The Hypothalamic-Pituitary-Gonad Axis in Male Cushing's disease Before and After Curative Surgery

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Abstract

Objective: Gonadal and sexual disturbances are commonly encountered in patients with Cushing's disease. Nevertheless, the prevalence of hypogonadism in male Cushing's disease, the risk factors as well as the recovery time have been scarcely reported. Therefore, we aimed to explore the prevalence of hypogonadism at baseline and its determinants. In addition, the recovery time of hypogonadism and risk factors for unrecovered gonadal axis in male Cushing's disease with biochemical remission were investigated.

Methods: We reviewed medical records of males with Cushing's disease managed between 2010 and 2020. Fifty-two male patients were enrolled according to the criteria. Each case attained biochemical remission after transsphenoidal surgery. Demographic details, clinical features, 24-hour UFC, hormonal profile [serum PRL, FSH, LH, TT, ACTH, cortisol, TT4/FT4, TT3/ FT3, TSH and IGF-1] were measured at baseline and during follow-up. The maximal tumor diameter on MRI was recorded at diagnosis.

Results: Hypogonadotropic hypogonadism was observed in thirty-nine patients (75%) at diagnosis. Total testosterone was negatively correlated with ACTH and 24-hour UFC. Midnight serum ACTH level at diagnosis was significantly associated with hypogonadism after adjusting for confounding factors. Thirty-two (80%) patients achieved eugonadism within 12 months after the surgery, of which twenty-eight (87.5%) achieved eugonadism within 3 months. Seven patients were persistently hypogonadal during the follow-up (>1 year), mainly due to the hypopituitarism as a complication of the therapies such as surgery.

Conclusion: Hypogonadotropic hypogonadism is frequent in male Cushing's disease, but it is reversible in most cases within one-year follow-up after remission.

Introduction

Gonadal and sexual disturbances are commonly encountered in patients with Cushing's disease. Decreased libido and potency are generally recorded in male Cushing's disease[1,2]. Nevertheless, the prevalence of hypogonadism in male Cushing's disease as well as the risk factors have been scarcely reported. In this study, we assessed the plasma levels of testosterone and gonadotropins prior to and after therapy of the Cushing's disease in males. We explored the prevalence of hypogonadism at diagnosis and its determinants. In addition, the recovery time of hypogonadism and risk factors for unrecovered gonadal axis in male Cushing's disease with biochemical remission were investigated.

Subjects And Methods

This combined cross-sectional and longitudinal cohort study was conducted at Huashan Hospital, Shanghai, China. The study was approved by the Human Investigation Ethics Committee at Huashan Hospital (No.2017M011). Medical records of males with Cushing's disease managed between 2010 and 2020 were reviewed. Inclusion criteria included (1) willingness to participate in the study, (2) age ≥ 18 years, (3) receiving regular follow-up, (4) diagnosis of Cushing's disease according to the updated

diagnostic criteria[3] and (5) attaining biochemical remission after transsphenoidal surgery. Exclusion criteria included (1) Cushing's syndrome other than pituitary origin, (2) loss of follow up, (3) uncured or relapse during the follow up, (4) with primary gonadal disease, (5) after radiation therapy and (6) with medication affecting androgens. Fifty-two patients were enrolled after their informed consent. Patients were followed for more than 1 year after transsphenoidal surgery.

Demographic details, clinical features, 24-hour urinary free cortisol (UFC), hormonal profile [serum prolactin (PRL), follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone (TT), adrenocorticotrophic hormone (ACTH), cortisol, total thyroxine (TT4)/free thyroxine (FT4), total triiodothyronine (TT3)/free triiodothyronine (FT3), thyroid-stimulating hormone (TSH), insulin-like growth factor 1 (IGF-1)] were recorded at diagnosis (pre-surgery) as well as during the follow-up (1,3,6,12,15,18,24 months after surgery). Maximal tumor diameter on MRI of each patient at diagnosis was noted.

