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INVITED REVIEW

Testosterone levels in healthy men and the relation to behavioural and physical characteristics: facts and constructs

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Abstract

This review summarises the correlations between testosterone levels and male physical appearance and behaviour. Methodological shortcomings concerning the measurement of testosterone could limit the value of these findings. In addition, testosterone measured in body fluids represents only one step in the cascade of action from production to biological effect, and could therefore provide only a limited view of the complexity of physiological events. Testosterone levels are influenced by conditions that are partly controlled or initiated by the hormone itself, but also by circumstances beyond hormonal or individual control. Different kinds of behaviour are not only subject to influence by environment, but also androgens can reinforce the particular kind of conduct and the behavioural impact can wield negative or positive feedback on testosterone secretion. Therefore, both generalisation and individualisation of study results will lead to doubtful conclusions and prejudices. Results of such studies must be viewed with caution, and over-simplification as well as over-interpretation should be avoided.

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Introduction

Testosterone is the best known hormone outside professional medicine. The popularity of the male sex hormone derives from the fact that it acts in all organs and systems and has a significant influence on important aspects of life such as physical appearance, behaviour, mentality, abilities, sexuality and social status. The media are focussed on testosterone and while they disseminate much information, they also indulge in speculations on its effects, as highlighted by the following quotation: 'the He hormone...has become a metaphor of manhood...it affects every aspect of our society, from high divorce rates and adolescent male violence to exploding cults of bodybuilding...' (1). Often scientific publications reinforce these speculations by finding yet another connection between high or low testosterone levels and physical or mental variables. However, because man consists of more than unrelated components, the question arises whether the one-dimensional ups and downs of serum testosterone levels are sufficient to explain the complexities of (hu)man life and whether the supposed/alleged connections may not be oversimplifying and misleading when generalised or applied to healthy eugonadal individuals not exposed to exogenous testosterone. The multitude of associations of low or high testosterone levels with behavioural and physical characteristics makes one wonder whether one hormone can be responsible for so many features and facets of life. In the current article we will review these associations as described in healthy men based on representative and, as far as possible, controlled studies, and point out methodological pitfalls and deficiencies in interpreting results.

Association of endogenous testosterone levels with physical exercise

There are numerous reports on the effects of physical exercise on testosterone levels and *vice versa*. Many of these studies lack control groups, have very low numbers of participants or combine different effectors on hormone levels. Moreover, a distinction has to be made between physical exercises requiring endurance and those that train strength.

Endurance training/physical stress

Endurance training can have a prolonged effect on androgen levels. Controlled trials involving men undergoing endurance training and control groups of sedentary men give the impression of generally lowered

androgen levels in exercising men. Normal feedback regulation would require luteinizing hormone (LH) levels to rise with falling testosterone levels. A suppression in the regulatory axis could explain that differences in gonadotropin levels are rarely seen in exercising vs. sedentary men despite marked differences in testosterone levels (2–7).

That training and competition in physical endurance also means exposure to physical stress is shown in controlled settings observing male participants of ultra-marathon competitions. Testosterone levels decrease during contests, whereas LH levels do not change. In addition, cortisol levels, as a prominent endocrine marker for physical or mental stress exposure, are elevated significantly in runners in comparison to controls (8). This is confirmed by other studies on stress and overtraining (9–12).

Patterns of the mental/psychological and physical stress response of the hypothalamic-pituitary-adrenal (HPA) axis are the same within one individual. Differential reactivity is seen between so-called high and low responders (13). This may apply to the HPA too; the lowering effect of endurance training on testosterone levels may be seen as a part of a general response pattern to stress in an individual. As described below, mental stress has a negative impact on testosterone secretion. In settings combining the mental and physical aspects of stress, testosterone can drop to clearly hypogonadal levels (14, 15). The decrease of testosterone levels under stressful situations is usually not sufficiently answered by the pituitary to compensate for the decrease.

Strength training

In men, muscle mass and strength are often described as being associated with testosterone levels. This applies to older men as well as to adolescents (16, 17). Strength training can have an acute effect on endocrine functions. Measurements immediately and 5 min post-exercise show an age-dependent increase in testosterone levels (18–22). Persons continuously involved in strength training, however, do not show significant changes in testosterone levels (20, 23, 24). Overtraining as a physical stress factor may decrease androgen levels. Abuse of exogenous testosterone for anabolic effects can also affect other parameters and will not be discussed further (22, 25–29).

Mental stress

The release of cortisol by activation of the HPA axis as a reaction to mental stress is well documented (23). Similarly, stress responses by the HPA axis are also seen. This applies not only to physical stress but also to psychologically disturbing events.

Stressful situations as experienced during work, before tournaments or anticipating exams have been shown to decrease testosterone levels (30–36). Stress release, on the contrary, can have an elevating effect on androgen levels, which is demonstrated by a controlled study involving volunteers practising transcendental meditation (37). The same effect was seen in men undergoing workplace reorganisation and threatened by unemployment. After the workplace situation changed for the better, testosterone levels clearly rose; however, there was a marked variation between subjects (38).

