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INFLUENCE OF SERUM TESTOSTERONE LEVEL ON AGGRESSION IN WOMEN WITH SCHIZOPHRENIA

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SUMMARY

Background: *Unlike in female population, the effect of testosterone on aggression in men has been investigated countless times so far. A scarce number of studies have examined the effect of testosterone on aggression in women. The results obtained so far are inconsistent for some studies indicated a positive, whilst others showed a negative correlation. Since testosterone turned out to be an important factor related to aggression in men, the aim of our study was to investigate whether this correlation existed in aggressive female patients with schizophrenia.*

Subjects and methods: *The sample consisted of 120 women, aged from 18 to 45 years, diagnosed with schizophrenia by DSM-5 criteria. Those who were breastfeeding or suffered from specific hormonal or other physical disorders were excluded from the study. They were divided into two groups of 60 - those with aggressive behavior and those with nonaggressive behavior. Psychopathology was measured by several tests (Positive and Negative Syndrome Scale - PANSS, Overt Aggression Scale - OAS and PANSS Extended Subscale for Aggression Assessment). Serum testosterone hormone assays were performed. Statistical data analysis was done by parametric statistical tests, Kolmogorov-Smirnov test, Student's t-test and simple linear regression. All data were presented as mean values and corresponding standard deviations (SD).*

Results: *Testosterone levels didn't differ significantly between aggressive and nonaggressive subjects. There were no significant differences between testosterone levels in suicidal aggressive subjects compared to nonsuicidal aggressive respondents ($t=0.616$; $p=0.540$). The largest number of subjects in both groups had referent testosterone levels.*

Conclusions: *Despite expecting a significant effect of testosterone levels on aggression in women with schizophrenia, conducted by previous studies, no correlation has been found. Suicidal behavior surprisingly didn't depend on the subjects' testosterone levels.*

Key words: *aggression - schizophrenia - testosterone - women*

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INTRODUCTION

Aggressive behavior is characterized by intention to openly harm another person, oneself or to destroy one's property. Physiological and pathological aggression are two main types of aggressive behavior whose distinction depends on the intensity of the reaction and the reason for such behavior (Barry et al. 2014, Moyer 1968).

Schizophrenia is often associated with various forms of aggression. The complexity and inconsistency of results pertaining to neuroendocrinological research on behavioral disorders that occur within the clinical picture of specific psychiatric disorders derive from the complexity of neuroendocrine systems and related mechanisms, as well as the complicacy of psychiatric disorders and altered behaviors that accompany them (Barry et al. 2014, King 2016). Numerous studies have shown that aggression is more common in schizophrenia than in general population (Fazel et al. 2009), whereas certain data enumerate the percentage of 5,2% of severe acts of violence to be committed by patients with schizophrenia (Fazel & Grann 2006). Aggression and violence in schizophrenia may be explained by psychopathological symptoms such as delusions or hallucinations, comorbid use of psychoactive substances, social deterioration, or other clinical symptoms, but different neurobiological mechanisms may also play a role in aggression (Fazel et al. 2009).

In aggressive behavior, testosterone, cortisol, estradiol, progesterone and oxytocin have been studied extensively in nonhuman animals, but less so in humans. The effect of testosterone on aggressive behavior in women has been particularly poorly studied (Denson et al. 2018). In mammalian species, males generally have higher testosterone levels and are more aggressive than females. Similarly, because men are more violent than women globally and men possess much higher testosterone levels than women, researchers suspected that testosterone is a strong cause of aggression in men. However, much less research has investigated this possibility in women.

Regarding women, aggression was associated with altered release and unequal concentrations of different sex hormones: a positive correlation between testosterone and/or oxytocin and aggression was found, as well as low cortisol concentrations and aggression (Denson et al. 2018). On the other hand, high levels of estradiol and progesterone were considered to be associated with low levels of aggression (Denson et al. 2018). The majority of studies describing gender differences in schizophrenia suggest sex steroid dysfunction, but not necessarily only estrogen dysfunction. A multitude of reproductive hormones may be implicated, including testosterone, progesterone or luteinising hormone as well and thus it is important to acknowledge that there is a complex interplay of hormones occurring (Herceg et al. 2018).

