Diseases / conditions affecting the steroid profile in blood

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Total testosterone in 10,098 males, 3 to 88 years:

(Kelsey et al., PLoS ONE 9: e109346, 2014)
Circadian rhythm of serum total testosterone in 10 young (23-33 yrs) and 8 elderly men (55-64 yrs) (Diver et al. Clin. Endocr. 58: 710, 2003)
Serum testosterone in 11 healthy men (37 – 51 yrs) after an overnight fast (●) or following a 550 kcal breakfast (○): A meal may decrease testosterone by 30%!

(Lehtihet et al. Andrologia 44: 405-410, 2012)
Testosterone and hemoglobin in 434 aging men

(Zitzmann & Nieschlag JCEM 92: 3844 – 53, 2007)
Secondary (hypogonadotrophic) hypogonadism

Late-onset hypogonadism (LOH)

Primary hypogonadism

Nieschlag, Behre, Nieschlag (eds) Andrology 3rd ed Springer 2010
Primary hypogonadism

Klinefelter syndrome 47,XXY
XX-Male syndrome
Gonadal dysgenesis
Anorchia, congenital or acquired
   e.g. trauma, torsion, tumor
Maldescended/cryptorchid testes
Orchitis, resulting in testicular atrophy
Radiation or chemotherapy

(Nieschlag, Behre, Nieschlag (eds) Andrology 3rd ed Springer 2010)
Phenotype of patients with Klinefelter syndrome

Incidence: 1 in 500 men
47,XXY karyotype
Small testes
Azoospermia
Gynecomastia

72 years
40 years
30 years
15 years
Hormone concentrations in 228 Klinefelter patients and 224 infertile patients with normal karyotype

(Nieschlag, Dtsch Ärztebl Int 110: 347-353, 2013)
Primary hypogonadism

Klinefelter syndrome 47,XXY
XX-Male syndrome
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All disorders result in low T, except some testicular tumours may cause elevated T and E2.
Leydig cell tumours

- Gynecomastia
- Loss of libido
- Erectile dysfunction
- Testicular tumour
- Elevated T and E2
Testicular ultrasonography showing a Leydig cell tumour

Leydig cell tumours cause elevated T and E2, but low gonadotropins.
Seminomas and choriocarcinomas may secrete hCG and elevate T.
Classification of male hypogonadism

Secondary hypogonadism

Isolated hypogonadotrophic hypogonadism (IHH) and Kallmann syndrome

Brain trauma

Pituitary tumor

Pituitary infections

Pituitary hemochromatosis

Hypopituitarism (= multiple pituitary hormone deficiency (MPHD))

Hyperprolactinemia

Congenital Adrenal Hyperplasia (CAH)
Trial of hCG and corifollitropin alfa (long-acting rFSH) in 17 patients with hypogonadotrophic hypogonadism for 16 and 52 weeks.

33 year old patient with Kallmann syndrome before and under substitution therapy. Signs of masculinization are clearly visible.
Classification of male hypogonadism

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Hypopituitarism (= multiple pituitary hormone deficiency (MPHD))
Hyperprolactinemia
Congenital Adrenal Hyperplasia (CAH)

All disorders result in low T, except CAH: increased T and 17OHP
WADA TUE Physician Guidelines 2016
differentiates between
organic and functional
hypogonadism / androgen deficiency

**Organic:** „There is a pathological physical change in the structure of an organ or within the hypothalamic-pituitary-testicular axis“ i. e. „long-lasting or permanent“.

**Functional:** „There is no observable pathological change in the structure of an organ or within the hypothalamic-pituitary-testicular axis“ i. e. „potentially reversible“.
Functional causes of hypogonadism / androgen deficiency

1. Severe emotional stress
2. Morbid obesity
3. Overtraining, malnutrition, eating disorders „Male Athlete Triad“
4. Medication e. g. androgens, SARMs, glucocorticoids, progestins, estrogens, medication-induced hyperprolactinaemia
5. Chronic systemic illness, e. g. chronic organ failure, diabetes mellitus, malignancy, rheumatic disease, HIV-infection, Crohn‘s disease, inherited metabolic storage disease
6. Const. Delayed puberty
7. Alcohol excess
8. Aging/Late-onset hypogonadism (LOH)
Serum T values from 445 elite male athletes grouped according to disciplines:

- Power Lifting
- Basketball
- Football
- Swimming
- Canoeing
- Rowing
- Cross Country Skiing
- Alpine Skiing
- Weight Lifting
- Judo
- Bandy
- Ice Hockey
- Handball
- Track and Field

(Sönksen et al Clin Diab Endocrinol 4: 3, 2018)
Serum testosterone in 12 men before and after a 30 min sub-maximal exercise and a maximal exercise until exhaustion (22.3 ± 2.4 min) (2 weeks between tests)

(Sgrò .... Di Luigi J Endocrinol Invest 37: 13-24, 2014)
LH and T in 5 athletes during a 20-day 1100 km run through Germany before and after the daily stretch of 45 – 65 km.