It remains unclear whether the drop of testosterone levels in exposure to mental stress is caused by decreased LH secretion or whether an adequate response at the pituitary level is not present. An additional impact factor might be the increased glucocorticoid secretion observed in stressful situations (due to increased corticotropin-releasing hormone production), which may be responsible for down-regulated testosterone biosynthesis in the Leydig cell (39).

Aggression

Aggression is one of the aspects of human behaviour that is often linked to testosterone levels; knowledge and assumptions are often derived from animal models. In a representative study, ten cynomolgus monkeys received injections of either testosterone propionate or a sham solution. Testosterone administration led to a significant increase in aggression, which was mediated by social status. Dominant animals were much more likely to present aggressive behaviour than subordinate ones (40).

In male prison inmates selected for high levels of aggressiveness, testosterone levels have often been described as being linked with violent behaviour (41–47), whereas correlations between testosterone and aggression were low when hostility inventories were applied in volunteers who had not been in conflict with the law (48, 49). This contradiction was explained by the fact that physically violent behaviour leading to legal prosecution is likely to occur in a desolate socioeconomic environment and can itself induce testosterone secretion (and thus result in a selection bias for many studies involving prison inmates). The induction of testosterone secretion by external stimuli of aggression should be seen to be dependent on additional factors, such as culture and education; social background can influence these reactions, as shown in students from the northern and southern parts of the USA, the latter describing themselves as having grown up in a 'culture of honour' in which insults diminish a man's reputation. When the volunteers were subjected to verbal insult, the Southerners reacted with significantly more aggressive and dominant behaviour, which was correlated with their rising serum testosterone levels (50). In a socially homogeneous group of German volunteers, levels of saliva testosterone did not change

during exposure to aggressive and violent films (51). It is possible that an environment constantly provoking aggressive behaviour may lead to various reactions and qualities of aggressive responses, which in turn may lead to differential hormonal secretion patterns (52).

There are strong indications that there is an interdependent feedback mechanism between testosterone and aggression that is modified by experiences of victory and defeat (see below), as well as by education, cultural and socioeconomic background. It seems that the subject's own behaviour can cause and reinforce the type of hormonal activity that stimulated the behaviour in the first place. This pattern of positive feedback seems to be necessary to maintain an emotionally stable personality. Emotional instability was found to be related to a greater variability in testosterone secretion (53).

The immense variety of individual response patterns to androgens is demonstrated by a controlled trial in which exceptionally high doses (600 mg/week) of testosterone cypionate were administered; maniac effects were reported in only 16% of the men. The psychological behaviour of the others remained unremarkable (54). Effects of external administration of testosterone on aggressive behaviour are controversial (55–58).

Depressive illness

In hypogonadal men whose often lethargic or depressive mood significantly improved under testosterone therapy (59), studies exploring the relationship between gonadal function and depressive episodes showed that testosterone secretion as well as mean levels were decreased significantly in patients (60, 61). The relationship of major depression to stress becomes evident by the increased baseline activity of the HPA axis in patients with the disease. Urinary cortisol secretion is significantly increased in depressive patients. This phenomenon is also observed in post-traumatic stress disorder, which can lead to depressive states (62, 63). Decreased testosterone levels in depressive illness can be seen as a permanently downregulated secretion, partially maintaining a state of mood that initiated it in the first place. The effects of depressive illness on androgen levels and *vice versa* are probably closely related to general stress reactions. The mutual character of the feedback mechanism found for testosterone and behaviour may also become evident in this aspect. External administration of testosterone is therefore considered for the treatment of depressive states (64, 65).

Cognitive abilities

Gender differences in cognitive function tests have been widely reported: men tend to excel in fields of spatial cognition, whereas women show greater abilities in verbal fluency (66, 67). Many factors influence the development of these abilities, such as environment, education, cultural background and inherited factors, but sex hormones also play a role in development and maintenance of cognitive functions. Variation and overlapping scores between genders show the limited extent of this impact; to a much higher degree, an individual's cognitive abilities are derived from experience, education and inheritance (68).

Visuo-spatial cognition

Gender differences in spatial cognition have been described frequently; males excel especially in tasks of mental rotation (69–73). Compared with women, a stronger cerebral lateralization concerning various tasks has been observed (74). Right hemisphere specificity in mental rotation procedures (75, 76) can explain the observed difference between genders in such tasks (69, 72). This is also the case in children of both sexes, suggesting an influence of differential foetal sex hormone levels on the formation of brain architecture (70). In healthy men, positive associations of testosterone levels with scores achieved in such tests have been reported (77, 78), but a curvilinear relationship between androgen levels and spatial cognition in humans has also been discussed (79) and some studies report negative relationships (80, 81). An association between the ultradian rhythms of gonadotropin and androgen secretion and performance levels of spatial cognition seems to exist (82).