Central hypothyroidism was defined as low FT4 (< 12pmol/L) with a low, normal, or mildly elevated TSH[4]. IGF-1 index was defined as the ratio of measured value to the respective upper limit of the reference range for age and sex. Hypogonadotropic hypogonadism (HH) was defined as low (< 6.68nmol/L) morning serum TT with low/normal serum FSH and LH levels. Biochemical remission of Cushing's disease was defined as morning serum cortisol < 2μg/dL (< 55nmol/L) within the week after surgery and disappearance of clinical signs and symptoms of hypercortisolism[3,5,6]. All patients were administered with 20mg of hydrocortisone 3 times daily after surgery to avoid steroid withdrawal syndrome, with a 10-day taper afterward[7]. When hydrocortisone was reduced to 10mg once a day for 10 days, the patient was followed up for the first time after surgery. The adrenal axis was evaluated with a morning cortisol level obtained before that day's glucocorticoid dose at each visit, followed by an ACTH stimulation test starting when the level is 2 ~ 10μg/dL (55 ~ 276 nmol/L). The adrenal axis has recovered if the baseline more than 10μg/dL (276 nmol/L) or stimulated level is approximately 18μg/dL (500 nmol/L) or greater[6,8–9].

Hormonal measurements were carried out by chemiluminescence assay (Advia Centaur CP). Intra-assay and inter-assay coefficients of variation were less than 8 and 10%, respectively, for the estimation of all hormones.

Statistical analysis

Statistical analysis was done using IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp. Categorical variables are expressed in actual numbers and percentages. Continuous variables were checked for normality prior to analysis, presented as means ± SD for normally distributed variables and median, 25th percentile, and 75th percentile (Median [P25, P75]) for variables without a normal distribution, respectively. Both anthropometry and biochemical measurements were compared between groups using independent t-tests for normally distributed continuous data and non-parametric tests for variables without a normal distribution. Multivariate logistic regression analysis was performed to evaluate the association between HH and specific variables after adjusting for confounding factors. The

correlation between serum ACTH concentration, 24-hour UFC and TT was examined by Pearson's correlation analyses. P-value < 0.05 was considered as statistically significant.

Results

Overall cohort

Fifty-two males with Cushing's disease were included. The mean age at diagnosis was 36.5 ± 13.7 years. HH was observed in thirty-nine patients (75%) at diagnosis. Thirty-two (80%) patients achieved eugonadism within 12 months after the surgery, of which twenty-eight (87.5%) achieved eugonadism within 3 months, while seven were persistently hypogonadal during the follow-up (> 1 year). 14, 14, 3 and 1 patient(s) achieved eugonadism in 1,3,6,12 month(s) after the surgery, respectively.

Comparison of patients with eugonadism vs. hypogonadism at diagnosis

As shown in Table 1, age and maximal tumor diameter at diagnosis were not significantly different between patients of the two groups. Patients with eugonadism had lower midnight serum cortisol [17.4(13.6, 30.4) vs 23.8(15.2, 34.9) μg/dL, p = 0.036] as well as lower ACTH levels at baseline than those who were diagnosed with hypogonadism. No significant differences were found between the two groups in PRL, FSH, LH, TSH, FT4, TT3 and IGF-1 index (Table 1).

Table 1
Comparison of characteristics between patients with eugonadism vs. hypogonadism at diagnosis

Variable	Patients with eugonadism	Patients with hypogonadism	P value
Number	13	39	/
Height(cm)	166.2 ± 10.0	171.8 ± 5.4	0.014
Weight(kg)	68.7 ± 11.8	79.7 ± 12.0	0.009
BMI(kg/m^2)	24.8 ± 2.8	27.0 ± 3.5	0.032
HbA1c(%)	5.9 ± 0.6	6.5 ± 1.3	0.067
Age(years)	30(19.5, 39.0)	32(28, 47.5)	0.164
Maximum tumor diameter(mm)	4(2.5, 6.0)	5(3, 6.75)	0.147
8a.m. serum cortisol(μg/dL)	28.1 ± 9.0	30.7 ± 13.8	0.409
16p.m. serum cortisol(μg/dL)	26.5 ± 11.3	28.3 ± 13.2	0.637
24p.m. serum cortisol(μg/dL)	17.4(13.6, 30.4)	23.8(15.2, 34.9)	0.036
24-hour UFC(μg/24-hour)	537.9(360.0, 760.0)	789.4(432.5, 1726.4)	0.095
8a.m. ACTH(pg/mL)	65.6(26.0, 110.2)	114.0(67.7, 159.0)	0.014
16p.m. ACTH(pg/mL)	70.5(52.4, 100.9)	92.3(79.3, 150.3)	0.024
24p.m. ACTH(pg/mL)	53.2(27.4, 78.4)	99.4(64.5, 145.1)	0.001
TSH(mIU/L)	0.91(0.57, 1.74)	0.76(0.33, 1.42)	0.328
FT3(pmol/L)	4.77 ± 1.31	3.66 ± 0.80	0.010
FT4(pmol/L)	15.05 ± 3.18	14.53 ± 2.51	0.631
TT3(nmol/L)	1.59 ± 0.72	1.20 ± 0.34	0.071
TT4(nmol/L)	87.77 ± 18.21	74.85 ± 19.38	0.041
IGF-1 index	0.69 ± 0.35	0.64 ± 0.23	0.687
FSH(IU/L)	5.81(4.67, 6.86)	5.47(2.88, 7.91)	0.643
LH(IU/L)	4.53(3.24, 5.58)	4.44(2.09, 5.48)	0.317
TT(nmol/L)	10.7(7.7, 14.8)	5.06(3.89, 5.60)	< 0.001
PRL(ng/mL)	15.5 ± 4.1	18.5 ± 11.8	0.352

