Several lines of evidence suggest that there is an association between testosterone and suicidal behavior. A link between testosterone and the neurobiology of suicidal behavior may be related to: a) a direct effect of testosterone on suicidality via certain brain mechanisms; and/or b) a testosterone influence on aggression and, consequently, suicidality; and/or c) a testosterone effect on mood and, consequently, suicidality; and/or d) a testosterone effect on cognition and, consequently, suicidality. At least one study has demonstrated a relation between high levels of testosterone and suicide in young people. A significant number of studies suggest that high testosterone levels are associated with aggression in adolescents and adults. Multiple lines of evidence indicate that aggression is associated with suicidal behavior. The effect of high testosterone levels on suicidality in adolescents and young adults may be mediated by testosterone-related elevated aggression. It is also possible that in young people, high testosterone levels are directly linked to suicidality via certain brain mechanisms. In older men, decreased testosterone levels are associated with depressive symptoms and reduced cognitive function while higher blood levels of testosterone are associated with better mood and cognitive functioning. Depression and reduced cognition are associated with suicidal behavior and may mediate the effect of decreased testosterone levels on suicidality. Therefore, it is reasonable to propose that suicidal behavior in adolescents and young adults is associated with high testosterone levels while suicidality in older men is associated with decreased testosterone secretion.

3.1 Introduction

Testosterone, a hormone from the androgen group, was isolated, synthesized and described in the 1930s by European researchers (1). The first research papers on the protein nature and on the isolation of androgen receptors from androgen target tissues were published at the end of the 1960s by several groups of investigators. Confirmation for a specific androgen-binding protein isolated from prostate tissue cytosol, was published by the research groups of Ian Mainwaring from the ICRF in London, Shutsung Liao at the University of Chicago and Étienne-Émile Baulieu at the INSERM Institute in Kremlin-Bicêtre in Paris (2–4).

Testosterone is produced from cholesterol in the Leydig cells in the testis. Testosterone synthesis in the fetal human testis begins during the sixth week of gestation. Leydig cell differentiation and the initial early testosterone production in the fetal testis are independent of luteinizing hormone (LH) (5–7). During testis development production of testosterone occurs under the influence of LH which is produced by
the pituitary gland. Synthesis and release of LH is regulated by the hypothalamus through gonadotropin-releasing hormone (GnRH) and inhibited by testosterone via a negative feedback loop (8). Testosterone is metabolized in some tissues to a more active metabolite, 5α-dihydrotestosterone.

Testosterone is present in the blood as free (unbound) testosterone, albumin bound and sex hormone-binding globulin (SHBG)-bound testosterone (5–8). Testosterone is a C19 steroid with an unsaturated bond between C-4 and C-5, a ketone group in C-3 and a hydroxyl group in the b position at C-17. It is mostly produced in the testes of males and the ovaries of females, although small amounts of testosterone are produced by the adrenal glands. Testosterone is found in mammals and other vertebrates. Blood testosterone levels are much greater in males than in females: an adult male body produces approximately ten-times more testosterone than an adult female body. Females are more sensitive to testosterone than males. Testosterone regulates male sexual development and affects muscle strength, levels of erythrocytes, bone density, sense of well-being and sexual and reproductive function in both males and females.

SHBG concentrations may be decreased or increased in many frequently observed medical conditions. In clinical practice, changes in SHBG are critically important to consider in the diagnosis of male hypogonadism. Because plasma total testosterone concentrations are affected by alterations in SHBG levels, precise measurements of free or bioavailable testosterone are necessary to evaluate the sufficiency of Leydig cell function, to clarify whether a patient is hypogonadal, and to monitor the testosterone replacement treatment in patients with changes in circulating SHBG concentrations.

### 3.2 Testosterone and suicide

Multiple studies suggest that testosterone plays a role in the regulation of mood and behavior. The research studies of the relationship between testosterone and suicidal behavior produced variable results (9–14). Some (10–13) but not all (14, 15) investigations of the relationship between testosterone and suicidality found associations between testosterone and suicidal behavior.

Tripodianakis et al compared plasma testosterone concentrations in men after a suicide attempt with testosterone levels in healthy men of the same age (10). The authors found that the suicide attempters had lower testosterone levels compared with controls, and that the attempters who used violent methods had lower plasma testosterone concentrations compared with the non-violent attempters. Markianos et al examined plasma testosterone levels in a group of male psychiatric patients who had attempted to commit suicide by jumping, in a group of male subjects who were hospitalized after unintentionally falling from a high height and in healthy controls (11). Both accident and suicide attempt patients had lower testosterone levels.
compared with the control group, and there was a trend towards lower testosterone levels in suicide attempters compared with the accident group. We have recently examined whether there is a relation between plasma testosterone levels and clinical parameters in bipolar suicide attempters and found that testosterone levels positively correlated with the number of manic episodes and the number of suicide attempts (12). Some other observations have shown that testosterone/anabolic androgenic steroids may play a role in the pathophysiology of suicidality (13).