Only drastically altered testosterone levels yield a coherent picture. In female-to-male transsexuals testosterone has an enhancing, not quickly reversible, effect on spatial ability performance; an opposite effect is reported for male-to-female transsexuals receiving androgen-ablation (83). In hypogonadal men, visuo-spatial abilities are impaired and most studies report improvement during androgen substitution (84–88). Cerebral neuroimaging suggests that this improvement is due to an androgen-mediated activating effect on cerebral structures involved in evaluating data of visuo-spatial content, such as the ventral visual processing stream (89). As long as subjects are not clearly hypogonadal, the learning effects of such tasks are likely to outweigh fluctuations in androgen levels.

Verbal skills

Indications are that testosterone levels seem to be negatively correlated to verbal skills in males (88). Testosterone substitution in elderly males can block the practising effect in verbal fluency (90). Female-to-male transsexuals show a steady decline in verbal fluency under testosterone administration (83). Corresponding effects were seen in male-to-female transsexuals receiving oestrogen treatment; their verbal skills increased in comparison to controls waiting for

hormone treatment (91). It has also been demonstrated that oestrogens can enhance verbal skills in post-menopausal women (92). In healthy elderly men, oestrogen levels are positively associated with verbal abilities (93).

Sex hormone-dependent brain formation processes take place during the prenatal period. In later life, androgens and estrogens seem to be able, and necessary, to activate neural pathways established earlier (94). This refers to the distinction between the states of eu- and hypogonadism, but the effects of shifting hormone levels within the eugonadal range are not distinguishable in individuals.

Musical skills

Empirical data concerning musical skills and testosterone levels are presented in an evaluation of 117 adults and 120 adolescents. Musical abilities were enhanced in men with low testosterone levels and in women with high testosterone levels relative to normal ranges (95). Because many factors influence hormone levels, it is difficult to assign an optimal testosterone range (which would have to be maintained) for the development of musical abilities (96).

Social status

Psychoendocrinological aspects of an individual's social status can be approached by focussing either on hormonal influences on the regulation of social behaviour or *vice versa*. Social interaction may elicit different activation pathways depending on former experiences of the respective individual. Rank in primates has been extensively studied. For example, in mandrills and squirrel monkeys, social rank is said to be correlated with testosterone levels. In squirrel monkeys, external testosterone cannot change rank-specific behaviour (97, 98). Regarding man, studies involving non-primate mammals are of restricted value, because these animals are often subject to seasonal influences.

In boys, a positive association of testosterone with social dominance as assessed by peer-rating was described. Inter-individual variation was high in these samples (99, 100). An occupation involving high demands and low decision latitude, indicating lower social status, was found to be associated with lower testosterone levels (waiters compared with physicians and air traffic controllers). Variable degrees of stress as a lowering vector of testosterone levels (see above) should be taken into consideration when regarding different occupational aspects in each subgroup (101).

To determine a possible role of testosterone in status ranking, chess players were tested before and after competition. Before and after tournaments, winners/winners-to-be had higher testosterone levels than losers (102). Similar results in regard to postcompetition

levels were described during tennis matches and wrestling competitions (103, 104). Also a history of previous success or membership in the host team can lead to an elevation of testosterone levels after the match (105). This indicates that personal experience of success as well as the feeling of dominance owing to 'territorial advantage' can influence the pattern of endocrine response to a competitive situation. An interdependence with other factors such as aggression and 'anti-social' behaviour, described as low levels of intraception, nurturance and responsibility, has been demonstrated (43). Socioeconomic status has been described as a moderating variable in testosterone-behaviour relationships. The constellation of dominance, competitiveness and sensation-seeking behaviour was found to influence the correlation of high testosterone levels with either 'anti-social' or 'pro-social' behaviour, the latter being dominant in individuals with higher socioeconomic status (106). From these data, a sequence of events was inferred: high testosterone levels could lead to aggressive, 'anti-social' behaviour, causing low education levels and thus low occupational status (107). Such a sociological analysis resulting in a singular causal chain is questionable, since hormonal feedback mechanisms and external factors, such as environmental, social and genetic influences should not be disregarded.

Ethnic differences

In violent sexual offenders, serum testosterone levels were significantly higher in the group of native Americans than in Caucasians (41, 108). Such analyses have led to conclusions that a predisposition to crime may be genetically based, have consistent racial variations and may be expressed as serum testosterone levels and brain size, which are supposed to cause different crime rates in Asian, Caucasian and African–Americans (109).

