Hypogonadism with Normal Serum Testosterone

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CASE DESCRIPTION

A 69-year-old man was referred to the endocrine clinic with a 3-year history of erectile dysfunction, reduced libido, and lack of nocturnal tumescence with no response to phosphodiesterase type 5 inhibitors (sildenafil and tadalafil). The symptoms troubled him to such an extent that he asked his general practitioner to be referred to a specialist clinic.

The patient had been through a normal puberty. Although he fathered no children, he was unconcerned about this and never sought fertility investigation or treatment. His past medical history was clinically significant for newly diagnosed interstitial lung disease owing to hypersensitivity pneumonitis, osteoarthritis, and gastroesophageal reflux; his only medications were ibuprofen gel and lansoprazole. He was never prescribed steroids, ketoconazole, or spironolactone. He had not undergone ionizing radiation and denied using over-the-counter or recreational drugs. He was an ex-smoker who drank 8 units of alcohol weekly. He did not recall a prior history of mumps or testicular trauma. He was unaware of any family members who had an autoimmune disorder or fertility issues.

On examination he was 178 cm tall and obese [body mass index (BMI) 37.3 kg/m^2]. His arm-span-to-height ratio was <1.05 and his cardiovascular examination did not reveal heart murmurs. He had a normal hair pattern and no gynecomastia. Testicular volume was reduced bilaterally at 12–15 mL (reference interval ≥15 mL).

Testosterone, measured by a 1-step chemiluminescent immunoassay (Abbott Architect, second generation testosterone assay) was 16.0 nmol/L (reference interval 4.9–32 nmol/L); his sex hormone–binding globulin (SHBG)[3] was increased at 153 nmol/L (13.5–71.4 nmol/L) as were luteinizing hormone (LH) and folliclestimulating hormone (FSH) at 33.4 IU/L (0.6 –12.0 IU/L) and 54.7 IU/L (1.0 –11.9 IU/L), respectively (Table 1). These results, which indicated hypergonadotropic hypogonadism, were confirmed on repeated testing 3 weeks later. At that time, testosterone was also measured by LC-MS/MS and the results confirmed a normal total testosterone, thus excluding a positive immunoassay interference. Low calculated values of bioavailable testosterone (bioT) [2.05 nmol/L (2.29 –14.5 nmol/L)] and free testosterone (FT) [0.106 nmol/L (0.174–0.729 nmol/L)] were consistent with hypogonadism. Further blood tests showed normal results for the routine metabolic panel, complete blood count, transferrin saturation, estrogen, thyroid tests, and prolactin. Plasma glucose, adjusted calcium, vitamin B12, and morning cortisol results were also unremarkable, making an autoimmune condition unlikely.

DOI: 10.1373/clinchem.2016.265124

After discussion with the patient, transdermal testosterone replacement was initiated. At follow-up 3 months later, his total testosterone had increased to 39 nmol/L; this was mirrored by a reduction in SHBG (73 nmol/L) and gonadotropins (FSH 16.0 IU/L, LH 8.9 IU/L). His libido, general well-being, and erectile function improved substantially. The etiology of his hypergonadotropic hypogonadism could not be further elucidated because of unexpectedly rapid progression of his interstitial lung disease leading to oxygen dependency. He declined further investigations and eventually stopped taking testosterone replacement upon learning of a poor prognosis of his rapidly progressing lung disease.

Table 1. Relevant patient results.[a]

Standard international units			US customary units		
	Patient results			Patient results	
Reference interval	Baseline	3 Months	Reference interval	Baseline	3 Months
Testosterone (4.9–32 nmol/L)	16	39	Testosterone (141–922 ng/dL)	461	1124
BioT (2.29–14.5 nmol/L)	2.05	12.1	BioT (66–417 ng/dL)	59	349
FT (0.174–0.729 nmol/L)	0.106	0.6	FT (5–21 ng/dL)	3.05	17.3
SHBG (13.5–71.4 nmol/L)	153	73	SHBG (13.5–71.4 nmol/L)	153	73
FSH (1.0–11.9 IU/L)	54.7	16	FSH (1.0–11.9 mIU/mL)	54.7	16
LH (0.6–12 IU/L)	33.4	8.9	LH (0.6–12 mIU/mL)	33.4	8.9
Albumin (35–55 g/L)	37	39	Albumin (3.5–5.5 g/dL)	3.7	3.9

[a] Follow-up testosterone, SHBG, LH, and FSH were measured while the patient was on testosterone treatment 3 months after the presentation.

QUESTIONS TO CONSIDER
• What are the criteria for LOH?
• What are the pitfalls of measuring serum total testosterone concentration?
• What common conditions cause increased SHBG?
• What methods should be used to determine FT and bioT?

Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the August 2017 issue of *Clinical Chemistry*. To view the case and comments online, go to http://www.clinchem.org/content/vol63/issue8 and follow the link to the Clinical Case Study and Commentaries.

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