Only few studies examined testosterone serum levels in women with schizophrenia. Although aggression and testosterone may be lower in women than in men, many studies observed a positive correlation between testosterone and aggression in women and men equally (Prasad et al. 2017, Probst et al. 2018). It was detected that aggression in women was associated with altered release, as well as concentration of different sex hormones: there was a positive correlation between testosterone and/or oxytocin and aggression and it was assumed that low cortisol concentration was associated with aggression (Denson et al. 2018). On the other hand, high concentrations of estrogen and progesterone were considered to be associated with low levels of aggression (Denson et al. 2018). It was presumed that there existed an interactive correlation between testosterone and cortisol and that their effect on aggression was moderated by the availability of serotonin (Montoya et al. 2012). In other words, high testosterone levels, low cortisol concentrations and low serotonin concentrations appeared to have an impact on increased risk of aggressive behavior (Kuepper et al. 2010).

The aim of this study was to determine whether there existed a correlation between testosterone levels in women with schizophrenia and aggressive behavior manifested by them. We set out a hypothesis that testosterone levels were higher in women with schizophrenia who demeaned aggressively during our research, which included four types of aggressive behavior: verbal aggression, physical aggression towards environmental objects, physical aggression towards oneself (self-injury and/or suicide attempt) and physical aggression towards other persons.

SUBJECTS AND METHODS

The research was conducted at the University Psychiatric Hospital Vrapče in Zagreb, at the Department of Psychotic Disorders in Women and the Department of Diagnostics and Intensive Care, as well as in the laboratory of the „Bonifarm“ Polyclinic. The study included female subjects who were diagnosed with schizophrenia by DSM-5 criteria during previous treatments or during their first treatment, when they manifested pathognomonic schizophrenic symptoms. The study included 120 respondents, who were hospitalized at the University Psychiatric Hospital Vrapče from March 1st, 2017 until March 1st, 2019. The subjects were 18 to 45 years old and those who were breastfeeding or suffered from specific hormonal or other physical disorders were excluded from the survey. The respondents were divided into two groups, 60 of them in each group. The indication for hospitalization in the first group was aggression regardless of whether the aggression was directed towards others or towards oneself (including possible suicidal behavior). The indication for hospitalization in the second group, which was also a control group, was a diagnosis of schizophrenia devoid of aggressive behavior. The clinical part of the study included psychiatric interview and psychiatric scales (Overt Aggression Scale or OAS, Positive end Negative Syndrome Scale or PANSS and PANSS Extended Subscale for Aggression Assessment) taken within 48 hours from subjects' arrival at the Hospital, as well as aggression assessment directed towards oneself or the others. Evaluation of clinical status and previously mentioned scales were done by an experienced psychiatrist. Hormone assays for serum testosterone were performed. The purpose and the goal of the research were explained to all respondents, hence they signed an informed consent. The Ethics Committee of the University Psychiatric Hospital Vrapče approved our research conduction. Each respondent was given an identification number due to data confidentiality.

Statistical data analysis was done using SigmaStat 3.5 Programme (Jandell Scientific Corporation, USA). The normality of the distribution was examined for each of the tested variables via Kolmogorov-Smirnov test. Since most of the data were normally distributed, all data were presented as mean values and corresponding standard deviations (SD). Parametric statistical tests were used for analysis. Simple linear regression was used to examine the effect of one independent variable (serum testosterone level) on the dependent variable and the Student's t-test examined the differences in two continuous numerical variables between two independent groups. The correlation between two continuous numerical variables (the dependence of the number of points on psychometric scales on serum testosterone level) was examined using Pearson's correlation coefficient, whilst the Chi-squaerd test (χ^2 test) was used to test the distribution of categorical variables within 2 or more groups. The significance level was set at $p<0.05$, with all tests being bidirectional.

