

## ORIGINAL ARTICLE

## THE TESTOSTERONE-CORTISOL MODEL AS A WAY TO UNDERSTAND THE MECHANISM OF ALCOHOL DEPENDENCE WHICH STARTED IN PUBERTY

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**ABSTRACT****The aim:** Is to analyze the role of testosterone and cortisol in the mechanism of alcohol use disorders formation for further development of early diagnosis and prevention methods.**Materials and methods:** 155 adolescents at the preclinical stages of alcohol use disorders formation and 87 young patients with diagnosed alcohol dependence were studied by enzyme-linked immunoassay techniques.**Results:** The analysis of the obtained materials shows that the onset of search behaviors on alcohol consumption, frequency and alcohol abuse in adolescents occur with the participation of age-related processes of somatic puberty and the related syndromes of hormonal tension. The phasing of development and course of alcoholic disease includes pubertal age and alcohol-induced changes in the internal environment of the body. There is an increase in the concentration of testosterone and cortisol that initiates interest in alcohol first, and then under the influence of its toxic effect, the level of these hormones decreases. It should be borne in mind that significant differences in hormone concentrations were observed within the regulatory framework.**Conclusions:** An increase of testosterone and cortisol levels in puberty, combined with regular consumption of alcohol, may indicate a risk of addiction early. Further decrease of the levels of these hormones along with an increase of the frequency of alcohol consumption may be an early diagnostic feature of the alcohol use disorders.**KEY WORDS:** alcohol use disorders, puberty, testosterone, cortisol

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**INTRODUCTION**

It was approved that acute and chronic effects of ethanol reduce testosterone (T) levels in male blood plasma due to a direct inhibitory effect on steroidogenesis and a decrease in testicular receptors [1,2]. Alcoholic lesions of Leydig cells of male gonads were detected at clinical stages of alcohol dependence (AD) [1,3]. Later on, chronic alcohol intoxication (AI) is already depleting the system of central regulation of sex hormones [4,5]. Early manifestations of lesions of the male reproductive glands have the ability to reverse; further there is atrophy of the gonads [6,7] and irreversible suppression of sexual function [8,9]. Even episodic alcohol consumption has a significant inhibitory effect on the hypothalamic-pituitary component of the male reproductive system [10].

For patients with AD, it is mandatory to reduce the level of T in the blood and increase the content of cortisol (F) [11-14]. Routine administration of ethanol to rats for 6 months reduced gonadal mass by 30% [15]. Comparison of alcohol abusers revealed a rapid onset of AD symptoms (within 3 years) in individuals with reduced androgen status [16]. The author concludes that patients with reduced androgen status are less protected from the toxic effects of ethanol.

The results of special pathoanatomical studies [17] indicate a high frequency of morphological changes on the

part of the external genitalia in persons abusing alcohol or drugs during their lifetime.

Sexual behavior is subject to deviation when there has been a prenatal exposure to alcohol, stress, or combinations thereof [18]. Such prenatal adverse effects in the future (in adulthood) cause initially low and then persistent low levels of T in blood.

In a basic review of research, it is emphasized that sex hormones throughout the life of an individual create both permanent and periodic "structural-organizational" and "functionally-activative" effects on the human brain and its behavior, in particular in the perinatal period of development [19]. There is also a certain sequence of increases in sex hormones and F in the blood in adolescence. T modulates the activity of addictive behavior. It also affects the rate of breakdown of alcohol in the body [20]. The hormone promotes both the initiation of adolescent puberty and the onset of alcohol abuse during puberty [21].

It is proved that the timing of the onset and the intense progression of puberty are of prognostic importance for the initiation or intensification of alcohol abuse in adolescence [22]. The sooner somatic puberty begins, the sooner boys and girls start smoking tobacco and drinking alcohol and other surfactants [23-25]. It is noteworthy that castration of hamsters before the onset of puberty leads to a dramatic reduction in aggressive behavior and reduces the risk of AD [26].

**Table I.** The content of hormones in the serum of adolescents at the stages of development of AUD, nmol/l

Hormone	Amount				
	Group I (n=34)	Group II (n=47)	Group III (n=26)	Group IV (n=29)	Group V (n=19)
T	8.57±3.12 <sup>1)</sup>	12.59±4.39 <sup>1)</sup>	22.15±5.83 <sup>1)</sup>	15.98±4.96 <sup>1)</sup>	18.43±5.74 <sup>1)</sup>
F	411.19±128.14	543.78±159.47 <sup>2)</sup>	521.75±130.87 <sup>2)</sup>	415.32±160.56 <sup>3)</sup>	435.21±126.70 <sup>3)</sup>

<sup>1)</sup> – differences with all other groups are statistically significant ( $p < 0.05$ );

<sup>2)</sup> – statistically significant difference with group I ( $p < 0.05$ );

<sup>3)</sup> – statistically significant differences with groups II and III ( $p < 0.05$ ).

