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## **HYPOGONADISM - WHAT IS A LOW LEVEL OF TESTOSTERONE?**

Testosterone, the male sex hormone, is produced by the Leydig cells of the testes and to a far lesser extent by the adrenal glands. Testicular production accounts for 95 percent of the circulating hormone. Testosterone within the circulation is principally bound to proteins, the most important of which is sex hormone binding globulin (SHBG). Only about 2 percent of testosterone is unbound (bio-available) and therefore free to enter cells in order to effect its biological actions by binding to androgen receptors.

Circulating levels of testosterone decline with age<sup>1-3</sup>, however levels of SHBG increase with age, thereby producing a significant fall in bio-available testosterone levels<sup>4-5</sup>.

A study evaluating plasma total testosterone levels by radio immunoassay in healthy non-diabetic Parisian telecommunication employees showed a gradual decline with age<sup>6</sup> (table 1).

**TABLE 1 - PLASMA TOTAL TESTOSTERONE (nmol/L) IN HEALTHY NON-DIABETIC MEN (Adapted from Simon D et al)<sup>6</sup>**

Age (years)	n	Mean	SD	Median	5 <sup>th</sup> Percentiles	10 <sup>th</sup> Percentiles	95 <sup>th</sup> Percentiles
<25	125	23.97	5.48	24.15	14.15	16.22	33.12
25-29	354	23.18	7.14	22.08	13.46	15.18	34.84
30-34	330	21.53	6.72	20.70	12.07	13.46	33.81
35-39	212	20.70	6.55	19.66	11.39	13.46	32.77
40-44	148	20.70	6.87	20.70	11.04	13.11	32.43
45-49	154	18.91	5.66	18.28	11.39	12.42	29.32
50-54	164	18.87	6.49	17.94	10.01	12.07	32.43
55-59	155	19.14	6.04	18.97	11.04	11.73	30.01

Another study of adult and elderly men has also shown the continuing decline in men as they age<sup>7</sup> (table 2).

**TABLE 2 - MEANS PLASMA SEX HORMONE LEVELS (nmol/L) IN HEALTHY MEN (SD). (Adapted from Vermeulen and Kaufman)<sup>7</sup>**

Age (years)	n	T	FT	SHBG
25-34	45	21.38 (5.90)	0.428 (0.098)	35.5 (8.8)
35-44	22	23.14 (7.36)	0.356 (0.043)	40.1 (7.9)
45-54	23	21.02 (7.37)	0.314 (0.075)	44.6 (8.2)
55-64	43	19.49 (6.75)	0.288 (0.073)	45.5 (8.8)
65-74	47	18.15 (6.83)	0.239 (0.078)	48.7 (14.2)
75-84	48	16.32 (5.85)	0.207 (0.081)	51.0 (22.7)
85-100	21	13.05 (4.63)	0.186 (0.080)	65.9 (22.8)

T = testosterone, FT = Free (bioavailable) testosterone, SHBG = sex hormone binding globulin

Testosterone deficiency is associated with a reduction in libido, male erectile dysfunction (MED), excessive sweating and symptoms associated with ageing, such as lack of energy, fatigue, central adiposity, reduced strength and stamina, cognitive decline and mood changes<sup>8-11</sup>. Depression is also a symptom of hypotestosteronaemia<sup>12</sup>.

In addition to symptomatic changes, biological changes also occur with hypotestosteronaemia, osteoporosis is a well recognised association, reduced red blood cell and haemoglobin production and cardio-vascular risk factors such as insulin resistance and the development of non-insulin dependent diabetes are also more prevalent<sup>13-16</sup>.

What appears unclear however is a biochemical definition of hypotestosteronaemia. The normal range for testosterone in serum levels in men is quoted in laboratories in the UK as being in the order of 10-35 nmol/L. There is slight variation around this range depending on assay type used by the laboratories. The range quoted by laboratories is for all adult men and does not take into consideration normal ranges for different age groups. There is no indication within the ranges given as to the median or mean levels for men of specific age groups.

A number of biochemical definitions for hypotestosteronaemia have been proposed including a serum testosterone below the lower range of normal for young male adults<sup>17</sup>,

or serum testosterone levels between the 5<sup>th</sup> and 10<sup>th</sup> percentiles of the relevant assay range. Hypotestosteronaemia levels quoted in papers vary between around 300 ng/dl (10.4 nmol/L) and 400 ng/dl (13.9 nmol/L)<sup>3, 18, 19, 22</sup>.

In a paper addressing clinical practice guidelines for screening and monitoring testosterone supplementation, Morales et al. do not give a biochemical definition of hypogonadism, but propose that men presenting with clinical features of reduced testosterone availability in conjunction with biochemical evidence that testosterone production is decreased, should get treatment<sup>20</sup>.

It is important that men with low levels of testosterone, that is levels that are below the 5<sup>th</sup> percentile for their age or below the 5<sup>th</sup> percentile for healthy young male adults up to the age of 30 years, are not considered as "normal". It is our experience that many symptomatic men are considered not to be suffering from hypotestosteronaemia because although levels are low they are within the normal range. Clearly a 30 year old man with a plasma testosterone level of 12 nmol/L will be below the 5<sup>th</sup> percentile for age but within the normal range quoted by the laboratory and potentially therefore be denied treatment. Men with hypotestosteronaemia should be offered treatment as long as contraindications do not exist<sup>21,22</sup>. The benefits of treatment go beyond the subjective improvements in sexual and erectile dysfunction, libido, well being and mood<sup>23-27</sup>, but also improvements in bone mineral density, insulin sensitivity and erythropoiesis<sup>8, 18, 28</sup>.

Of great interest is a recent finding that men with coronary artery disease have significantly lower levels of plasma testosterone than controls<sup>29</sup> and that intracoronary testosterone infusion in men with coronary artery disease increases coronary blood flow<sup>30</sup>. Such findings suggest that age related declines in testosterone in men may be associated with heart disease and not the presence of testosterone *per se* as previously thought.

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