Total testosterone was negatively correlated with ACTH and 24-hour UFC

To further explore the correlation between TT and the cortisol level, Pearson's correlation analyses was performed. As shown in Fig. 1, Total testosterone was negatively correlated with midnight serum ACTH level (r=-0.427, p = 0.0025) and 24-hour UFC (r=-0.334, p = 0.022).

ACTH was independently associated with hypogonadism at diagnosis

To go deep into the association between the prevalence of hypogonadism and serum ACTH levels, we divided the 52 patients into three groups according to tertiles of ACTH levels. Compared to individuals with low levels of 8a.m. ACTH (Fig. 2), 16p.m. ACTH (Fig. 3), and 24p.m. ACTH (Fig. 4), the prevalence of hypogonadism in those with high levels of ACTH was significantly higher. The multiple logistic regression model shown in Table 2 demonstrated that plasma levels of midnight ACTH at diagnosis was significantly associated with hypogonadism, even after adjusting for age, body mass index (BMI), maximal tumor diameter, LH, FSH, TT4, PRL and midnight serum cortisol at diagnosis (Table 2).

Table 2
ACTH was independently associated with hypogonadism at diagnosis

	B (SE)	P value	Exp(B) (95% IC)
Model 1	1.778 (0.671)	0.008	5.92 (1.59, 22.04)
Model 2	1.653 (0.688)	0.016	5.22 (1.36, 20.10)
Model 3	1.801 (0.846)	0.033	6.06 (1.15, 31.82)
Model 4	1.968 (0.996)	0.048	7.15 (1.02, 50.35)
Data are odds ratios (95% confidence interval).			
Model 1: unadjusted			
Model 2: adjusted for age, midnight serum cortisol and BMI at diagnosis			
Model 3: model 2 further adjusted for LH, PRL and maximum tumor diameter at diagnosis			
Model 4: model 3 further adjusted for FSH and TT4 at diagnosis			

Comparison of patients achieving eugonadism vs. persistent hypogonadism

It turned out that patients with persistent hypogonadism had a higher percentage of hypothyroidism (71.4% vs 3%, p < 0.001) as well as a higher prevalence of central diabetes insipidus (42.9% vs 0%, p < 0.001) than those who attained eugonadism after remission of Cushing's disease, while none was diagnosed with hypothyroidism and central diabetes insipidus at baseline before the surgery. The change in LH from last visit to baseline was significantly lower among patients with persistent hypogonadism compared to the other [-2.2 (-6.1, 0.3) vs 1.3 (-0.3, 2.8), p = 0.002]. No significant differences were found between the two groups in age, follow-up time, maximum tumor diameter, change in FSH, change in

weight and combined drug use (Table 3). Characteristics of seven males with persistent hypogonadism after follow-up (≥ 1 year) were shown in Table 4. No obvious lesion was detected by MRI in Case1#. And the lesion of Case 4# was flat and thin. Case 2#, 5# and 6# suffered from pituitary macroadenomas. Case 7# had experienced two times of surgery. Case 1#, 3# and 5# attained adrenal axis recovery during the follow-up.