RESULTS

We found that the age of the subjects, as well as the duration of the disease, were approximately equal in both of examined groups (aggressive and nonaggressive subjects). Significant differences were observed in the length of their hospital stay, which was significantly longer in aggressive subjects (t=-2.287; p=0.024, Student's t-test), as much as in the received dose of antipsychotics expressed in chlorpromazine equivalent doses, with aggressive subjects receiving on average about 3 times higher dose of antipsychotics (t=-6.533; p=1.7E-9, Student t-test) (Table 1). Although the number of smokers didn't differ significantly between the two groups (approximately 70% of aggressive and 67% of nonaggressive respondents were smokers; χ^2=0.154; p=0.422, Chi-squared test), the number of cigarettes smoked per day was much higher in the group of aggressive patients (t=-2.380; p=0.020, Student t-test) (Table 1). Moreover, it can be seen that the total number of points scored on the PANSS scale, as well as on the PANSS Subscale, was significantly higher in aggressive respondents (Table 1). Besides, nonaggressive subjects didn't show symptoms of suicidal behavior, in contrast to aggressive subjects (roughly 30% of suicidal subjects) (Table 1).

Table 1. Demographic and clinical data of subjects with schizophrenia divided into two groups according to the presence of aggression, presented as mean values±standard deviation (SD) or as total number of subjects (frequency of occurrence %)

	Subjects divided according to aggression		
	Nonaggressive (N=60)	Aggressive (N=60)	Statistics
Demographic data			
Age/Years	37±8	35±7	t=1.383; p=0.169
Disease Onset/Age	9±6	8±6	t=0.183; p=0.855
Duration of Disease/Years	28±6	28±7	t=1.094; p=0.276
Duration od hospital Treatment/Days	24±8	28±10	t=-2.287; p=0.024
Antipsychotics Dose*/mg/day	180.9±115.5	343.8±154.7	t=-6.533; p=1.7E-9
Cigarettes Smokers/Number (%)	40 (66.7%)	42 (70.0%)	χ^2=0.154; p=0.422
Number of Cigarettes/Day	11±9	16±11	t=-2.380; p=0.020
Psychometric data			
Total PANSS	94±9	103±11	t=4.860; p=3.6E-5
PANSS-POS	24±3	27±4	t=-4.375; p=2.6E-5
PANSS-NEG	19±5	22±5	t=-3.225; p=0.002
PANSS-GEN	51±4	54±5	t=-3.959; p=1.3E-4
PANSS-AG	-	10±5	-
OAS	-	12±6	-
Suicidal Subjects/Number (%)	0 (0.0%)	18 (30.0%)	-

* Chlorpromazine Equivalent Doses; OAS – The Overt Aggression Scale; PANSS – The Positive and Negative Syndrome Scale; PANSS-AG – The Extended Scale for Aggression; PANSS-GEN – The Sum of the General PANSS Symptoms; PANSS-NEG – The Sum of Negative PANSS Symptoms; PANSS-POS – The Sum of Positive PANSS Symptoms

Table 2. Association between testosterone levels with aggression in subjects with schizophrenia; Data are presented as mean values±standard deviation (SD) or as total number of subjects (frequency of occurrence %)

	Subjects divided according to aggression		
	Nonaggressive (N=60)	Aggressive (N=60)	Statistics
Testosterone/nmol/l	1.46±0.88	1.34±0.76	t=0.766; p=0.446*
Testosterone <0.22 nmol/l	2 (3.3%)	2 (3.3%)	
Testosterone 0.22-2.9 nmol/l	56 (93.3%)	56 (93.3%)	χ^2<0.001 p=1.000**
Testosterone >2.9 nmol/l	2 (3.3%)	2 (3.3%)	

* Student's t-test; **Chi-squared test

Table 3. Association between testosterone levels with age, smoking and severity of symptoms of schizophrenia (PANSS), aggression (PANSS-AG, OAS) and suicidal behavior in aggressive and nonaggressive subjects with schizophrenia