Not biased by selection of subjects in conflict with the law, other studies demonstrate similar testosterone levels in African–American and Caucasian American men. (110, 111). In contradiction to the so-called predisposition theories on crime rates and race, another study involving 1127 men and adjusting data for age and body mass index (BMI), showed levels of total and bioavailable testosterone to be highest in Asian Americans, followed by African–Americans and lowest in Caucasian Americans (112). A greater risk for African–Americans of developing prostate cancer in comparison to Caucasians or Asians seems to exist; testosterone levels are not different, but hereditary factors concerning polymorphism in androgen receptors and 5α-reductase activity are held responsible (113). Supporting results were found comparing Americans of Chinese or Caucasian origin, explaining the lower expression of beard and body hair in Asians (114). Ethnic differences in sex hormone-dependent

features are obviously restricted to genetic polymorphisms, leading to differential enzyme and receptor activity, but not to different testosterone levels (115, 116). The cultural background can also influence testosterone levels through nutritional factors (see *Dietary influences*; 117).

Sexuality

Androgens play an important role in male sexuality. This is impressively demonstrated by activation/reactivation of sexual activity in hypogonadal men receiving substitution therapy. Self-reported decline of sexual functions starts at levels <5–8 nmol/l (118–120).

Behaviour in male heterosexuality

In eugonadal men, testosterone levels have no significant association with different kinds of sexual activity, except for frequency of masturbation (48). Similar results were reported in couples; in men there was no correlation of testosterone levels to sexual activity of any kind but in women sexual gratification, as well as frequency of intercourse, were positively related to testosterone levels (121). It can be assumed that in men testosterone levels are positively linked to libido, but that sexual activity in the partnership is moderated by the relationship itself. In eugonadal men, external administration of high doses of testosterone was said to increase sexual awareness and arousability, but this is not reflected in any general modification of sexual activity (122, 123).

As seen with other behavioural aspects, a mutual relationship between testosterone levels and specific behaviour (in this case sexuality) can be discerned; a sexual stimulus can increase testosterone levels. This has been demonstrated in male volunteers exposed to films with sexual content (51, 124). Cerebral neuroimaging during such films showed sexually stimulated activation of temporal areas to be associated with testosterone levels. This may reflect a positive feedback effect, as testosterone is released by sexual stimulation and can lead to further activation of these areas (125). These data are consistent not only with natural phenomena observed during sexual arousal, but also with the mutual character of hormone-behaviour interaction.

Behaviour in male homosexuality

It has been suggested that testosterone levels might be decreased in homosexual men. Most of the earlier studies did not find significant differences in total serum testosterone levels but tendencies towards lower free testosterone and higher gonadotropins in comparison to heterosexual men were described (126–128).

A differential organisational effect of possibly sub-normal testosterone levels during foetal brain development in homosexual men has been discussed. Thus, differences in LH secretion to an oestrogen stimulus, a dissimilar gonadotropin-releasing hormone pulse frequency and lower neuronal density of hypothalamic nuclei involved in sexual activity, which have been reported in homosexual men, could be explained (129–135). However, homosexuality is as varied and multifold in its behavioural aspects as heterosexuality and postnatal hormone levels do not seem to play a different role from that in heterosexuality.

Violent sexual offences

When sexual offenders receive anti-androgenic gestagens, a clearly hypogonadal state is achieved and sexual activity decreases and, with it, criminal potential. The rate of re-offence is much higher in delinquents not receiving, or discharged from, medication (136). In violent sexual offenders, testosterone serves as a catalyst to initiate the expression of aberrant desires already present, and withdrawal of androgens can inhibit delinquency. The conclusion that higher testosterone levels within or above the normal range would therefore mean a higher risk for sexual aggression cannot be drawn from this information.

Comparing testosterone levels between violent rapists with non-violent sexual offenders and controls has yielded contradictory results (137–139). Sexual aggression as expressed in viewing time of slides with sexually aggressive content vs. control slides showed a slightly positive correlation with free testosterone serum levels (140).

Case reports of patients with low testosterone levels and aggressive sexual behaviour towards women have been published (141–143). Testosterone substitution of these patients who present with often clearly hypogonadal androgen levels can cause aggression to disappear (144). Adaption to psychosexual behaviour that is considered normal and cessation of feelings of inferiority evolve during testosterone substitution (145, 146). This observation stresses the importance of environmental and social factors on sexually aberrant behaviour.

Advancing age

'Andropause' is a term appearing recently in various publications. Alluding to the female menopause, it indicates that in men there could be a precipitous and definite end to gonadal steroid production and fertility, as it occurs in women. In healthy men, however, the decrease in androgen production is rather a slow process. It was shown that with advancing age the proportion of men presenting with testosterone levels in the sub-normal range increases significantly. Low levels can be found in <1% of men aged below 40 years, but in >20% of men older than 60 years and >40% in men above 80 years. These results are confirmed by longitudinal studies. Inter-individual variation is

marked and men aged 70 years can still be fertile (147–154). Increased levels of sex hormone binding globulin (SHBG) further decrease bioavailable testoster-one. Reduced levels of growth hormone and insulin-like growth factor 1, which inhibit SHBG production in hepatocytes, are responsible for this phenomenon (152). A low protein diet may elevate SHBG levels in elderly men (155). Although healthy older men are more likely to present with lower testosterone levels than younger men, many men aged over 80 years (about 55%) still have relatively normal androgen values. With chronic diseases in different subpopula-tions, other pictures emerge (see below).