Ratio	Amount				
	Group I (n=34)	Group II (n=47)	Group III (n=26)	Group IV (n=29)	Group V (n=19)
F/T	52.96±23.87	46.43±14.56	25.44±10.72*	27.21±10.71*	24.38±5.22*

\* – statistically significant differences with groups I and II ( $p < 0.05$ ).

Hormone	Amount		
	Average norm	Withdrawal syndrome	After WS
F	490.00±260.00	512.00±141.72 <sup>2)</sup>	392.64±92.12 <sup>1)</sup>
T	33.02±21.50	9.01±1.25 <sup>1)2)</sup>	7.76±2.15 <sup>1)</sup>
F/T	14.84	56.83 <sup>1)</sup>	50.60 <sup>1)</sup>

<sup>1)</sup> – statistically significant differences with norm ( $p < 0.05$ );

<sup>2)</sup> – statistically significant differences between the first and second examinations ( $p < 0.05$ ).

As the norm used indicators calculated by the Department of Biochemistry of SI "INPN NAMSU".

Healthy men (students) have higher T level content associated with higher levels of alcohol use [27]. At the same time, men with high T levels are more likely to consume ethanol and are more likely to become addicted to alcohol than individuals with low T levels [28,29].

The biological effects of T are determined not only by its absolute values in the blood, but also by the level of sensitivity of tissues and target organs to this hormone [30].

Thus, biological (hormonal) factors cause a high risk of developing pathological attraction to substances, activities or objects during adolescence. Androgens determine the attitude of humans and animals to alcohol. Male sex hormones are involved in the occurrence of states of substance, object and action dependence and through involvement of structures of the opioid brain system. Ethanol is undoubtedly a gonadotoxic substance.

The dynamics and intensity of clinical manifestations of alcohol use disorders (AUD), the severity of the complications that arise and the pathogenic consequences, may be due to puberty and age-related changes in the adaptation and compensatory capacity of the adolescent organism. The leading tasks of modern addictology are the questions of finding reliable biological (including hormonal) markers for assessing the degree of risk of clinical manifestations of alcohol and other addictions, their early diagnosis and prevention.

## THE AIM

The working hypothesis is that AUD, its negative effects and complications are procedural phenomena that began

in the perinatal period. It goes through the life of an addict, manifests at puberty, with the participation of physiological changes in metabolic status during somatic puberty and early onset of exotoxicosis at puberty – alcohol, tobacco, narcotic or other intoxication. The testosterone-cortisol component of early onset AUD development should be studied in order to further search for markers for early diagnosis at the preclinical stage.

## MATERIALS AND METHODS

Enzyme-linked immunoassay study of T and F content included 155 male students aged 15 to 19 years, divided into 5 groups (group I – abstinent, they do not consume alcohol, group II – occasional consume no more than once a month, group III – regularly consuming alcohol (2-14 times a month), group IV – with some signs of mental dependence (addiction), group V – with some signs of physical dependence). Additionally, similar studies were conducted on a sample of patients with AD (87 male, 21-33 years old) at the stages of alcohol withdrawal syndrome (WS) and after cupping of it (group VI, clinical). Groups were seen as a continuum. The processing was carried out with the non-parametric U Mann-Whitney criterion on R-Studio.

## RESULTS

The lowest content of T in the blood was found in adolescents who did not consume alcohol (8.57±3.12 nmol/l) (Table I). Such concentrations of T are too low to provide the impe-

tus for hormonal intensification and do not stimulate the development of alcohol motivations. This conclusion is also consistent with low content of F ( $411.19 \pm 128.14$  nmol/l). Significant increase in the content of T in the serum of adolescents by 46.91% in group II and by 158.46% in group III relative to group I ( $p < 0.05$ ) is a powerful hormonal factor for the activation of complex processes of somatic puberty. It is responsible for the occurrence of testicular hormonal stress and contributes to the appearance of search behavior before drinking. The concentration in the blood of F increases in group II – by 32.25% and in group III – by 26.89% ( $p < 0.05$ ) relative to group I.

Thus, already in the preclinical stages of addictive disorder, there is a link between the physiological increase of T in blood, the increase in the level of F and the appearance of alcohol search behavior. This defined the age range in which the teenager searches for a means of relieving frustration that is the beginning of drinking. Further, at the stages of formation of states of AD (groups IV and V) toxic effects of ethanol begin to accumulate, which leads to the transformation of hormonal (testicular) homeostasis. This transformation is manifested by a decrease of T content relative to the highest levels in group III by 27.86% in group IV, and by 16.79% in group V.

According to the content of T the level of F was decreased too by 23.62% in group IV and 19.96% in group V (relative to the highest concentrations in group II). This indicates a positive anti-stress effect of regular alcohol consumption during adolescence, which further ensures that AD is fixed.

