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The effect of oral dexamethasone administration on testosterone levels in combat veterans with or without a history of suicide attempt

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ABSTRACT

Combat exposure has been linked to increased risk of suicidal ideation, suicide attempts, and death by suicide, and suicidality has been linked with altered testosterone levels. In this study, we examined morning baseline free and total testosterone levels and the effect of dexamethasone administration on testosterone levels in male combat veterans with or without a history of suicide attempt. Demographic and clinical parameters of the study participants were assessed and recorded. Blood samples were collected between 8:00 and 8:30 a.m. on the day prior to and following dexamethasone (0.5 mg) ingestion. Suicide attempters had higher schedule for suicidal ideation (SSI) scores in comparison to non-attempters. Baseline free and total testosterone levels were lower in suicide attempters compared to non-attempters. In the whole sample, both baseline free and total testosterone levels negatively correlated with SSI scores. Free testosterone levels decreased after dexamethasone administration among non-attempters but not among attempters. Free testosterone post-dexamethasone levels positively correlated with aggression scores among non-attempters but not among suicide attempters. Our findings indicate that there are substantial differences in the testosterone regulation between combat veterans with or without a history of suicide attempt. Studies of the relation between the testosterone function and suicidal behavior among combat veterans may lead to improvement in detection of suicidality and finding new pharmacological targets for prevention of suicide among veterans.

1. Introduction

Multiple lines of evidence suggest that combat veterans are at elevated suicide risk (Boehmer et al., 2004; Pietrzak et al., 2010; Sher and Yehuda, 2011; O'Toole et al., 2015; Thomas et al., 2017). Research on suicidality has shown that combat exposure is associated with increased suicidal ideation, suicide attempts, and death by suicide (Boehmer et al., 2004; Pietrzak et al., 2010; O'Toole et al., 2015; Thomas et al., 2017). In one study, 12.5% of about 300 U.S. combat veterans reported considering suicide in the two weeks prior to completing the survey (Pietrzak et al., 2010). A study of about 1500 U.S. veterans showed that compared to noncombat veterans, combat veterans had 68% greater odds of having attempted suicide (Thomas et al., 2017). Another study showed that relative risks for suicidal ideation, planning and attempts were 7.9, 9.7 and 13.8 times higher for male Australian Vietnam combat veterans compared with the age-sex matched Australian population statistics (O'Toole et al., 2015). The uniqueness of the combat experience as a contributor to suicidal behavior warrants specific studies of both psychological and biological factors that may be associated with suicidality in combat veterans. Combat exposure is associated with multiple psychological and environmental factors affecting testosterone function (Diamanti-Kandarakis et al., 2009; Reijnen et al., 2015; Toufexis et al., 2014; Westat, 2010; Zitzmann and Nieschlag, 2001).

Several lines of evidence indicate that testosterone may be involved in the pathophysiology of psychiatric disorders (Elman and Breier, 1997; Seidman and Walsh, 1999; Zarrouf et al., 2009; Tsujimura, 2013; Reijnen et al., 2015; Ford et al., 2016) and suicidal behavior (Roland et al., 1986; Gustavsson et al., 2003; Tripodianakis et al., 2007; Markianos et al., 2009; Sher et al., 2012, 2014; Kiraly and Sher, 2015; Zhang et al., 2015; Stefansson et al., 2016; Lenz et al., 2019). Some observations suggest that blood testosterone levels are lower among suicide attempters in comparison to non-attempters (Tripodianakis et al., 2007; Markianos et al., 2009)).

In men, testosterone is mainly produced by Leydig cells in testes, although some amount of testosterone is secreted by the adrenal glands

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(Nussey and Whitehead, 2001; Ceccato et al., 2018). The adrenal glands also produce dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and androstenedione which are partially metabolized to testosterone (Nussey and Whitehead, 2001; Ceccato et al., 2018; Antoniou-Tsigkos et al., 2019). Testosterone in the blood is bound to sex hormone binding globulin and to albumin (Hammond et al., 2012; Antonio et al., 2016). A small fraction of testosterone circulates as nonprotein bound or free testosterone. Only this free fraction is biologically active. Free testosterone can enter cells and activate androgen receptors.

