Lack of Association between Testosterone and Suicide Attempts

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Key Words

Androgens • Gender • Suicide • Suicide attempt

Abstract

Objective: To determine whether testosterone levels differ in male suicide attempters versus healthy controls and to explore the associations between testosterone levels and time of blood collection, and between testosterone levels and characteristics of suicide attempts. **Method:** A sample of 112 male suicide attempters was studied. Thirty-seven male blood donors were recruited as controls. **Results:** The mean testosterone levels were 5.1 ± 2.9 ng/ml in male attempters and 4.6 ± 1.6 ng/ml in controls. Group differences in testosterone levels were not significant when we studied the interaction with time of extraction ($F = 0.37$; d.f. = 2; $p = 0.70$) or when matched by age and time of extraction ($t = -0.74$; d.f. = 26; $p = 0.47$). When partial correlations were performed correcting for the effect of time of extraction, significant partial correlations were found in testosterone levels with history of aggressive behavior and lethality of the attempt. **Conclusions:** When circadian variation and age were consid-

ered, we found no support for the putative role of testosterone as a biological marker of suicidal behavior. Further research should consider: (1) testosterone and neurosteroids; (2) serial determinations with a minimal time gap between the attempt and the blood extraction; (3) controls within the same time periods, and (4) other variables that may affect testosterone levels, such as body mass index, physical activity and sleep disturbances.

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Introduction

Completed suicides are more frequent among men, and suicide attempts are more frequent among women [1–9], although there are several exceptions for this gender distribution [10, 11]. The greater completion rate in males has been explained by different hypotheses, such as differences in the methods used for attempting suicide, which may condition lethality [12].

Other sociological and cultural factors, such as industrialization or understanding of suicide, have also been

Table 1. Sociodemographic data and psychiatric history

		Cases	Controls	Statistics
Age, years	Mean $\pm$ SD 95% CI	36.2 $\pm$ 11.1 34.2–38.3	32.8 $\pm$ 11.3 18.7–62.5	F = 2.65; d.f. = 1; p = 0.105
Marital status	Single Married/couple Divorced/widowed	52 (46.4) 34 (30.4) 26 (23.2)	19 (51.4) 17 (45.9) 1 (2.7)	χ^2 = 8.57; d.f. = 2; p = 0.014
Education	Less than high school High school College degree	41 (36.9) 45 (40.5) 25 (22.5)	6 (16.7) 14 (38.9) 16 (44.4)	χ^2 = 8.19; d.f. = 2; p = 0.017
Prior admissions to inpatient unit	No 1–3 admissions >3 admissions	61 (54) 29 (26) 14 (13)	– – –	– – –

Information on marital status was missing for 4 cases, on educational level for 1 case and 1 control, and on prior admissions for 8 cases. CI = Confidence interval; figures in parentheses are percentages.

proposed to explain the gender differences in suicidal behaviors [11]. Biological hypotheses have focused on gender differences in morphological and functional development of the central nervous system, hormonal and genetic factors [1].

Some authors have postulated that there are substantial similarities between aggression against the self and aggression against others, based on the clinical and epidemiological findings that suicide attempters may share personality traits with violent criminals [13] and that in adolescents suicidal thoughts may be associated with higher aggressiveness scores [14]. Studies have shown significantly higher cerebrospinal fluid (CSF) testosterone levels in alcoholic offenders compared to both nonalcoholic offenders and healthy controls [15] and in alcoholic, impulsive offenders with antisocial personality disorder compared with healthy controls [16].

However, studies on the relationship between suicidal behavior and testosterone levels to date suggest that suicidal behavior and aggression may have different biological bases. In male suicide attempters, aggressiveness has been associated with low testosterone levels [17], but this finding has not been replicated [18, 19]. Gustavsson et al. [20] did not find any significant association between testosterone levels and suicidal behaviors or aggressive-impulsive temperament. CSF testosterone levels in their aggressive violent patients were significantly lower than those reported by Virkkunen et al. [16] in a healthy control group. Higher CSF testosterone levels after suicide attempts were only described in one study in a subgroup

of suicide attempters with mood disorders other than major depressive disorder (depression not otherwise specified and dysthymia) compared to patients with major depressive disorder, adjustment disorder, substance use disorder or anxiety [20].