Weight

The BMI, defined as kg/m^2, is a useful tool to measure obesity. For the whole range of BMI values there is a negative correlation to serum testosterone levels, but levels of SHBG are also decreased. Thus, levels of bioavailable testosterone remain almost unchanged (156, 157); only in extreme obesity (BMI $>$ $40\,kg/m^2$) do testosterone levels decrease to a greater extent than SHBG levels.

Leptin as a messenger of the body's energy resources is positively related to BMI; it is inversely correlated to serum testosterone levels (158). Leptin is most probably involved in the regulation of the hypothalamic-pitui-tary-gonadal (HPG) axis. Although there is a negative correlation between leptin and serum testosterone levels under normal nutritional conditions, another picture emerges in hunger and massively decreased weight; in severe cases, these conditions can affect the HPG axis. Gonadotropins and steroids are reduced, often to clearly hypogonadal levels. Reduced leptin levels and the interaction with neuropeptide Y are held responsible for this phenomenon. In fasting rhesus monkeys, external leptin can restore the function of this axis via normalising (increasing) LH pulse fre-quency (159).

Dietary influences

The effects on hormone levels of fibre-rich, vegetarian diets and 'western-type' diets containing meat protein and more fat have been described. Urinary secretion of androgens (representing a fraction of bioavailable testosterone) in black and white North American men and rural black South African men was found to be significantly higher in those subjects living on a meat-rich western diet. Swapping nutritional habits had corresponding effects (117). Comparing total serum testosterone levels in omnivorous men to those on a vegetarian diet showed no differences, but in the latter group there were significantly higher levels of SHBG, leading to decreased levels of bioavailable testosterone (160). The kind of diet is most likely to influence the

fraction of bioavailable testosterone, but not total levels of this hormone (161–165).

Influence of altitude/air pressure

A comparison between boys living at 3600 m or 420 m showed significantly lower levels of saliva testosterone in the first group (100). Corresponding results were reported from men changing the altitude of their place of residence ((166); but also see (11, 167, 168)). Considering the pattern of hormonal change, exposure to low air pressure could mean a type of physical stress that has similar effects as endurance training.

Voice

Mutation of the male voice to a lower frequency occurs during puberty. It is well established that castrates, when orchiectomized before sexual maturation, main-tain the high voice of a child. During puberty, there is a clear association between the decreasing frequency of the voice, testicular volume and testosterone levels (169, 170). This correlation can also be found in adult males. In male singers, the deeper voices of bass and baritone singers are related to higher plasma testoster-one levels in comparison to tenors. As the deepness of the voice depends on the size of the larynx, it reflects the hormonal situation and organ sensitivity during sexual maturation. That testosterone secretion can be preserved at its relative level is shown in groups of singers 50–70 years of age (171). Due to marked inter-individual variation, estimation of testosterone levels by vocal register is not possible in individual persons.

Hair pattern

In contrast to hypogonadal men, many men within the eugonadal range tend to develop balding patterns of the scalp whereas beard growth is not inhibited. Hair growth in children shows that display of so-called terminal hair is not androgen-dependent. In puberty, pubic and axillary hair develop, these follicles being dependent obviously on sexual hormones. The amount of body hair is highly variable and differs between races and families. The degree of male balding is also inherited (172). Density and pattern of distribution of androgen receptors as well as 5α-DHT levels and 5α-reductase activity also play a pivotal role in secondary sex characteristics (173–175). Men without any sign of balding and no beard growth are most likely to be androgen-deficient or -insensitive.

In eugonadal men, a significant association of free testosterone levels with the development of vertex and frontal baldness was reported (176). In another group, healthy young men showed a disposition to balding in those subjects with an increased ratio of 5α-DHT/ testosterone. Absolute serum testosterone levels were

not associated with balding patterns (177). Differences in beard growth, body hair and balding seen between races are probably determined by various degrees of 5α-reductase activity; the ratio 5α-DHT:testosterone was higher in Caucasians than in Asians living in the US and Canada (112).

## Influence of systemic non-gonadal diseases on testosterone levels

Major burns, myocardial or cerebral infarctions or traumatic injuries as severe, acutely life-threatening diseases cause extreme stress to the individual. Pulsatile LH secretion is often (reversibly) diminished in these patients, leading clinically to hypogonadal states (178). Gonadal function is also influenced by inflammatory mediators (179). Uraemic hypogonadism can be caused by chronic renal diseases via the pituitary (180). Subnormal testosterone levels but gonadotrophin levels within the eugonadal range can be present in chronic liver diseases (181). Gastrointestinal diseases resulting in maldigestion or malabsorption and, therefore, undernutrition can also have a suppressive effect on testosterone secretion (182). Hyperthyroidism, haematological and autoimmune diseases can also alter androgen production (183, 184).