Table 3
Comparison of characteristics between patients achieving eugonadism vs. with persistent hypogonadism

	Patients achieving eugonadism	Patients with persistent hypogonadism	P value
Number	32	7	/
Age (years)	37.5 ± 13.7	41.4 ± 9.9	0.397
Follow-up time (month)	12.0 (3.0, 24.0)	12.0 (12.0, 18.0)	0.375
Maximum tumor diameter (mm)	5.0 (3.0, 6.0)	5.0 (3.0, 35.0)	0.419
Involvement of thyroid axis, n (%)	1 (3%)	5 (71.4%)	< 0.001
Prevalence of central diabetes insipidus, n (%)	0 (0%)	3 (42.9%)	< 0.001
Change in LH (from last visit to baseline, IU/L)	1.3 (-0.3, 2.8)	-2.2 (-6.1, 0.3)	0.002
Change in FSH (from last visit to baseline, IU/L)	-2.1 (-3.6, -0.2)	-2.4 (-6.0, -0.5)	0.382
Change in weight (from last visit to baseline, kg)	-2.0 (-6.5, 0.0)	-4.5 (-9.0, -0.25)	0.280
Aspirin (%)	1 (3.1%)	0 (0%)	0.636
ACEI/ARB (%)	4 (12.5%)	3 (42.9%)	0.058
Calcium-channel antagonist (%)	6 (18.8%)	2 (28.6%)	0.560
Metformin (%)	1 (3%)	1 (14.3%)	0.225

Table 4
Characteristics of 8 males with persistent hypogonadism after follow-up (≥ 1 year)

Patient	Age (years)	Maximum tumor diameter (mm)	Times of surgery	Involvement of thyroid axis	Present with central diabetes insipidus	Recovery of adrenal axis	Follow-up (months after surgery)
1	51	Unclear	1	/	/	Yes	24
2	48	36	1	Yes	Yes	/	18
3	36	4	1	Yes	/	Yes	15
4	53	5	1	/	/	/	12
5	43	15	1	Yes	/	Yes	12
6	31	35	1	Yes	Yes	/	12
7	28	3	2	Yes	Yes	/	12

Discussion

In the present study, we reported that hypogonadotropic hypogonadism occurred in 75% male Cushing's disease at diagnosis. The negative correlation found between plasma testosterone and ACTH, 24-hour UFC (Fig. 1) in our study reinforced the role of hypercortisolism playing on the suppression of gonadal axis. Midnight serum ACTH level at diagnosis was significantly associated with hypogonadism after adjusting for age, maximum tumor diameter and other confounding factors.

Eugonadism occurred spontaneously in 80% male Cushing's disease who achieved biochemical remission after the surgery over a median follow up of twelve months, and most of which (87.5%) achieved eugonadism within 3 months. Seven were persistently hypogonadal during the follow-up (> 1 year) after remission. As listed in Table 4, there were some risk factors affecting gonadal axis recovery other than hypercortisolemia. Firstly, it would be more likely to damage normal pituitary tissue since recurrent pituitary surgery and too tiny/unclear/flat pituitary tumors also increased surgical difficulty and risk of impaired pituitary function. It should be noticed that most patients with persistent hypogonadism developed hypopituitarism including central hypothyroidism and central diabetes insipidus after curative surgery, suggesting hypogonadism mainly due to the hypopituitarism as a result of surgical complications. Secondly, pituitary macroadenoma compressing normal tissue resulted in hypopituitarism.

Shekhar S's team studied the pre- and post-surgical characteristics of the gonadal and thyroid axis hormones in 23 adult Cushing syndrome patients who received curative surgery with follow-up for 6–12 months. But only two men were enrolled in their study. It turned out that one was already taking testosterone at baseline and the other one received gonadal axis recovery at 6-month follow up[10]. The recovery time reported by Shekhar S's team was consistent with our study.

The spontaneous recovery of hypogonadism after resolution of hypercortisolemia suggested that a wait-and-watch approach may be reasonable during the follow up less than one year when surgical remission is anticipated. In addition, our study may also help clinicians for timely initiation of testosterone/gonadotropin treatment if male patients were persistent hypogonadism during the follow up more than one year, especially patients with macroadenoma, too tiny pituitary tumors and recurrent pituitary surgeries.