In previous work we have found that sexual hormones may influence suicide attempts in females [21–23]. In this study we examine the relationship between testosterone and biological and clinical variables in male suicide attempters, which appears to be more complex than expected.

We hypothesize that circadian variations in testosterone levels might modulate the putative association of lower testosterone levels after suicide attempts. Therefore, we studied testosterone levels in male suicide attempters versus healthy controls after controlling for age and time of extraction of the blood samples.

Additionally, we examined the relationship between testosterone levels and psychiatric diagnoses, attempt impulsivity, lethality and method, and history of aggressive behavior.

Methods

Sample

Suicide attempters were defined according to the definition provided by O'Carroll et al. [24]. The 112 male suicide attempters were recruited from two general hospitals in Madrid (Spain) during a 4-year inclusion period (1999–2003) and the 37 male controls from healthy blood donors from one of these hospitals.

Table 2. Psychiatric diagnoses of the cases (n = 107)

	All cases	MDE	Dysthymia	Bipolar disorder	Anxiety disorder	SUD	Psychotic disorder
Number	112 (100)	67 (62.6)	6 (5.3)	12 (11.2)	32 (29.9)	48 (44.8)	32 (29.9)
Age (mean $\pm$ SD), years	36.2 $\pm$ 11.0	37.7 $\pm$ 11.1	38.1 $\pm$ 9.7	41.5 $\pm$ 13.9	37.7 $\pm$ 11.3	36.2 $\pm$ 9.92	34.8 $\pm$ 16.9
Testosterone levels (mean $\pm$ SD), ng/ml	5.54 $\pm$ 2.80	5.52 $\pm$ 2.96	6.34 $\pm$ 3.10	5.89 $\pm$ 2.05	5.42 $\pm$ 2.39	5.89 $\pm$ 3.13	6.35 $\pm$ 2.11
Violent attempt, n	18 (16.1)	11 (16.4)	0	1 (8.3)	3 (9.4)	11 (22.9)	0
Student's t	–	–0.23	–0.77	–0.55	0.11	–1.39	0.91
d.f.	–	105	105	105	105	105	105
p	–	0.812	0.441	0.584	0.905	0.166	0.362

Information on diagnosis was missing for 5 subjects.

MDE = Major depressive episode; SUD = substance use disorder; figures in parentheses are percentages.

Sociodemographic data is detailed in table 1. Post hoc power calculation showed that the effect size for group differences in testosterone levels was 0.32, which according to the definition provided by Cohen [25] is a medium effect size, and statistical power was 0.52. Blood extractions were performed in all cases within 24 h after the attempt, with an approximate mean time of 3 h. All participants were male Spanish Caucasians over 18 years of age who agreed to sign consent forms approved by the two hospital Institutional Review Boards for this study, which has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Subjects with age >65 years were excluded from the study, due to the steep 13% annual decrease in free testosterone blood levels from this age [26, 27]. Assessment of the control group was based on the medical charts and a personal interview. Exclusion criteria for the control group were psychiatric treatment longer than 6 months of the patient or first-degree relatives, personal history of suicide attempt or of completed or attempted suicide in first-degree relatives, 12-item General Health Questionnaire scores >8 [28], or suspicion of substance abuse or dependence established by CAGE/TWEAK scores >1 [29] and South Oaks Gambling Screen scores >1 [30].