The administration of dexamethasone or other glucocorticoids reduces testosterone levels (Doerr and Pirke, 1976; Cumming et al., 1983; Juniewicz et al., 1987; Kamischke et al., 1998; Whirledge and Cidlowski, 2010; Geraghty and Kaufer, 2015). This effect may be related to two mechanisms: the influence of glucocorticoids on the hypothalamic-pituitary-gonadal (HPG) axis and the feedback effect of glucocorticoids on the hypothalamic-pituitary-adrenal axis (HPA) (Whirledge and Cidlowski, 2010; Geraghty and Kaufer, 2015; Antoniou-Tsigkos et al., 2019).

The administration of dexamethasone can decrease testosterone levels because glucocorticoids regulate the HPG axis at all levels (Whirledge and Cidlowski, 2010; Geraghty and Kaufer, 2015). Glucocorticoids inhibit release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, inhibit gonadotropin synthesis and release in the pituitary, and inhibit testosterone synthesis and release from the gonads (Whirledge and Cidlowski, 2010; Geraghty and Kaufer, 2015). Glucocorticoids are localized in several different cell populations within the testes, including the Leydig cells, where steroidogenesis occurs in the testes.

In healthy individuals, dexamethasone and other glucocorticoids provide negative feedback to the pituitary gland to suppress the secretion of adrenocorticotropic hormone (ACTH). Adrenal androgens, i.e., testosterone, DHEA, DHEAS, and androstenedione are secreted by the adrenal glands in response to ACTH (Antoniou-Tsigkos et al., 2019). Therefore, a decrease in ACTH leads to a reduction of secretion of adrenal androgens in healthy individuals. ACTH suppression also results in decreased cortisol levels (Carroll et al., 1981; Lowy and Meltzer, 1987; Yehuda et al., 1988, 2004; Cronin et al., 1990). The dexamethasone suppression test (DST) was one of the first biological challenge tests to be used in suicide related research (Coryell and Schlesser, 1981; Chabrol et al., 1983; Targum et al., 1983; Asberg et al., 1984; Yehuda et al., 1988). Many studies reported that ACTH and cortisol levels were not reduced in suicidal individuals after a dexamethasone administration (Targum et al., 1983; Norman et al., 1990; Lester, 1992; Coryell and Schlesser, 2001; Mann and Currier, 2007; Jokinen et al., 2008; Jokinen and Nordström, 2009).

To further explore factors that may be involved in the neurobiology of suicidality among combat veterans, we examined morning baseline free and total testosterone levels and the effect of dexamethasone administration on testosterone levels in male combat veterans with or without a history of suicide attempt. We hypothesized that baseline testosterone levels would be lower among suicide attempters compared to non-attempters and that the administration of dexamethasone would reduce testosterone levels among suicide non-attempters but not in attempters.

2. Materials and method

Thirty-two male combat veterans who made (n = 15) or did not make (n = 17) post-deployment suicide attempts were included in the study. Only suicide attempters who made an attempt within 5 years preceding the day of initial assessment were enrolled. Suicide attempts were described as self-destructive acts with the intent to die. Non-attempters were recruited from the same population of psychiatric patients at the James J. Peters VA Medical Center. Veterans were informed that participation in the study was voluntary and their choice to participate (or not) would not affect their care or access to VA services and all participants provided written informed consent for participation. The research project was approved by the James J. Peters VA Medical Center Institutional Review Board.

A trained clinician interviewed study participants using the *Mini - International Neuropsychiatric Interview (MINI)* (Sheehan et al., 1998) to determine DSM-IV diagnoses, the *Montgomery-Åsberg Depression Rating Scale (MADRS)* (Montgomery and Asberg, 1979) to assess severity of depression, the *Brown-Goodwin Aggression Scale* (Brown and Goodwin, 1986) to examine aggression, and the *Scale for Suicidal Ideation (SSI)* (Beck et al., 1979) to examine suicidal ideation.

The *MINI* is a structured diagnostic interview for the psychiatric disorders which assesses the 17 most common psychiatric conditions (Sheehan et al., 1998). The *MADRS* is a 10-item diagnostic interview used to measure the severity of depressive symptoms including suicidality (item 10) (Montgomery and Asberg, 1979). *The Brown-Goodwin Aggression Scale* is an 11-item four-point scale used to obtain a history of aggressive behavior (Brown and Goodwin, 1986). The *SSI* is a 19-item scale that measures the intensity, pervasiveness, and characteristics of suicidal ideation (Beck et al., 1979).