A recent study found no difference between male suicide attempters and male controls with regard to plasma testosterone levels (14). A study of associations between neuroactive steroids and suicidality in military veterans with posttraumatic stress disorder also found no association between serum testosterone levels and a history of a suicide attempt (15).

Disappointment over rejections at attempts for sexual interactions has been cited several decades ago as an important trigger for suicide (16). Impending divorce, marital difficulties, threat of losing a love partner and rejection by a loved one were also regarded as motives for suicide for many years (17). It has been observed that rejection of sexual intercourse was often associated with male suicides and suicidal ideation (18). A link between testosterone and the neurobiology of suicidal behavior may be related to (9):
(a) A direct effect of testosterone on suicidality via certain brain mechanisms; and/or
(b) A testosterone effect on aggression and, consequently, suicidality; and/or
(c) A testosterone effect on mood and, consequently, suicidality; and/or
(d) A testosterone effect on cognition and, consequently, suicidality.

### 3.2.1 Testosterone and suicidal behavior in adolescents and young adults

**Suicide and testosterone/anabolic androgenic steroids**

At least one study has demonstrated a relation between high levels of testosterone and suicide in young people (19). Twenty-nine subjects (17 suicides, 12 sudden deaths) in the ages 23–45 years were included in the study. Analysis indicated no significant difference in ages between the two groups of subjects (suicide M = 33.35 year, sudden death M = 35.67 year). There was a significant difference in the mean testosterone level (p < 0.007) between victims of suicide (M = 376.41 ÷ 183.64 ng/ml) and victims of sudden death (M = 241.83 ÷ 117.3 ng/ml).

Eight cases of suicide, in 21- to 33-year-old males, with a history of current or recent use of anabolic androgenic steroids (AAS) have been described in a case series report (20). Five suicides were committed during current use of AAS, and two following 2 and 6 months after AAS withdrawal. The authors suggested that long-term use of AAS may contribute to completed suicide in predisposed persons.
A possible role of aggression

A significant number of studies suggest that high testosterone levels are associated with aggression (9). It has been shown that violent persons have higher plasma, saliva and CSF testosterone levels compared to non-violent controls (21–23). For example, in a study of impulsive offenders with alcoholism and antisocial personality disorder, higher CSF testosterone levels were observed compared to healthy controls (24). The authors proposed that high CSF testosterone levels may be associated with aggressiveness or interpersonal violence. In the same paper, the authors reviewed the scientific literature on the link of testosterone to aggression in humans, and proposed that both a repetitive pattern of aggressive behavior starting early in life, and a repetitive pattern of aggressive behavior under the effect of alcohol are associated with increased levels of testosterone. Researchers have observed that individuals receiving testosterone are more likely to have an aggressive reaction to perceived threats than subjects receiving placebo (25–27).

Fluctuations of testosterone concentration may be associated with aggression and mood changes in adolescents (28–30). Salivary testosterone concentrations were evaluated in 40 children, aged 7–14 years (37 boys and three girls), with a history of aggressive behaviors and an association between higher testosterone levels and aggressive behaviors was observed (29). In another study of adolescent males, higher testosterone levels were associated with provoked verbal and physical aggression, a finding suggesting that reactive impulsive aggression is correlated with higher testosterone levels (30). Fifty-eight healthy 15–17-year-old boys, public school students participated in this study. A high level of testosterone led to an amplified readiness to respond energetically and forcefully to provocations and threats. Testosterone also had an indirect and less strong effect on another aggression dimension: high plasma concentrations of testosterone made the boys less patient and more irritable, which in turn intensified their predisposition to engage in aggressive-destructive behavior. Therefore, aggression may mediate the effect of high testosterone levels on suicidal behavior in adolescents and young adults. Not all studies have observed differences in testosterone levels between aggressive and non-aggressive boys (31). A study of 4–10 year olds found no evidence of a relationship between testosterone levels and aggressive behaviors. This indicated that such a relationship may be non-existent in prepubertal children.

