired Student's *t*-test was used for normally distributed data and Wilcoxon signed-rank test for non-normal distributed data. For ratio comparisons, the Chi-square test was used. Correlations between quantitative variables were assessed using Spearman's or Pearson's correlation analysis as indicated. A logistic regression analysis was used to assess normalization of gonadal function (serum T concentrations ≥200 ng/dl regardless of the gonadotropins levels) as a function of several quantitative (age, Barthel index at entry, hospital stay, glucose, creatinine, albumin, cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, FSH, LH, T, PRL, E2, and SHBG) and qualitative (diabetes, hypertension, and hyperlipidemia) variables at admission. Differences were considered significant when $p < 0.05$.

Results

Clinical features and analytical data

A group of 43 hypogonadal males [mean age, 86.7 ± 5.7 year; body mass index, 25.9 ± 4.4 kg/m^2; and Barthel index at admission, 75 (50–90)] was studied. The main causes of admission at the hospital were: congestive heart failure (11 patients, 25.6 %), respiratory tract infection (7 patients, 16.3 %), acute cerebrovascular disease (4 patients, 9.3 %), coronary heart disease (3 patients, 7.0 %), acute digestive hemorrhage (2 patients, 4.7 %), exacerbation of chronic obstructive pulmonary disease (2 patients, 4.7 %), cancer (1 patient, 2.3 %), anemia (1 patients, 2.3 %), and other (12 patients, 27.9 %). The prevalence of diabetes, hypertension, and hyperlipidemia was 30.2, 62.1, and 20.9 %, respectively.

Analytical data of the patients are summarized in Table 1. Median FSH, LH, PRL, and E2 were in the normal range. Twenty (46.5 %) patients were hypergonadotropic, 20 (46.5 %) patients were normogonadotropic, and 3 (7.0 %) patients were hypogonadotropic. The presence of diabetes and hyperlipidemia did not influence on serum FSH, LH, PRL, and E2 concentrations. FSH, PRL, and E2 were also similar in hypertensive and non-hypertensive patients. Only hypertensive patients showed significantly higher serum LH concentrations than non-hypertensive patients [11.3 mU/l (7.4–24.6) vs. 7.4 mU/l (4.0–10.3), $p = 0.041$)]. The presence of diabetes, hypertension, or hyperlipidemia did not influence on serum T concentrations. In the bivariate correlation analysis, serum T concentrations did not show any correlation with any of the analytical parameters analyzed. We also did not find any relationship between serum T levels and used drugs, including glucocorticoids.

Table 1 Analytical data of the 43 hypogonadal males at hospital admission and one month after discharge