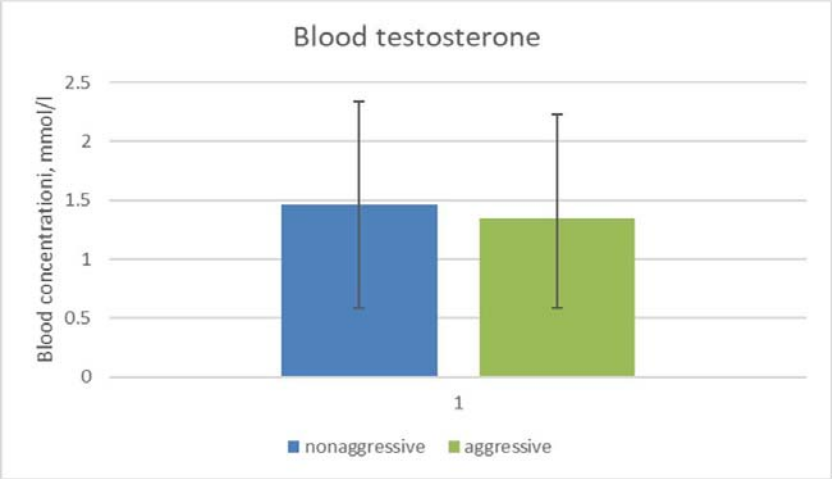
	Subjects divided according to aggression	
	Nonaggressive (N=60)	Aggressive (N=60)
Age/Years	β=-0.140; p=0.286	β=-0.149; p=0.299
Antipsychotics Dose*	β=-0.168; p=0.221	β=0.087; p=0.626
Smoking	β=-0.169; p=0.192	β=-0.007; p=0.963
PANSS	β=-0.118; p=0.379	β=0.056; p=0.711
PANSS-AG	-	β=0.135; p=0.468
OAS	-	β=-0.126; p=0.513
Suicidality	-	β=0.011; p=0.945
Model	**R^2=0.118; F=1.846; p=0.133	**R^2=0.044; F=0.344; p=0.930

* Chlorpromazine Equivalent Dose; ** R^2 - Adjusted R^2; OAS – The Overt Aggression Scale; PANSS – The Positive and Negative Syndrome Scale; PANSS-AG - The Extended Scale for Aggression

Table 4. Association between testosterone levels with suicidal behavior in aggressive subjects with schizophrenia; Data are presented as mean values±standard deviation (SD) or as total number of subjects (frequency of occurrence %)

	Aggressive subjects divided according to suicidal behavior		
	Nonsuicidal (N=42)	Suicidal (N=18)	Statistics
Testosterone/mmol/l	4.724±1.072	4.550±0.806	t=0.616; p=0.540*
Testosteron <0.22 nmol/l	2 (4.8%)	0 (0.0%)	
Testosterone 0.22-2.9 nmol/l	39 (92.9%)	17 (94.4%)	χ^2=1.241 p=0.538**
Testosterone >2.9 nmol/l	1 (2.4%)	1 (5.6%)	

* Student's t-test; ** Chi-squared test



* $p < 0.05$; Concentration x 10^{-3} mmol/l

Figure 1. Association between testosterone levels with aggression in subjects with schizophrenia; Data are presented as mean values±standard deviation (SD)

The results showed that testosterone levels didn't differ significantly between aggressive and nonaggressive subjects (Table 2, Figure 1). Additionally, the prevalence of subjects with reduced or elevated testosterone wasn't significantly different between these two groups of subjects (Table 2, Figure 2).