Influence of medications on testosterone levels

There are multiple pathways by which medications can influence the secretion or the action of androgens. Opiates can alter LH pulsatility; steroidogenic enzymes can be inhibited by ketoconazole. Androgen receptors can be blocked by cimetidine or spironolactone. Testosterone metabolism can be increased via hepatic enzyme induction by barbiturates and other anticonvulsants (183). The use of medication can, especially in uncontrolled, cross-sectional studies, contribute to a bias distorting the results concerning endocrine secretion patterns.

Influence of recreational drugs on testosterone levels

In large study groups, tobacco smoking has been associated with elevated testosterone levels (185, 186). The effect of marijuana smoking has no significant effect on gonadotropin or testosterone levels (187). Excessive alcohol consumption has toxic effects on hepatocytes and leads to hypothalamic dysfunction associated with lower testosterone levels. Moderate consumption of alcohol will have no effect, but a personality trait of sensation-seeking behaviour has been described as associated with higher testosterone levels and higher frequency of alcohol consumption (188). Chronic abuse of cocaine will lead to an impairment of hypothalamic-pituitary function and
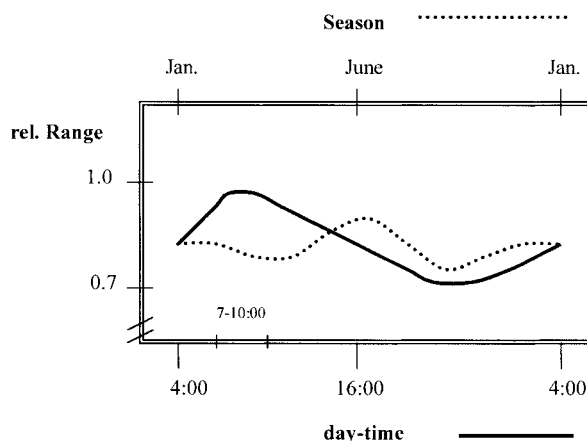

Figure 1 Pattern of relative changes in serum testosterone levels due to diurnal (solid line) and seasonal (dotted line) variations of testosterone secretion (derived from (191–197, 201–203)).

further to decreased testosterone levels (189). The same applies to chronic abuse of opioids, for example, heroin (190). In the cases of long-term illegal drug abuse or excessive consumption of legal substances, other factors, such as an impaired nutritional state and adverse socioeconomic circumstances, will also influence the endocrine pattern.

Discussion

Many of the studies reviewed here have a controlled design; some, in the case of hormone administration, involve placebo groups. Most of the cross-sectional studies have examined data from larger numbers of participants. However, methodological problems of measuring testosterone in body fluids are often overlooked. Serum testosterone levels are determined routinely by radioimmunoassays or luminescence immunoassays. Because there is a strong diurnal variation with morning concentrations being approximately 20–30% higher than evening values (Fig. 1; (191–197)), samples should always be taken during the morning hours. Only then will single point samples be representative (198–200). Seasonal variations of testosterone levels should also be taken into consideration, at least in studies comparing several groups at different time points (Fig. 1; (201–203)). Because testosterone is a small molecule and present in relatively low concentrations, it is not surprising that there is marked inter- and intra-assay bias and variation (Fig. 2). Therefore, comparing testosterone levels determined with different assays and/or in different laboratories becomes questionable. Quality control uncovers this problem, but has not contributed to its solution. Direct measuring of free testosterone concentrations, which are found at much lower concentrations than the total amount of this steroid (about 2%), is subject to even greater difficulties. The
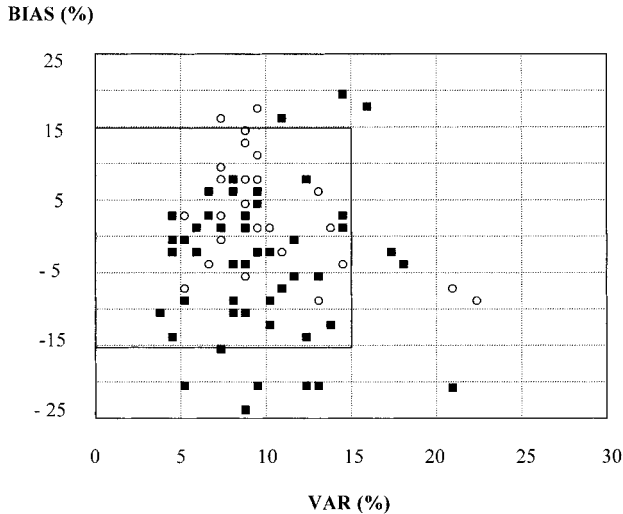
BIAS (%)

Figure 2 Bias and variation of different testosterone assays in males, derived from a quality control programme on steroid assays with 131 participants (222). This means, e.g. when a sample with a 'true' value of total serum testosterone of 12 nmol/l is measured in a laboratory with bias of 15% and variation of 15%, values between 11.7 and 15.9 nmol/l are returned. In another laboratory with bias −15% and variation 15% the same sample is measured between 8.7 to 11.7 nmol/l. Thus, for the 'true' value of 12 nmol/l all values between 8.7 and 15.9 nmol were still acceptable for this quality control programme. Open circles, non-isotopic methods; solid squares, RIA; acceptable range marked by full lines.