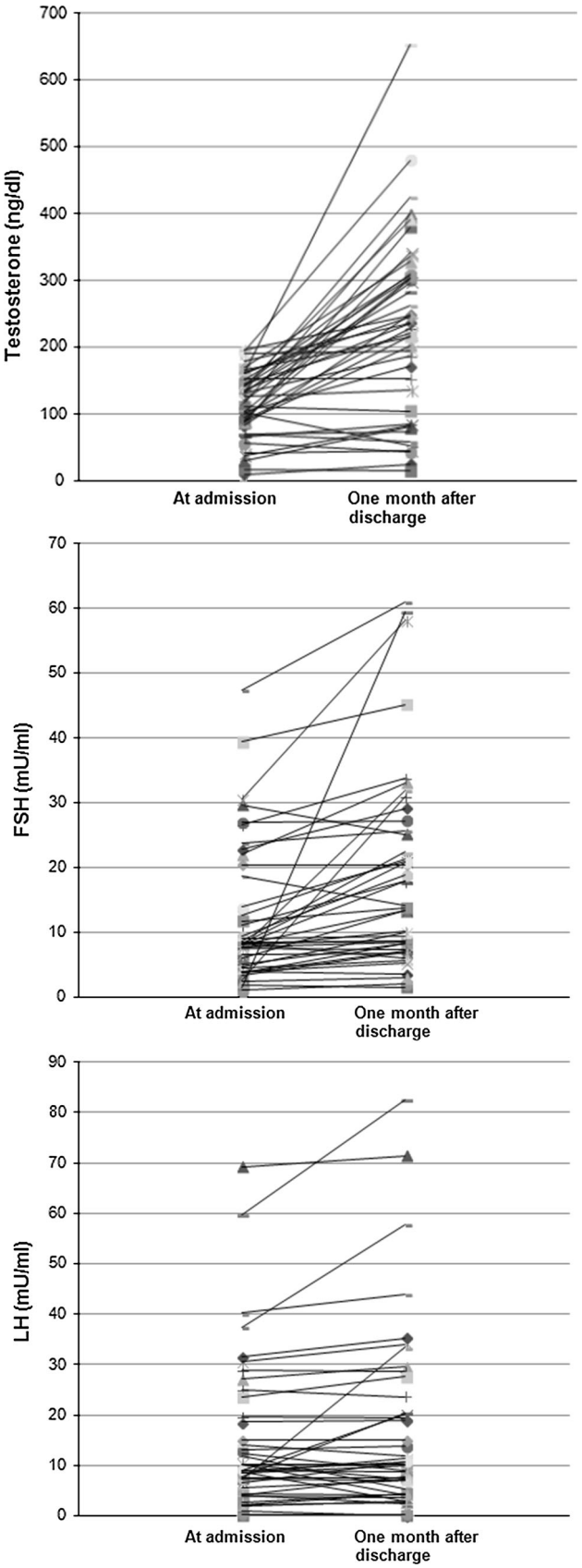
	At hospital admission	One month after discharge
Biochemical data		
Glucose (mg/dl)	100.9 ± 22.7	106.3 ± 25.4
Creatinine (mg/dl)	1.28 ± 0.37	1.23 ± 0.32
Cholesterol (mg/dl)	139.8 ± 36.9	168.1 ± 38.7***
LDL cholesterol (mg/dl)	80.7 ± 28.3	98.5 ± 34.2**
HDL cholesterol (mg/dl)	39.7 ± 10.3	48.1 ± 14.4***
Triglycerides (mg/dl)	97.5 ± 48.9	94.9 ± 47.7
Albumin (g/dl)	3.4 ± 0.4	3.8 ± 0.5***
Hematological data		
Hemoglobin (g/dl)	12.3 ± 2.2	14.7 ± 5.7*
Hematocrit (%)	37.1 ± 6.5	38.6 ± 8.2
Hormonal data		
FSH (mU/ml)	8.3 (4.5–18.7)	13.9 (7.5–25.7)***
LH (mU/ml)	9.1 (4.4–19.6)	10.2 (4.3–23.6)*
PRL (ng/ml)	8.7 (6.5–16.3)	9.4 (7.2–14.6)
Estradiol (pg/ml)	12.4 (6.9–25.8)	25.0 (11.8–37.3)*
Testosterone (ng/dl)	115.4 ± 48.0	230.9 ± 135.6***
Sex hormone-binding globulin (nmol/l)	47.2 ± 24.3	60.1 ± 28.2**
Free testosterone (ng/dl)	2.1 ± 1.2	3.3 ± 1.9***
Bioavailable testosterone (ng/dl)	38.9 ± 23.8	69.6 ± 43.4***

Figures indicate the number of patients (%) and/or the mean ± SD for normal variables and median (interquartile range) for nonparametric data

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Hormonal study after discharge

One month after discharge (41.2 ± 6.8 days after admission) serum concentrations of T ($p < 0.001$), FT ($p < 0.001$) and BioT ($p < 0.001$) increased significantly. SHBG also significantly increased ($p < 0.01$). At this point, serum T



◀**Fig. 1** Serum testosterone and gonadotropin (FSH and LH) concentrations at admission and one month after discharge in the 43 aged hypogonadic male patients