Our study has several strengths. It is the most comprehensive and largest longitudinal study to date describing the gonadal function status of male Cushing's disease before and after curative surgery. Secondly, we analyzed multiple markers of hypercortisolemia, including maximum tumor diameter, 24-hour UFC and the circadian rhythm of cortisol and ACTH. Thirdly, we were able to demonstrate the dose-response relationship between baseline hypercortisolemia and gonadal hormone abnormalities.

The main limitation of the present study is the lack of analysis data on semen and free testosterone. In addition, the extrapolation of the conclusions of our study is limited because ethnic differences might play a role in gonadal axis suppression. Since a further follow-up is crucial to prove whether gonadal axis recovery would occur over time in those with persistent hypogonadism, the follow-up duration in our study was comparatively shorter. Thus, larger scale clinical trials with longer follow-up duration, including various ethnic groups, are required to further validate the conclusions.

In conclusion, the retrospective study demonstrated that hypogonadotropic hypogonadism was common among male Cushing’s disease at diagnosis. Midnight serum ACTH level at diagnosis was significantly associated with hypogonadism after adjusting for confounding factors. Hopefully, hypogonadotropic hypogonadism is reversible in male Cushing’s disease in most cases within one year follow-up after remission.

Abbreviations

UFC, urinary free cortisol;

PRL, prolactin;

FSH, follicle-stimulating hormone;

LH, luteinizing hormone;

TT, total testosterone;

ACTH, adrenocorticotrophic hormone;

TT4, total thyroxine;

FT4, free thyroxine;

TT3, total triiodothyronine;

FT3, free triiodothyronine;

TSH, thyroid-stimulating hormone;

IGF-1, insulin-like growth factor 1;

HH, hypogonadotropic hypogonadism;

BMI, body mass index.

Declarations

Declaration of interest

The authors declare that there is no conflict of interest.

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None.

Author Contributions

HPZ and QW analyzed the data and wrote the manuscript. QYS, QLC, WW and LJJ collected the data. ZYM, MS, XFS, YFW and YZ performed transsphenoidal surgeries. YML and ZYZ revised the study and manuscript. BL and MH recruited patients. HYY and SZ conducted the study design and quality control. All authors read and approved the final manuscript.

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Data Availability

The data analyzed during the study are not publicly available due to relevant regulations, but are available from corresponding authors on reasonable request.

Disclosure summary

The authors have nothing to disclose.