Table 1 Testosterone levels: absurdities and prejudices created by applying various one-dimensional associations to individuals. An overview of study results examining singular qualities. Positive associations of testosterone levels of physical and behavioural characteristics.

Aspect		Range of testosterone level		
		Low	Medium	High
Hair pattern	Balding		●	●●
	Beard growth		●	●●
Sexuality	Non-abusive		●	●
	Criminal aspects			●
Physical abilities	Strength		●	●●
	Endurance	●		
Stress		●		
Depression		●		
Social behaviour	Aggression		●	●(●)
	Physical violence		●	●(●)
	Dominance		●	●(●)
	Submission	●		
Cognitive traits	Spatial cognition		●	
	Verbal abilities	●		
Voice	Deep		●	●●
	High	●		
Altitude of habitation	Mountains	●		
	Sea level		●	
Ageing		●		
Diet	Vegetarian	●		
	'Western'		●	
Ethnic group	African			(●)
	Caucasian		(●)	
	Asian	(●)		
	Native American			(●)

● Positive association; ●● relatively strong association; (●) questionable.

same applies to determination of testosterone levels from saliva samples, which are correlated with free testosterone in serum. Reliable assays are still under development (204). Additional measurement of SHBG and its ratio to total testosterone is more reliable when estimating the bioavailable fraction of testosterone (198, 205). In summary, although assays have been available for over 30 years, measurement of serum testosterone is still relatively unreliable and represents a significant bias when interpreting results and correlating them with biological phenomena. Unfortunately, peer-reviewed journals as the ultimate filter have not contributed much to improve the reliability of published values. Therefore, all reported variations of testosterone levels and their associations with physical and mental aspects must be viewed very critically.

When interpreting testosterone levels, it is often overlooked that levels of the hormone in body fluids are only a small and transitory step in the cascade of hormone action from production to biological effect. The Leydig cell as the primary source of androgens in the male is subject to influence by various substances such as testosterone itself (206), oestradiol (207) and glucocorticoids, which are also produced in a diurnal rhythm (208). Transforming growth factor-β, basic fibroblast growth factor and tumour necrosis factor-α are other substances that vary with extratesticular changes (i.e. as inflammation markers) and can decrease Leydig cell steroidogenic responsiveness

(209–211). Androgen receptor polymorphisms (e.g. CAG repeats) can modify testosterone action. The length of the CAG repeats varies among individuals and these polymorphisms are believed to be related to the transcriptional activity of the activated receptor. This applies to forms of prostate cancer (212), breast cancer (213) and benign prostate hyperplasia (214, 215). It can be assumed that CAG repeat length influences androgen susceptibility in other tissues as well. Tissue-specific androgenicity is not solely dependent on testosterone levels; modification is exerted by tissue-specific coactivators of the androgen receptor (216–220). Finally, gene transcription initiated by the activated androgen receptors can be mediated by polymorphisms in the respective promoter regions (221). Thus, serum testosterone levels are only one of many factors forming the cascade of androgen action and all the other factors may follow a pattern independent of serum testosterone levels.