Animal models have contributed important data regarding the effects of anabolic androgenic steroid (AAS) use on aggression (32, 33). For example, studies in rodents confirmed that exposure to the AASs testosterone and nandrolone increases aggression. A side effect of AAS use reported in humans is “roid rage,” a state of unselective and unprovoked aggression. It has also been observed that pubertal rats receiving AASs respond appropriately to social cues and they are more aggressive toward intact males than are castrates. Testosterone-treated male rats are most aggressive in their home cage. Probably, adolescent AAS exposure may increase aggressive behaviors.
Some authors have postulated that there are substantial similarities between aggression against the self and aggression against others, based on the clinical and epidemiological observations that some suicide attempters may share personality traits with violent criminals (34). We have also observed an association between aggression and suicidal behavior in our studies (35, 36). For example, we have observed that a history of suicide attempt in bipolar disorder is associated with lifetime aggressive traits (35). We have also shown that the higher prevalence of suicide attempters among depressed patients with a history of alcoholism compared to depressed patients without a history of alcoholism was related to higher aggression scores in the group with alcoholism (36).

In summary, high testosterone levels may be associated with suicidal behavior in adolescents and young adults. This effect of testosterone on suicidality in adolescents and young adults may be mediated by testosterone-related elevated aggression. It is also possible that in young people, high testosterone levels are directly linked to suicidality via certain brain mechanisms.

### 3.2.2 Testosterone and suicidal behavior in older men

Testosterone deficiency or hypotestosteronemia is a commonly known hormonal change associated with male aging (37–39). The prevalence of testosterone deficiency may be as high as 30% in men aged 40–79 years (40, 41). In up to 12% of affected men, hypotestosteronemia can be associated with clinical symptoms (40, 41). Age-related plasma testosterone decrease is a result of different biological alterations such as primary structural gonadal damage, age-related degenerative changes of the pituitary gland, insufficiencies of the neurohypothalamic system, and primary peripheral metabolic abnormalities such as the age-associated increase in the concentration of serum SHBG, with a consequent decrease in free testosterone (39). In the aging man, there is about a 1–2% decrease of total testosterone levels per year with a more rapid drop in free testosterone levels because of a concomitant increase in SHBG with aging. Because of this gradual decrease in testosterone levels the androgen deficiency of the elderly man is defined as partial androgen deficiency of the aging male (PADAM) or late onset hypogonadism (LOH).

Symptoms of testosterone deficiency in men include sexual symptoms (such as reduced erectile function and diminished libido), decreased muscle and increased fat mass, and reduced bone density among others. It is unclear whether aging is to be considered as the only variable linked to age-related testosterone decrease. Various aspects such as genetic factors, chronic diseases, medications, obesity, and the lifestyle may affect the testosterone metabolism (37, 42–44).

Decreased testosterone levels are associated with depressive symptoms, poor cognitive function and Alzheimer’s disease (9, 45–48). Increased incidence of hypogonadism is observed in men with major depression (9, 47). Depressed men frequently
have low plasma or serum testosterone (9, 48). Testosterone has mood-enhancing properties and antidepressant effects in men (9, 49–51). Testosterone replacement effectively improves mood. Testosterone users sometimes develop manic or hypomanic symptoms during testosterone use and depressive symptoms during testosterone withdrawal (52–55). In rodents, testosterone has antidepressant effects in aged male mice and protective effects against the development of depression-like behaviors in rats (56, 57). A recent study found a testosterone-dependent regulation of hippocampal ERK2 expression which suggests that ERK2 signaling within the dentate gyrus area of the hippocampus is a vital mediator of the antidepressant properties of testosterone (58).

Experimental studies suggest that testosterone has neuroprotective effects (59). However, intervention clinical research on elderly men showed that testosterone replacement had a beneficial influence on mood only if men had clearly subnormal testosterone levels (60). It is important note that sexual dysfunction can have a major effect on the quality of life and emotional well-being (61, 62). The results of placebo-controlled randomized studies of the effects of testosterone on the quality of life and depressed mood have been inconsistent and often the quality of life as assessed by different questionnaires did not improve significantly (63).

Higher blood levels of testosterone are associated with better cognitive functioning, especially in older men (45, 46). For example, greater serum levels of testosterone late in life predict a lower risk of future Alzheimer’s disease development in older men (45). Higher blood testosterone levels are associated with better visuospatial abilities, semantic memory and episodic memory in men, with larger positive effect with increasing age (46).

Both depression and cognitive impairment are associated with suicidal behavior (64–67). At least 60% of individuals who commit suicide suffer from depression. Hence, depression and cognitive impairment may mediate the effect of testosterone deficiency on suicidality in older men. This suggests that the treatment of hypogonadism in older men may improve mood and cognition, and consequently, reduce suicidal behavior.

3.3 Conclusions

In summary, it is reasonable to propose that suicidal behavior in young men is associated with high testosterone levels while suicidality in older men is associated with decreased testosterone secretion. This indicates that the effects of testosterone on suicidality in men should be studied separately in young and old individuals. It is likely that plasma and salivary testosterone assays can help in identifying pediatric and adult patients that would respond best to certain treatments. Further studies of the role of testosterone in the pathophysiology of psychiatric disorders and suicidal behavior are merited.
References