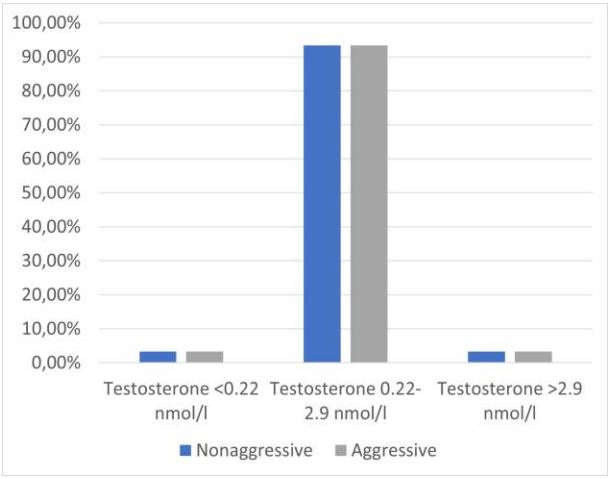


Figure 2. Prevalence of subjects with elevated, decreased or reference testosterone values in aggressive and nonaggressive subjects with schizophrenia

We also found that none of the examined variables (age, received dose of therapy, smoking, severity of schizophrenic symptoms and aggression measured by total PANSS score, OAS score and extended PANSS score, and the presence of suicidal behavior) significantly contributed to the model of aggressive or nonaggressive subjects, that is, testosterone levels didn't significantly depend on none of the mentioned variables (Table 3).

It showed that suicidal behavior wasn't associated with blood testosterone levels (Table 4). No significant differences were found between testosterone levels in suicidal aggressive subjects compared to nonsuicidal aggressive subjects (t=0.616; p=0.540) (Table 4). Moreover, the largest number of subjects in both groups had referent testosterone levels, whereas only minority of them had lower or higher testosterone levels than the reference (Table 4).

DISCUSSION

Aggressive respondents scored significantly higher points on the PANSS scale and related subscales, which was consistent with findings of one study (Sisek-Šprem et al. 2015) that the degree of aggressiveness and scores for the PANSS, as well as the positive subscale, were significantly higher in the violent group compared to nonaggressive and suicidal groups, which underscored the influence of psychopathology (particularly symptoms such as hostility, poor impulse control and thought disturbance) on aggressive behavior (Hodgins 2008, Nolan et al. 2005).

Notwithstanding that the plenty of studies have shown a positive correlation between testosterone levels and aggressive behavior and criminality in general population and in patients with personality disorders (Booth & Osgood 1993, Dabbs et al. 1991, Räsänen et al. 1999, Sánchez-Martín et al. 2000, van Bokhoven et al. 2006), association between criminal behavior and testosterone levels in patients with schizophrenia has not been found (Räsänen et al. 1999). This finding was particularly interesting because several studies have found significantly lower levels of serum testosterone in men with schizophrenia during acute psychotic episodes, but generally not during the maintenance phase (Huber et al. 2005, Ko et al. 2007, Taherianfard & Shariaty 2004). However, another study showed no correlation between testosterone level and degree or type of aggression (Sisek-Šprem et al. 2015).

Contrary to our expectations, there were no considerable differences in testosterone levels between aggressive and nonaggressive women, furthermore, the

majority of respondents had referent serum testosterone levels. Regardless of what we assumed, there were several studies that corroborated our findings. For instance, two studies showed (Horesh 1999, Lester 1968) that the degree of aggressiveness wasn't correlated with testosterone level. Suicidal and violent behavior have been postulated to be manifestations of the same aggressive impulse arising from reduced serotoninergic neurotransmission (Horesh 1999) and the resultant impact on testosterone (Birger 2003). In opposition to previously mentioned results, one study of 87 women inmates in a maximum-security prison found that testosterone levels correlated with aggressive dominance in prison (Dabbs & Hargrove 1997). This relationship was reduced among older women, presumably due to lower testosterone levels. Similarly, a study of a women's rugby team found that the pregame rise in testosterone was positively correlated with aggressiveness during the game (Bateup et al. 2002). Another study measured testosterone in 155 men and 151 undergraduate women (Harris et al. 1996). Men reported greater aggression than women and had five times more testosterone than women. Despite these mean differences, the authors found positive correlations between testosterone and self-reported aggression in both women and men. Another double-blind placebo-controlled testosterone administration study suggested that testosterone might have increased aggression because it had reduced sensitivity to punishment and had increased reward sensitivity (van Honk et al. 2004).