In the studies discussed here, data have been obtained within a confined scope of parameters (Table 1). In most cases, the drastic effects of testosterone substitution in hypogonadal men are mirrored in eugonadal men by somewhat weaker correlations of endogenous testosterone levels with various aspects. Because of the great inter-individual
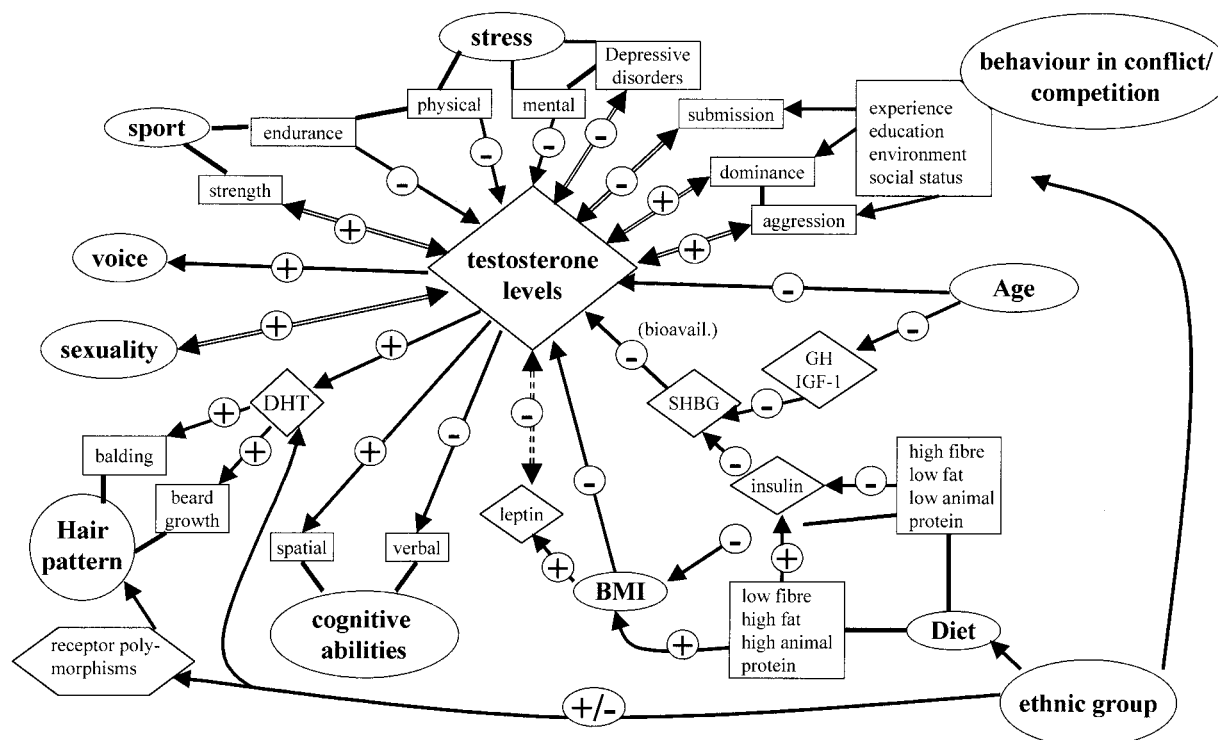
Figure 3 Interactions and feedback-mechanisms of testosterone levels with behavioural and physical dimensions. Arrows indicate the direction of influence, plus or minus signs imply the nature of impact. GH, growth hormone; IGF-1, insulin-like growth factor type 1; DHT, dihydrostestosterone.

variation, application of these results to individuals is questionable. A generalisation towards phenomenological structures would also require sublimation of various one-dimensional findings. Combining results concerning hormone interactions with physical or psychological phenomena to create new constructs explaining sociological observations can be dangerous and misleading. It is too easy a step from assigning high testosterone levels to aggressive people to the explanation of legal offences of violent nature and further, discrimination of racial or subcultural groups. This could mean, for example, that persons involved in regular marathon training are likely to show a submissive kind of conflict management and will not develop a balding hair pattern, or that watching blue movies would lead to premature balding which could then be prevented by a strict vegetarian diet or by moving to the mountains. It could mean that a man exposed to increased mental stress is likely to show extraordinary verbal fluency.

Regarding all results mentioned, a person with high testosterone levels would then be living at sea level, would refrain from endurance training, enjoy high socioeconomic status as well as daily consumption of meat and sexual pleasures, but avoid gaining too much weight. He would be characterised by increased spatial cognition, but not be able to utter sentences fluently. He

would have a deep voice, sing in the bass register, his beard growth would be prolific and his head would be bald. He would react rather aggressively to threatening situations. A person with low testosterone levels would be a mountaineer, exercising daily by long runs, living a frugal life with vegetarian food, without a partner and constantly harassed by his environment. He would have a full head of hair, a high-pitched voice, and would converse fluently about his submissive behaviour and his lack of ability to solve mathematical problems (see Table 1).

The described persons might exist, but they are likely to be rare, and just how high their actual testosterone levels would really be remains open to question. The rest of the male population cannot be judged by testosterone levels and we cannot guess their androgen levels by looking at their lives.

Simplifying approaches are likely to produce results with simple structures, which, while logically consistent in themselves, do not conform to the external structures we experience. Many other factors of influence are omitted in these approaches such as experiences that are partially reinforced by hormonal feedback on behaviour that caused them and that social and physical environment and genetic background affect not only an individual's personality but also a single parameter such as testosterone levels.

Hence, levels of this hormone are influenced by conditions which are partly due to control by the hormone itself, but are also affected by conditions which are beyond individual or hormonal control (Fig. 3). Scientific evaluation of androgen action by carefully planned studies which correct for parameters of additional influence has resulted in useful and fascinating information about the interactions between testosterone and, for example behavioural aspects. It should be viewed for what it is: restricted, but valuable, information on certain domains of hormones and their actions, but it should not be manipulated to create constructs about individuals or groups which inevitably fail. A holistic approach allows a careful application of these principles in individual cases but requires various perspectives of the complex picture of psycho-endocrinological and sociological interactions.

Acknowledgements

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