Baseline blood samples were collected via venipuncture of the arm between 8:00 and 8:30 a.m. Participants took a 0.5-mg dose of dexamethasone that evening at 11:00 p.m. Blood was drawn the next morning again between 8:00 and 8:30 a.m.

Free and total testosterone levels were measured using ELISA kits (ALPCO Diagnostics, Windham NH). The kits utilize a competitive immunoassay specifically designed and validated for the *in vitro* diagnostic measurement of free and total testosterone in human blood. The free testosterone assay sensitivity is 0.018 pg/mL. The intra-assay and inter-assay coefficients of variation for the free testosterone assay are 8.1% and 6.9%, respectively. The total testosterone assay sensitivity is 0.022 ng/mL. The intra-assay and inter-assay coefficients of variation for the total testosterone assay are 8.0% and 7.3%, respectively. Dexamethasone in plasma samples was measured using ELISA kit (Neogen Corporation, Lexington KY). The dexamethasone assay sensitivity is 0.23 ng/mL. The intra-assay and inter-assay coefficients of variation for this assay are 9.8% and 10.1%, respectively.

Demographic and clinical data were compared using Student's t-test and chi-square test, as appropriate. Student's t-test was also used for intergroup comparisons of baseline free and total testosterone levels, and dexamethasone levels. An ANCOVA was used to compare baseline free and total testosterone levels controlling for age and MADRS scores because age and depression may affect testosterone levels (Sternbach, 1998; Seidman and Walsh, 1999; Zarrouf et al., 2009; Golan et al., 2015). A repeated measures ANOVA was used to test for group (non--attempters vs. attempters) by intervention interactions. A repeated measures ANCOVA was used to test for group (non-attempters vs. attempters) by intervention interactions controlling for age and MADRS scores. T-test was used for intragroup comparisons of free and total testosterone levels before and after dexamethasone administration. We have also calculated testosterone decline = baseline levels – post-dexamethasone levels. The SPSS 26 program was used for statistical analysis.

3. Results

3.1. Demographic and clinical parameters

There was no difference between non-attempters and attempters with regard to age, marital status, and the educational level (Table 1). The groups did not differ in the proportion of patients with mood disorders, posttraumatic stress disorder, and substance use disorders (Table 2). Suicide attempters had higher SSI scores in comparison to non-attempters (Table 2). MADRS suicidality item scores were also higher among attempters than among non-attempters (Table 2).

Table 1
Demographic features of combat veterans with or without a history of suicide attempts.

Parameter	Attempters		Non-attempters		Analysis		
	Mean or N	SD or %	Mean or N	SD or %	t/χ^2	df	p
Age	38.3	12.0	35.7	10.8	−0.65	30	0.52
Marital status							
Single	6	40.0%	6	35.3%	1.88	3	0.60
Married	4	26.7%	8	47.1%			
Separated	1	6.7%	1	5.9%			
Divorced	4	26.7%	2	11.8%			
Education							
Completed high school	5	33.3%	3	17.6%	2.79	3	0.43
Attended college, but did not receive four year academic degree	4	26.7%	6	35.3%			
Completed college, received four year academic degree	0	0%	2	11.8%			
Completed post-graduate training	6	40%	6	35.3%			

3.2. Baseline free and total testosterone levels

Both baseline free and total testosterone levels were lower in suicide attempters compared to non-attempters (Table 2). These differences remain statistically significant controlling for age and MADRS scores (Table 2). In the whole sample, free testosterone and total testosterone levels negatively correlated with SSI scores ($r = -0.57$, $p < 0.001$; and $r = -0.36$, $p = 0.04$, respectively), and free testosterone levels negatively correlated with MADRS suicidality item scores ($r = -0.48$, $p = 0.006$).

3.3. Effects of dexamethasone administration on free and total testosterone levels

We have observed a group by intervention interaction in free testosterone levels ($F = 6.17$, $p = 0.015$). This interaction remained significant controlling for age and MADRS scores ($F = 6.14$, $p = 0.019$). Intragroup t-tests demonstrated that free testosterone levels decreased after dexamethasone administration among non-attempters but not among attempters (Table 3). We did not find a group (non-attempters vs. attempters) by intervention interaction with regard to total testosterone levels ($F = 1.22$, $p = 0.278$). There was no difference with regard to the dexamethasone levels between the groups (Table 2).