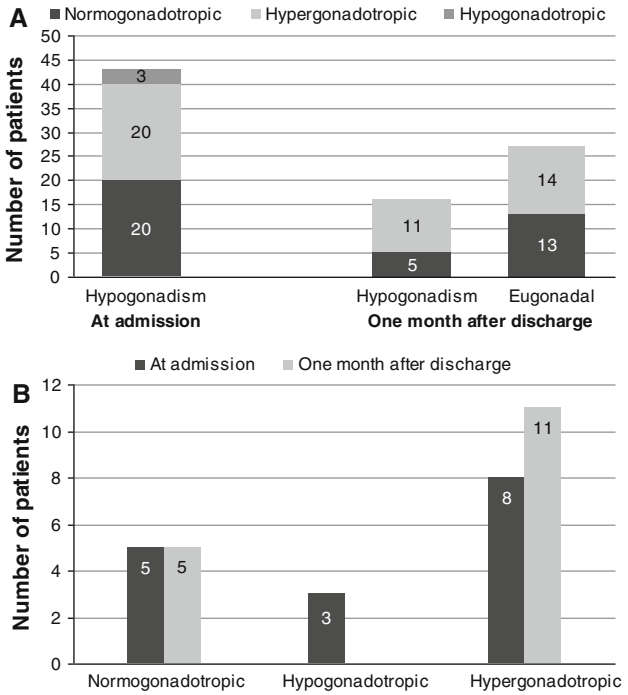


Fig. 2 Distribution of the 43 patients according to gonadotropic status at admission and one month after discharge (**a**). Distribution of the 16 hypogonadal patients one month after discharge according to gonadotropic status at admission and one month after discharge (**b**)

concentrations increased in 37 (86 %) patients, decreased in 5 (11.6 %) patients, and remained unchanged in 1 (2.3 %) patients. Patients who showed an increase in their serum T levels presented with higher serum T concentrations at admission in comparison with those who showed a decrease in T at the end of the study (120.3 ± 49.6 vs. 71.6 ± 37.7 ng/dl, $p = 0.032$).

Both gonadotropins, FSH ($p < 0.001$) and LH ($p = 0.04$) also increased one month after discharge (Table 1; Fig. 1). Similarly, the number of patients that showed an increase in FSH (83.7 %) and LH (55.8 %) was higher than that showed a reduction of their levels at the end of the study (14 and 37.2 %, for FSH and LH, respectively). No significant differences in serum FSH concentrations at admission between those patients who showed an increase in their serum FSH levels and those who presented with a decrease in FSH at the end of the study were found. A similar finding was observed with LH concentrations. Lastly, PRL did not modify whereas E2 significantly ($p = 0.013$) rose (Table 1).

Table 2 Clinical and analytical data of the 43 hypogonadal male patients at hospital admission according to spontaneous evolution of gonadal function one month after discharge

	Hypogonadism one month after discharge $n = 16$ (37.2)	Eugonadal status one month after discharge $n = 27$ (62.8)
Clinical data		
Age (years)	88.9 ± 6.8	85.4 ± 4.7
Diabetes	6 (37.5)	7 (25.9)
Hypertension	11 (68.7)	17 (63.0)
Hyperlipidemia	4 (25.0)	5 (18.5)
Weight (kg)	68.3 ± 15.7	63.8 ± 11.4
BMI (kg/m^2)	27.3 ± 4.6	25.1 ± 4.2
SBP (mmHg)	125 (99–144)	125 (105–139)
DBP (mmHg)	70 (55–84)	70 (58–80)
Biochemical data		
Glucose (mg/dl)	101.7 ± 26.2	100.5 ± 20.9
Creatinine (mg/dl)	1.27 ± 0.30	1.30 ± 0.42
Cholesterol (mg/dl)	132.2 ± 23.9	144.3 ± 42.7
LDL cholesterol (mg/dl)	73.8 ± 18.8	85.0 ± 32.4
HDL cholesterol (mg/dl)	40.6 ± 10.4	39.1 ± 10.4
Triglycerides (mg/dl)	90.9 ± 43.8	101.5 ± 52.1
Albumin (g/dl)	3.4 ± 0.4	3.4 ± 0.4
Hematological data		
Hemoglobin (g/dl)	12.2 ± 1.7	12.4 ± 2.5
Hematocrit (%)	37.0 ± 5.4	37.2 ± 7.2
Hormonal data		
FSH (mU/ml)	8.2 (3.9–25.9)	8.3 (4.7–14.0)
LH (mU/ml)	9.6 (4.7–29.1)	8.7 (4.4–14.1)
PRL (ng/ml)	7.6 (4.4–15.5)	8.9 (7.1–17.6)
Estradiol (pg/ml)	11.8 (6.9–19.2)	15.9 (7.0–27.3)
Testosterone (ng/dl)	82.8 ± 51.6	134.7 ± 33.9***
Free testosterone (ng/dl)	1.4 ± 1.0	2.5 ± 1.1**
Sex hormone-binding globulin (nmol/l)	47.0 ± 19.8	47.3 ± 26.9
Bioavailable testosterone (ng/dl)	25.2 ± 17.8	47.0 ± 23.5**