(Schürmeyer, Jung & Nieschlag Int. J. Androl. 7, 276, 1984)
Testosterone and cortisol levels in 6 runners and 10 cyclists before and after a 160 km race across frozen Alaska:
(Finish times: runners 34 ± 6 h, cyclists 22 ± 6 h)

Effect of treadmill running on male fertility parameters:
5 sessions per week for 60 weeks.
HIE group = high intensity (n=143)
MIE group = moderate intensity (n=143)

Exercise-Induced Hypogonadism
(Hackney & Aggon J Biochem Physiol 2018 epub)
Historical overview of testosterone preparations available for clinical use.

1940
1954
1977
2006
1992
1995
2008
since 2002
since 2004
since 2004
USA 2014
Serum testosterone levels under 4 x 250 mg testosterone enanthate (TE) or 1 x 1000 mg testosterone undecanoate (TU)

(compiled from Nieschlag, Behre, Nieschlag „Testosterone“ 4th ed 2012)
Serum testosterone levels in 27 LOH patients 2 hours after application of AndroGel 1% and in 20 patients receiving placebo on 3 different days (A, B and C)

(Swerdloff et al. JCEM 100:3280-87, 2015)
Effect of testosterone (n=27) vs placebo (n=35) treatment for 12 months in aging men with unexplained anemia.

(Roy et al. JAMA Intern Med. 177: 480-490, 2017)
Effect of weekly injections of 19-nortestosterone* on serum hormone levels in 5 volunteers.

* 1000 mg 19-nortestosterone-hexoxyophenylpropionate for 3 weeks followed by 200 mg weekly injections for 10 weeks (Schürmeyer.....Nieschlag, Lancet i, 417-420, 1984)
Diseases / conditions affecting the testosterone profile in blood

**Men**
- Lower testosterone
- Elevated testosterone

**Women**
- Lower testosterone
- Elevated testosterone

**Disorders of Sex Development (DSD)**
Total and free testosterone in normal women, 18 to 75 years old.

Testosterone levels in women

Testosterone excess in women

- Polycystic Ovary Syndrome (PCOS)
  hirsutism, acne, anovulation
- Congenital Adrenal Hyperplasia (CAH)
  small stature, hirsutism, anovulation
- Androgen-secreting ovarian tumours
- Androgen-secreting adrenal tumours

Low testosterone in women

- Turner’s syndrome (45,X)
- Bilateral oopherectomy
- Premature ovarian failure (POF)
- Adrenal insufficiency (Addison’s disease)
Disorders of Sex Development (DSD)

Congenital variants of biological Anlagen resulting in ambiguous categories to which neither „male“ nor „female“ are strictly applicable.

Disorders of Sex Development = DSD
Hughes et al. The Chicago Consensus 2006
(Arch Dis Child 91: 554 – 562, 2006)

Formerly: Intersexuality
Incidence of 46, XY DSD among elite female athletes

- 849 athletes from 163 countries participating in the 2011 IAAF World Championships in South Korea
- 168 on oral contraceptives
- 5 detected as Anabolic Androgenic Steroid abusers
- 5 cases of 46, XY DSD i.e. 7 per 1000 women = 140 times more than in general population!

Testosterone biosynthesis, transport and intracellular action: Effect of 17ß-hydroxysteroid dehydrogenase defect.

(Nieschlag et al „Andrology“ 3rd ed. Springer 2010)
Serum testosterone (by LC-MS) in normal men and women as well as in PCOS and 46,XY DSD patients

(adapted from data in Handelsman et al Endocrine Reviews 39: 803-829, 2018)
Best chronometric performance in 3 hyperandrogenic female distance runners with disorders of sex development before and under testosterone-lowering therapy (Bermon, Curr Opin Endocrinol Diabetes Obes. 24: 246-251, 2017)
Diseases / conditions affecting the testosterone profile in blood
- Summary -

T shows a diurnal rhythm, high levels in the morning, low in the evening.
Hypogonadism of all forms is characterized by low T, except in some testicular tumors and in CAH.
Short exercise increases T, exhaustive long exercise lowers T (= exercise-induced hypogonadism).
AAS lower gonadotropins and T.

T can be above the normal range in PCOS, CAH, adrenal and ovarian tumors.

46,XY DSD phenotypic females have T levels above the normal female range.