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Figures

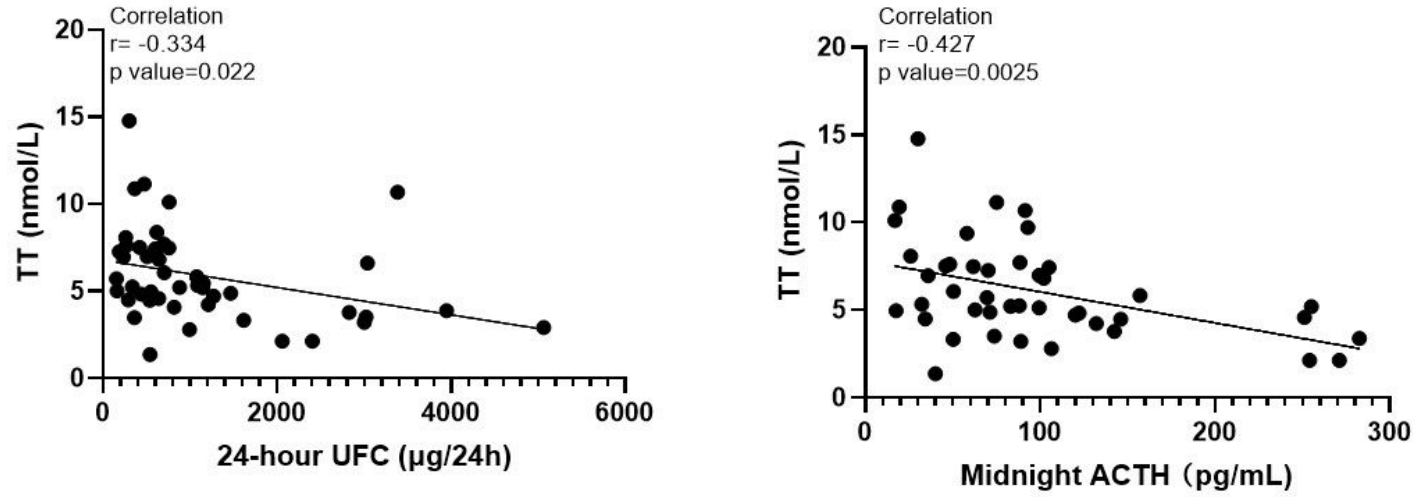

Figure 1

Total testosterone was negatively correlated with ACTH and 24-hour UFC

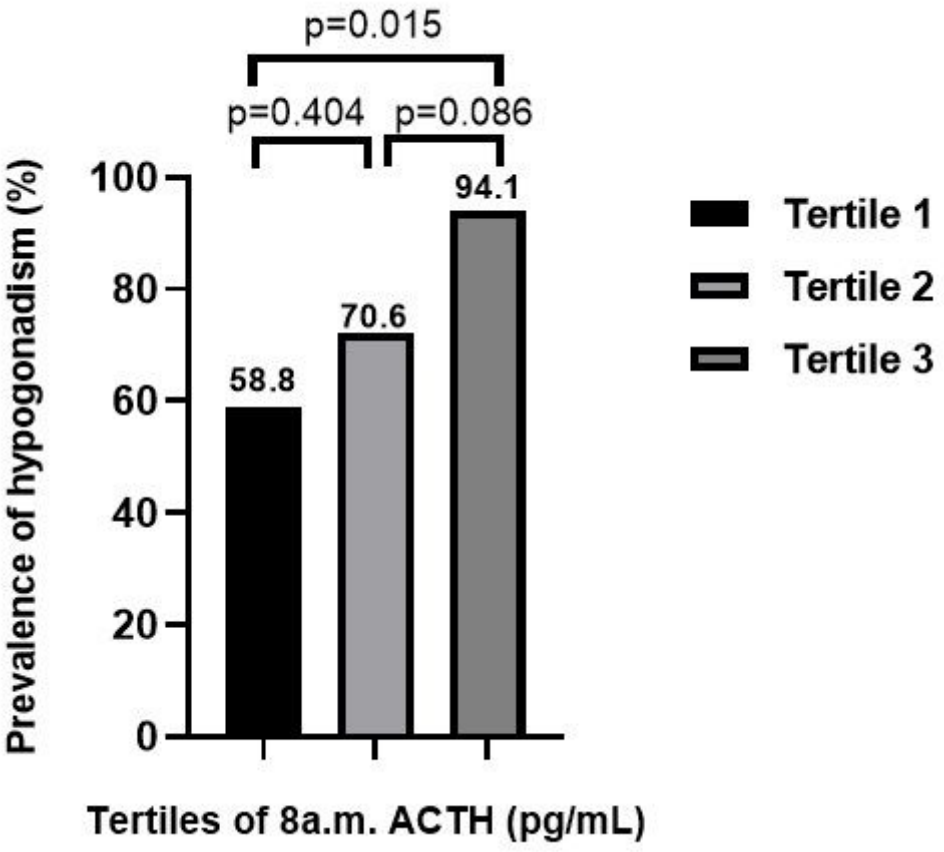

Figure 2

Prevalence of hypogonadism according to tertiles of 8a.m. ACTH (%)