Figures indicate the number of patients (%) and/or the mean ± SD for normal variables and median (interquartile range) for nonparametric data

** $p < 0.01$; *** $p < 0.001$

Eugonadal versus hypogonadal status after discharge

One month after discharge, more than half of the patients ($n = 27$, 62.8 %) showed normal serum T concentrations. Of them, 13 (48.1 %) patients showed normal serum gonadotropin concentrations and the rest showed high gonadotropins levels (Fig. 2a). On the other hand, in 16 (37.2 %) patients, hypogonadism persisted. The gonadotropin status distribution in these hypogonadotropic patients was significantly ($p = 0.005$) different to that found at admission. In this setting, there was an increase of hypergonadotropic patients and a decrement of hypogonadotropic patients (Fig. 2b).

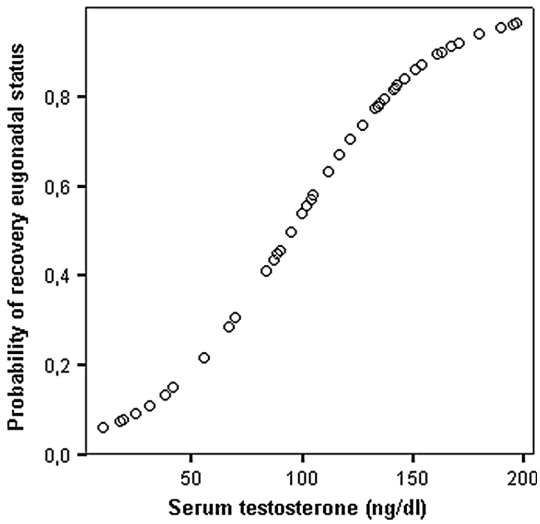


Fig. 3 Probability of recovery eugonadal status one month after discharge in aged hospitalized hypogonadal male patients in relation to serum testosterone concentrations at admission according to a model of logistic regression analysis

From the 43 hypogonadal aged male patients, we compared patients who normalized their serum T concentrations ($n = 27$, 62.8 %) one month after discharge with those who did not ($n = 16$, 32.7 %) (Table 2). Significantly higher values of T (134.7 ± 33.9 vs. 82.8 ± 51.6 ng/dl, $p < 0.001$) were found in the former group in comparison with the latter. (Table 2). A model of logistic regression analysis performed to study the influence of several quantitative (age, Barthel index at entry, hospital stay, glucose, creatinine, albumin, cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, FSH, LH, T, PRL, E2, and SHBG) and qualitative (diabetes, hypertension, and hyperlipidemia) variables at admission on the normalization of gonadal function one month after discharge showed that serum levels of T were the only independent predictor for achieving a eugonadal status (OR 1.030; CI 95 %, 1.010–1.050; $p < 0.001$). In this setting, hypogonadal male patients with higher values of T at admission had higher probability of normalizing their serum T concentrations one month after discharge (Fig. 3).

Discussion

Assessment of gonadal function one month after discharge in aged male patients diagnosed of hypogonadism during

hospitalization for an acute disease showed that normalization of serum T concentrations is a frequent event. In fact, more than half (62.8 %) of the patients of this sample normalized their serum T concentrations at this time. Both FSH and LH levels significantly rose after discharge. Lastly, serum T concentration at admission was the only independent predictor for achieving eugonadal status one month after discharge.

Gonadal function is commonly altered in the setting of acute illness [23–25]. In middle-aged men, serum T concentrations usually decline approximately between 40 and 60 % within the first 24 h after acute injury such as myocardial infarction, brain injury, or elective surgery [23]. Sustained decrease of serum T below the normal range occurs in about 60 % of men with acute illness of different etiology and severity admitted to intensive care units (ICUs) [24]. This percentage has been reported to be even more elevated in ventilator-dependent chronically critically ill men transferred from ICUs, where 96 % of the patients had bioT concentrations below the lower limit of normal for their age [25]. More recently, we found that hypogonadism was present in 53.3 % of aged male patients hospitalized for an acute disease and, in this population, low T concentration behave as an important and independent predictor for hospital mortality [12]. In the present study, we evaluated a major sample of these patients who survived to acute illness. In this cohort, serum T concentration was not influenced by the presence of diabetes, hypertension, or hyperlipidemia as it has been previously reported elsewhere [26, 27].