Assessment Instruments

The same research team evaluated cases and controls. The Spanish version of the Mini International Neuropsychiatric Interview was used to obtain axis I DSM-IV diagnoses [31]. The most frequent axis I diagnoses in the sample were: 62.6% (n = 67) major depressive episode, 44.8% (n = 48) substance use disorder, 29.9% (n = 32) anxiety disorder and 29.9% (n = 32) nonaffective psychotic disorder. Detailed results can be seen in table 2. The lethality of the suicide attempt was assessed using the Lethality Rating Scale and Method Attempt Coding (LRS) [32], which rates the attempt's medical consequences on a scale from 0 (no consequences) to 8 (death). A score >2 suggests a 'high-lethality' attempt and indicates the need for major medical interventions to treat the patient. Attempts were classified as having high lethality or low lethality [33].

The Suicide Intent Scale (SIS) [32] global score indicated the severity of the attempt. The first item of the Risk-Rescue Rating

Scale [34] was used to classify the method of suicidal attempt: (i) ingestion, cutting, stabbing; (ii) drowning, asphyxiation, strangulation, and (iii) jumping, shooting. History of aggressive behavior was measured by the Brown-Goodwin Scale, which included 9 categories [35]. A score ≥ 2 on this scale was considered high [36]. The Spanish version of the 11-item Barratt Impulsiveness Scale [37] was used to measure impulsivity traits using 30 self-reported items scored from 0 to 4. A score of 48, the 75th percentile of the control sample, was used to define high levels of impulsivity [36].

Hormonal Determinations

All determinations were done in the same laboratory. Blood samples were stored at a temperature of 2–8°C and processed during working hours (during the same day or the morning following blood extraction). Total plasma levels of testosterone were measured with an automated chemiluminometric high-sensitivity testosterone assay (Immulite®; Diagnostic Products Corp., Los Angeles, Calif., USA) using an Immulite automated analyzer. The dynamic range of the Immulite testosterone assay is 0.14–15.86 ng/ml, and the average interassay coefficient of variation is 13.7% at a concentration of 4.27 ng/ml of testosterone.

Statistical Analysis

The Statistical Package for Social Sciences (version 14.0) was used for statistical analyses. Analysis of variance included testosterone levels as the dependent variable. Independent variables were group (suicide attempters versus controls) and extraction time. The extraction times were classified in 3 groups (6.00–14.00; 14.00–18.00; 18.00–6.00 h) according to previous findings [27]. To further control for confounding factors, a Student's t test for matched samples compared levels between suicide attempters (n = 27) and controls (n = 27) previously matched by age and time of extraction. Student's t test for independent samples was used to compare testosterone levels by diagnosis within the case group (table 2). Diagnoses were computed as dichotomic variables.

ANOVA was used to study testosterone level differences by sociodemographic variables and suicidal method. Finally, in order to explore the association between testosterone levels and dimensions of suicidal behavior measured with ordinal scales,

Spearman-Brown correlation coefficients were applied. Dimensions of suicidal behavior included: (i) aggression, measured using the Brown-Goodwin scale; (ii) impulsivity, measured using the Barratt Impulsiveness Scale; (iii) lethality, measured using the LRS and Beck's SIS expected lethality subscale, and (iv) severity, measured using Beck's SIS.

Results

The mean testosterone levels (ng/ml) were 5.54 (standard deviation, SD = 2.80) in male attempters and 4.76 (SD = 1.97) in controls. Group differences were not significant when we studied the interaction with time of extraction ($F = 0.37$; d.f. = 2; $p = 0.70$). Similarly, there were no significant differences in the analysis when matched by age and time of extraction ($t = -0.74$; d.f. = 26; $p = 0.47$). Though sociodemographic disparities were found between the case and control groups (table 1), testosterone levels in the sample did not vary by educational level ($F = 0.40$; d.f. = 2; $p = 0.67$) or marital status ($F = 1.39$; d.f. = 2; $p = 0.25$).