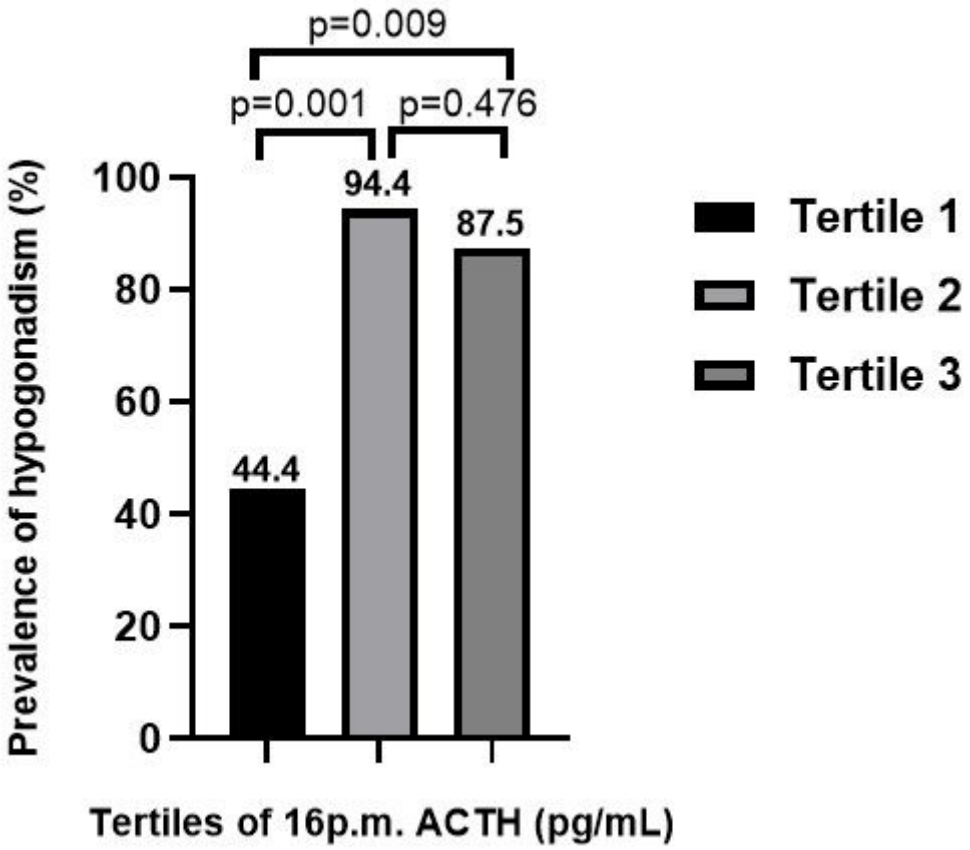

Figure 3

Prevalence of hypogonadism according to tertiles of 16p.m. ACTH (%)

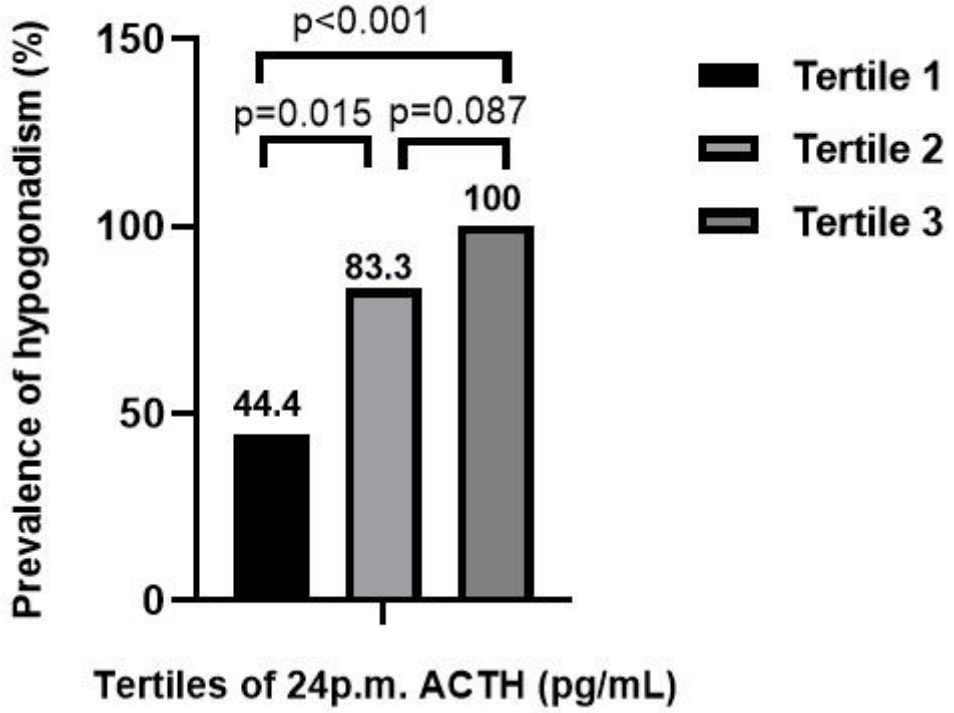

Figure 4

Prevalence of hypogonadism according to tertiles of 24p.m. ACTH (%)