One meta-analysis (Archer et al. 2005) approved our hypothesis for it revealed that the correlations between testosterone and aggression were small, but significant in both men (r=0.08) and women (r=0.13). Thus, the relationship between testosterone and aggression seemed to be not so particularly strong in humans. Indeed, a review of the literature suggested that testosterone should be considered as promoting dominance seeking behavior, rather than solely aggression (Eisenegger et al. 2011). In order to explain these weak correlations between testosterone and aggression, researchers examined cortisol as a moderator of this relationship. The dual hormone hypothesis suggested that low cortisol levels facilitated the potentiating effect of testosterone on aggressive and dominant behavior, whereas high cortisol blocked this effect (Mehta & Prasad 2015). This pattern of data was observed in forensic samples of men and boys (Dabbs et al. 1991, Popma et al. 2007), but evidence was mixed in women. For instance, one study of 53 healthy undergraduate women found the opposite pattern; women with high concentrations of both Salivary testosterone and cortisol showed the most aggression in the competitive reaction time test (Denson et al. 2013). Other studies failed to find support for the dual hormone hypothesis in women (Buades-Rotger et al. 2016, Cote et al. 2013, Geniole et al. 2013, Welker et al. 2014). However, a recent study of 326 adolescent girls and 134 boys found that testosterone derived from hair samples correlated with self-reported aggression at low levels of cortisol in both boys and girls (Grotzinger et al. 2018). Estimates derived from hair samples might reflect stable trait-like individual differences in cortisol and testosterone more so than values derived from saliva. Thus, these data suggested that interactions between testosterone and cortisol might influence aggression in women. However, more research is needed with large samples and behavioral measures of aggression (Denson et al. 2013). The dual hormone serotonergic hypothesis goes one step further by positing that the interactive relationship between testosterone and cortisol on aggression is further moderated by serotonin availability. Specifically, high testosterone, low cortisol, and low serotonin are thought to increase risk for aggression (Montoya et al. 2012).

We also found that suicidal behavior wasn't related to blood testosterone levels. In addition to that, the majority of both examined groups had referent testosterone levels. Speaking of men with schizophrenia who attempted suicide, one study detected a significantly lower level of plasma testosterone than in their non-suicidal counterparts, possibly due to the hormonal influence on an individual's sense of well-being; that is, low testosterone could lead to depression, thereby increasing the risk of suicide (Tripodianakis et al. 2007), which was in contrast to women. On the other hand, one study didn't detect any differences in testosterone levels between suicidal and other men with schizophrenia, and there was no correlation between testosterone and degree of suicidality (Sisek-Šprem et al. 2015).

Our study had some methodological limitations that required caution in the interpretation of our results. Some respondents didn't show aggressive outbursts at the time of our study, although they had previously been hospitalized countless times due to their aggressive behavior. Several subjects didn't clearly express suicidal thoughts and intentions and were therefore not included in the suicidal group of patients. It is possible that it would be wise to extend the study in terms of determination of serum cortisol levels as a potential additional marker of aggression in women. A rather insufficient number of subjects could be another limitation of the study.

CONCLUSION

We found that testosterone levels didn't differ significantly between aggressive and nonaggressive subjects and that the prevalence of subjects with low or high testosterone wasn't significantly different between these two groups. Serum testosterone level wasn't significantly dependent on any of the examined variables. Suicidal behavior wasn't associated with testosterone levels, in other words, there weren't substantial differences in testosterone levels in suicidal aggressive subjects compared to nonsuicidal aggressive respondents. We consider this investigation to be continued on a

bigger sample size to highlight feasable effects of testosterone levels on aggressiveness in women with schizophrenia and would also like to expand our research next time on the effect of cortisol levels on aggression in our patients.

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Conflict of interest: None to declare.

Contribution of individual authors:

Adela Klemenčić designed the study, wrote the manuscript, carried out literature searches and analyses and interpretated given data.

Miroslav Herceg came up with the idea of the manuscript, carried out literature searches and helped with data analyses.

Dora Herceg & Krešimir Puljić collected the clinical data from the patients and files.

Mirna Sisek-Šprem helped with literature research and data collection.

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