In the whole sample, decline in free testosterone levels negatively correlated with SSI scores ($r = -0.45$, $p = 0.009$) and with MADRS suicidality item scores ($r = -043$, $p = 0.014$). There was a trend towards a positive correlation between decline in free and total testosterone levels and total impulsivity scores ($r = 0.5$, $p = 0.071$; and $r = 0.5$, $p = 0.067$, respectively) among suicide attempters but not among non-attempters ($r = 0.08$, $p = 0.76$; $r = -0.11$, $p = 0.67$).

Free testosterone post-dexamethasone levels positively correlated with adolescent, adult, and total aggression scores among non-attempters ($r = 0.50$, $p = 0.047$; $r = 0.62$, $p = 0.008$; and $r = 0.56$, $p = 0.018$, respectively) but not among suicide attempters ($r = 0.19$, $p = 0.49$; $r = -0.22$; $p = 0.43$; and $r = -0.15$, $p = 0.60$, respectively).

4. Discussion

This is the first demonstration of reduced baseline free and total testosterone levels in association with a history of suicide attempts in male military veterans. Also, this is the first demonstration of testosterone non-suppression by dexamethasone in veteran suicide attempters.

4.1. Baseline testosterone levels

Our observations that free and total testosterone levels are lower among veterans with a history of suicide attempt in comparison to veterans who do not have a history of suicidal behavior and that free

Table 2
Clinical and biological characteristics of combat veterans with or without a history of suicide attempts.

Parameter	Attempters		Non-attempters		Analysis		
	Mean or N	SD or %	Mean or N	SD or %	$t/F/\chi^2$	df	p
% of subjects with mood disorders	14	93.3%	16	94.1%	0.008	1	0.93
% of subjects with posttraumatic stress disorder	13	86.7%	11	64.7%	0.52	1	0.15
% of subjects with substance use disorder	13	86.7%	11	64.7%	0.52	1	0.15
% inpatients at the time of study entry	12	80.0%	11	64.7%	0.92	1	0.34
Montgomery-Åsberg Depression Rating Scale (MADRS)	27.47	6.33	20.94	14.28	−1.63	30	0.11
MADRS – suicidality item	2.00	1.46	0.82	1.47	−2.26	30	0.031
Beck Suicide Ideation Scale at the time of study entry	21.0	7.37	2.0	5.78	−8.17	30	<0.001
Brown-Goodwin Aggression Scale	24.53	7.80	22.59	9.17	−0.64	30	0.53
Dexamethasone levels (ng/mL)	92.03	40.62	102.34	69.10	0.51	30	0.62
Free testosterone levels (pg/mL)	11.09	7.33	18.67	6.34	30	3.14	0.004
Free testosterone levels (pg/mL) controlling for age and MADRS score					1,28	9.45	0.005
Total testosterone levels (ng/mL)	3.12	1.06	5.71	3.85	30	2.52	0.02
Total testosterone levels (ng/mL) controlling for age and MADRS score					1,28	4.25	0.049

Table 3
Intragroup comparisons of free and total testosterone levels before and after the dexamethasone suppression test.

		Baseline (Before DST)		After DST		Analysis		
		Mean	SD	Mean	SD	df	t	p
Non-attempters	Free testosterone (pg/mL)	18.67	6.34	13.96	5.22	16	5.16	<0.001
	Total testosterone (ng/mL)	5.71	3.85	5.42	4.45	16	1.28	0.22
Attempters	Free testosterone (pg/mL)	11.09	7.33	10.92	8.40	14	0.11	0.92
	Total testosterone (ng/mL)	3.12	1.06	3.20	1.51	14	−0.32	0.75

testosterone and total testosterone levels negatively correlated with SSI scores are consistent with previous observations which showed that plasma testosterone levels in suicide attempters were lower than in non-attempters (Tripodianakis et al., 2007; Markianos et al., 2009; Kiraly and Sher, 2015). Tripodianakis et al. (2007) found that male suicide attempters had significantly lower blood testosterone levels compared to non-attempters. Markianos et al. (2009) compared total plasma testosterone concentrations in male psychiatric patients who had attempted suicide by jumping from a high place, males who were hospitalized after accidently falling from a high height, and healthy controls. Researchers observed that compared to the healthy control group both accident and attempt groups had lower blood testosterone concentrations with lowest levels in the attempters. Also, we reported a case of a young combat veteran who presented with an impulsive suicide attempt that had a high potential for lethality and had a low serum level of testosterone compared to established normal limits (Kiraly and Sher, 2015).