Both hyper- and hypogonadotropic hypogonadism have been reported in acute illness in men [23, 24]. This finding has also been found in hospitalized aged male patients for an acute disease [12]. In this population, more than half (56 %) of the hypogonadal patients showed central or secondary (hypo- or normogonadotropic) hypogonadism [12]. In the cohort analyzed, in the present study, the percentage of patients with secondary hypogonadism was maintained (53.5 %) mainly at the expense of normogonadotropic patients ($\sim$87 %). However, primary (hypergonadotropic) hypogonadism was present in a non negligible percentage (46.5 %) of patients, indicating that in aged hospitalized men, acute illness affects at different levels of hypothalamic–pituitary–gonadal (HPG) axis. These findings are similar to those found in younger males with acute illness [24].

Reversibility of hypogonadism associated to acute illness has been reported in middle-age men [23, 24]. Some authors have found a temporary hypogonadotropic gonadal insufficiency in a group of 35 men (mean age, 44.2 year) regardless of the illness with normalization in serum T concentrations from 2 weeks to 8 months after the patients had recovered [23]. Other study reported that both hyper- and hypogonadotropic hypogonadism occurred transiently in a group of 55 men (mean age, 57.8 year) with acute illness with a follow-up period of up to 6–12 months [24]. Recovery of gonadal hypofunction in aged patients with acute illness has not been clearly established. Given the elevated prevalence of hypogonadism associated with advanced age, we should keep in mind that many of elderly male patients could be hypogonadal just before presenting acute illness. Therefore, it is expected that the percentage of patients with spontaneous recovery of hypogonadism in this population should be lower than that found in younger men. Our study showed that gonadal function significantly improves one month after hospital discharge in this population. It is possible that the percentage of eugonadal patients at this time was more elevated with longer follow-up period. Our study showed that gonadal function significantly improves one month after hospital discharge in this population as evidenced by the fact that mean serum T concentration doubled, T increased in 86 % of patients and, lastly, complete normalization of T levels was achieved for more than half of the patients (62.8 %). It can be speculated that this percentage of eugonadal patients could be more elevated with longer follow-up period.

We found a significant increment in serum concentration in both gonadotropins one month after discharge, although more evident in FSH compared to LH. This increase was observed even in those patients with elevated baseline serum gonadotropins concentrations. These findings suggest that acute illness in aged male patients would mainly affect at central level of HPG axis. We found that the probability of recovery eugonadal status one month after discharge in this population was significantly and independently related to serum T concentrations at admission and not to any of the clinical and biochemical parameters assessed. As a matter of fact, the probability of normalizing serum T levels in patients with serum T concentration $>$100 ng/dl at admission was greater than 50 %.

We also found an increase in the concentration of SHBG. This protein is produced mostly by the liver and its serum levels are influenced by several factors, such as age, hormonal changes (sex hormones, sensitivity to insulin, and adipocytokines) and proinflammatory (cytokines) and nutritional states [28]. We think that increasing SHBG levels after discharge might be in relation to an increase in the levels of estradiol, the improvement in catabolic and nutritional states, as well the improvement in liver function (evidenced by an increase in albumin) following the recovery from the acute illness.

Our study has limitations derived from the limited sample size and the short observation period after discharge. A remarkable number of patients did not attend their scheduled visit at our clinic. However, in this age group, it is not easy to get that all patients attend the visits

after discharge. Another limitation is related to the heterogeneity of the population studied with different diseases and degrees of severity which can differently influence recovery of gonadal function. On the other hand, the strength of our study is that this is the first report aimed to assess in detail spontaneous changes in gonadal function in hypogonadal elderly patients discharged after acute illness.

In conclusion, our study shows for the first time, the short-term spontaneous evolution of gonadal function (T and gonadotropins) in a group of hypogonadic aged patients hospitalized for acute illness. The main findings were an increase in T levels in nearly 90 % of patients with normalization of serum T in approximately two-thirds of the patients, and an increase in gonadotropins levels, especially FSH. Serum T levels at admission were the main variable positively related to the normalization of serum T concentrations.

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Conflict of interest None declared.

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