Testosterone levels showed no significant differences across suicidal methods in our sample ($F = 0.67$; d.f. = 3; $p = 0.568$). Correlations of suicidal dimensions with testosterone levels were also nonsignificant both for cases and for controls (data not shown). However, partial correlations of testosterone levels with attempt lethality and aggression by time of blood extraction were significant. Significant correlations of testosterone levels and attempt lethality were found with both LRS and Beck's SIS expected lethality subscale: (i) with LRS when blood was drawn between 14.00 and 18.00 h ($\rho = -0.51$; $p = 0.033$; $n = 17$) and between 18.00 and 6.00 h ($\rho = 0.43$; $p = 0.002$; $n = 46$), and (ii) with Beck's SIS subscale when blood samples were drawn between 6.00 and 14.00 h ($\rho = -0.32$; $p = 0.038$; $n = 40$) and between 18.00 and 6.00 h ($\rho = 0.32$; $p = 0.022$; $n = 48$). An inverse significant correlation was found between the Brown-Goodwin score and testosterone levels ($\rho = -0.53$; $p = 0.042$; $n = 15$) in those suicide attempters from whom the blood samples were drawn between 14.00 and 18.00 h.

Levels of testosterone across psychiatric disorders showed no significant differences (table 2). No significant difference in testosterone levels was found between violent ($n = 18$) and nonviolent ($n = 94$) suicidal methods ($t = 0.56$; d.f. = 110; $p = 0.575$).

Discussion

In this study in males, we found no significant differences in testosterone levels between suicide attempters and controls when circadian variation and age were taken into account. This result does not support the putative role of testosterone as a biological marker for suicidal behavior, as has been proposed by Tripodianiakis et al. [17]. The association of high testosterone levels with specific axis I diagnoses [20] was also contradicted by our results, which show no differences between broad axis I categories.

Several confounding factors addressed in the present study may explain this difference. The time elapsed between the suicide attempt and blood extraction was not specified in previous studies. Matsumoto and Bremner [38] stated that total testosterone levels may vary with time of day, the assay used and sex hormone-binding globulin levels, thus not reflecting the bioavailable testosterone levels. The relevance of the time lapse between the suicide attempt and the blood sampling might be best judged considering the half-life of biological testosterone: 30–60 min [39]. The present study controls most of these factors establishing time of blood extraction and the same laboratory conditions for all samples, though determinations of sex-hormone-binding globulin levels were not performed. The present sample was homogeneous from the racial point of view, and old age was excluded as a confounding factor. However, due to the limitations of the study, the possibility of a false-negative result should not be disregarded.

Aggressiveness has been associated with high testosterone levels in nonsuicidal patients [15, 16]. Suicide has been the object of research looking for an association with testosterone levels, and previous studies reported low plasma T levels after suicide attempts [17, 20]. This could reflect a downpeak reaction due to previous self-directed aggression. Among the attempters in the current study this association was not found, and the trend was in the opposite direction (higher testosterone levels among suicide attempters compared to controls). Butterfield et al. [40] reached similar findings studying steroid levels among hospitalized male veterans with posttraumatic stress disorder that had made suicidal attempts. In our study the partial correlation after correcting for time of extraction was significant but inverse, suggesting that a longer history of aggressive behavior was associated with lower testosterone levels. The partial correlations between testosterone levels and the lethality of the attempt, measured with different instruments, suggest a

putative association. These associations might be mediated by an alteration of the circadian rhythm instead of a linear change of testosterone levels. Timed testosterone determinations may be needed to clarify the behavior of testosterone levels after the attempt.

Limitations of this study include (1) using only one determination for testosterone levels in each subject, (2) lack of male controls available for all time periods and (3) some variables that may affect testosterone levels which were not considered: smoking status [41], body mass index, educational level, physical activity, marital status, sleep disturbances and pharmacological treatment. Ideally, the design should include serial determinations with minimal time gap between the attempt and the blood extraction, and controls within the same time period.

Future studies analyzing the relationship between testosterone levels and suicide attempts should include: (1) testosterone and neurosteroids, (2) serial determinations

with minimal time gap between the attempt and the blood extraction, (3) controls within the same time periods and (4) other variables that may affect testosterone levels, such as body mass index, physical activity and sleep disturbances.

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