It is worth noting that several research groups found lower testosterone levels in depression, a psychiatric condition frequently associated with suicidal behavior (Carnahan and Perry 2004; Sankar and Hampson, 2012; Khera, 2013; Ford et al., 2016). For example, low testosterone has been associated with depression in older (Ford et al., 2016) and younger (Sankar and Hampson, 2012) male samples.

4.2. Effects of dexamethasone administration

Our observation that free testosterone levels decreased after dexamethasone administration among non-attempters but not among attempters may be related to differences in the glucocorticoid modulation of the HPG axis in non-attempters and attempters. Dexamethasone, similarly to other glucocorticoids, inhibits the HPG axis at all levels and reduces testosterone levels (Whirledge and Cidlowski, 2010; Geraghty and Kaufer, 2015). We observed this effect in suicide non-attempters but not among attempters. This indicates a dysregulation of the corticosteroid – HPG interaction among suicide attempters.

A difference in changes in free testosterone levels between suicide non-attempters and attempters in response to dexamethasone administration may also indicate that the dexamethasone does not suppress ACTH and consequently, secretion of adrenal androgens among suicide attempters. This is consistent with several research reports indicating that in people with a history of suicidal attempt dexamethasone does not suppress cortisol production by the adrenal glands (Targum et al., 1983; Jokinen et al., 2008; Jokinen and Nordström, 2009). For example, Jokinen and Nordström (2009) showed that DST non-suppression was associated with a history of suicide attempt in young adult patients with mood disorders. Targum et al. (1983) observed that in unipolar depressed inpatients, DST non-suppression was associated with a history of suicide attempts. Several studies also found that DST non-suppression is associated with death by suicide (Norman et al., 1990; Lester, 1992; Coryell and Schlesser, 2001; Mann and Currier, 2007).

Our findings that in the whole sample, decline in free testosterone levels negatively correlated with SSI scores and with MADRS suicidality item scores, that there was a trend towards a positive correlation between decline in free and total testosterone levels and total impulsivity scores among suicide attempters but not among non-attempters, and the fact that free testosterone post-dexamethasone levels positively correlated with adolescent, adult, and total aggression scores among suicide non-attempters but not among attempters may be further evidence that the testosterone system is involved in the pathophysiology of suicide.

4.3. Clinical observations

Our observations that veterans with a history of suicide attempt had higher suicide ideation scores in comparison to non-attempters and that MADRS suicidality item scores were higher among attempters than among non-attempters are consistent with observations that suicide attempters remain at elevated suicide risk for a long time after a suicide attempt (Beck et al., 1997; Sher et al., 2006, 2017; Valtonen et al., 2005). Suicidal ideation may be a chronic trait and may lead to a suicide plan resulting in non-lethal suicide attempt or suicide death (Rihmer, 2007; ten Have et al., 2009; Serafini et al., 2015; Simon et al., 2019). A history of a suicide attempt is a major risk factor for both repeated nonfatal suicidal behavior and suicide. Childhood maltreatment is also an important risk factor for suicidality (Pompili et al., 2014).

A modest sample size is a limitation of our study. Also, only combat veterans who volunteered to take part in the research project were included in the study. This could affect the results of the study.

Future studies will resolve whether relatively lower levels of free testosterone in combat veterans with increased suicidal ideation or resistance of free testosterone levels to exogenous administration of dexamethasone serve as persistent markers of suicide risk. Equally important, future studies will determine whether therapeutic targeting of testosterone dysregulation attenuates severity of suicidal ideation and, thereby, reduces suicide risk.

In summary, our findings indicate that there are substantial differences in the testosterone function between male combat veterans with or without a history of suicide attempt. Studies of the relation between the testosterone function and suicidal behavior among combat veterans may lead to improvement in detection of suicidality and finding new pharmacological targets for prevention of suicide among veterans.

Contributors

Authors LS and RY designed the study and wrote the protocol. Author LS managed the literature searches and analyses. Author LS undertook the statistical analysis. Authors LS and LB wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Declaration of competing interest

None.

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