The F/T ratio (Table II) showed that abstinent (group I) and those who consume alcohol sporadically (group II) have its highest rate due to the high content of F and low T ( $52.96 \pm 23.87$  and  $46.43 \pm 14.56$  respectively). This reflects the features of premonitory somatic and sexual development, the adaptation processes and the state of their hormonal support outside the transformative influence of AI. In the subsequent stages of alcohol consumption (groups III, IV and V) the F/T ratio decreases. This probably shows the important role of this indicator in the fixation of AUD. Hormonal cortisol-testosterone balance in the body of a teenager is already achieved through regular AI.

The concentration of T at WS was almost four times lower than the average, and the F/T ratio was almost four times higher ( $p < 0.05$ ) (Table III).

In the treated patients with AD, as a result of WS relief, a decrease in F excretion was observed by 30.40% ( $p < 0.05$ ). Probably this can be explained by the process of the reverse development of WS, which was a powerful frustrating factor for the patient with AD. T concentrations and major stress hormone F immediately after treatment continued to decrease: T from ( $9.01 \pm 1.25$ ) to ( $7.76 \pm 2.15$ ) nmol/l (by 13.87%); F from ( $512.00 \pm 141.72$ ) to ( $392.64 \pm 92.12$ ) nmol/l (by 23.31%). This may indicate the depletion of endocrine homeostasis, F and T deficiency in the body under the influence of early and prolonged (for 1-15 years) alcohol abuse. Perhaps, it may take a long period of complete sobriety to normalize the cortisol and testosterone levels of homeostasis in patients with AD.

## DISCUSSION

The data obtained generally confirm the important role of the shift of T concentration as a risk factor for the formation and rapid formation of AUD [31,32]. This is consistent with the fact that the hyperfunction of the sex glands led to an acceleration of the rate of development of dependence [33]. The author suggests that premonitory hypertestosteronemia can be a prognostic sign of the development of addiction, even with episodic contact with surfactants. Further increasing of AI causes changes in the endocrine system, fixes the state of dependence on alcohol and forms a new functional system of life of the organism after P. K. Anokhin [34]. Ethanol primarily inhibits the production of sex steroid hormones, which secondarily (after the phase of compensatory growth of pituitary gonadotropin excretion) leads to depletion of endocrine function, decrease in spermatogenesis, disorders of sexual identification and behavior, social and functional disorders. This study showed that the T and F levels increase within normal limits in combination with systematic use of alcohol may be an early prognostic sign of the AUD with the beginning in puberty.

## CONCLUSIONS

Founded relations between the level of T, F in the blood and the AI in groups I–V (which reflect the stages of AUD formation) has theoretical and clinical significance. On the one hand, increasing of T content in the body of a teenager is a metabolic prognostic marker of a risk of early developing of AUD, and on the other hand, ethanol itself adversely affecting hormonal metabolism in the subsequent stages of ontogeny secondary changes in T and F content. The testosterone-cortisol component of the onset of AUD is likely to be related to the pubertal period. It should be noted that all differences are observed within (lower and upper limits) of the norm.

The occurrence of AUD in adolescents occurs with the participation of physiological pubertal increase of T in the blood. This intrinsic stress is also manifested by the corresponding increase in the blood content of F (a leading stress hormone). It is responsible for the occurrence of a wide range of psycho-emotional and behavioral disorders that relate to stress-adaptive syndrome in adolescents. The identified changes create the need to find a simple energy-efficient strategy for regulating well-being and initiate the occurrence of interest in drinking alcohol in adolescents of II and III groups, the occurrence of such use: first occasionally, and then regularly.

Adolescence in the process of regular alcohol consumption in the III, IV, V groups weakens the mental, emotional and negative component of the state of stress. At the same time, in the III, IV, V groups, under the influence of chronic AI on the gonads, the production of T in the body decreases. This forms the metabolic basis for the occurrence of a state of addiction as early as adolescence. In the group of patients with AD aged 21-33 years with a greater experience of alcohol abuse, there are also more significant toxic

effects: reducing the level of T in the body. The above is most significant in the ratio of hormones: the F/T factor in groups I and II was higher, and in groups III, IV, V, and VI it decreased, fixing a new alcohol-distorted metabolic homeostasis in the body. The above mechanism works, initially, as a certain sequence of relationships between the main male hormone (T) and the main stress hormone (F) precisely during the period of unstable equilibrium and the formation of numerous functions that is in puberty. In the future, at a more advanced age, they are joined by more complex hormonal changes. The fixation of AUD is based on the anti-stress effects of ethanol, with which the person seeks to restore mental and physical comfort.

Given the important role of testosterone and cortisol in providing complex energy, metabolic and adaptive processes in the body, it is possible to assume the participation of revealed changes in hormonal homeostasis in the occurrence and fixation of the state of AUD in adolescence. Undoubtedly, in the formation of AUD other pathogenetic (endocrine and nonendocrine) changes are important.

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**Conflict of interest:**

*The Author declare no conflict of interest.*

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**A** – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article