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Research Article

Effects of Serum Testosterone Levels on Functional Recovery in Acute Ischemic Stroke

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Abstract

Aim: To investigate the serum levels of testosterone in patients with acute ischemic stroke patients and their relations with illness severity and prognosis.

Methods: The serum levels of testosterone in 100 male patients (mean age 76, range 60 - 80) with acute ischemic stroke patients (cerebral ischemic group) and 100 male healthy people (control group) were determined. Written consent was obtained from all participants. All the patients were scored by score of The National Institutes of Health Stroke Scale (NIHSS) (the score of neurological impairment). According to the degree of nerve function defect (NIHSS), the subjects were divided into mild (0~5), moderate (6~15), severe (> 15) three groups. and compared in groups. Serum concentration of testosterone was measured upon admission and 14 days after admission. We can compared in two groups.

Results: The differences of the serum levels of testosterone at admission between cerebral ischemic group and the control group were not statistically significant ($P > 0.05$). The difference of mean testosterone serum level testosterone level 14 days after admission between control group and cerebral ischemic group was statistically significant ($P < 0.05$). The mean testosterone level of cerebral ischemic group significantly lower than the average level of testosterone in control group, but there was no significant difference. There was no statistically significant between T1 and T2 in mild patient, the mean serum level of testosterone in male patient with mild illness was moderate, and low in severe patients ($P < 0.05$), the differences of testosterone serum level of T1 and T2 between moderate group and severe patients groups were not statistically significant ($P > 0.05$). The mean serum levels of testosterone in mild patients were higher than those in severe patients ($P < 0.05$). the differences of the mean testosterone serum level between moderate group and severe group were not statistically significant ($P > 0.05$). The serum levels of testosterone with deterioration patients were significantly decreased and that in mild group was increased respectively, Correlation between testosterone and NIHSS and other parameters (height, body mass) was performed using the Pearson's test, linear regression analysis and one-way analysis of variance. By contrast, levels of testosterone were not associated with height, weight. Levels of testosterone was negatively correlated with the score of neurological impairment.

Conclusion: The testosterone level in the patients with cerebral infarction is maintained a relatively low level and the level of which is closely related to disease severity and prognosis.

Keywords: *Testosterone Acute; Ischemic Stroke; NIHSS*

Abbreviations

T1: Level of Testosterone at admission; T2: Level of Testosterone at 14 Days after Admission; BGCI: Basal Ganglia Cerebral Infarction

Subjects. Data Basal Ganglia Cerebral Infarction; BSI: Brain Stem Infarction; FTLI: The Frontal and Temporal Lobe Infarction; POLI: The Parietal and Occipital Lobe Infarction; MPG: Mild Patient Group; MDPG: Moderate Patient Group; SPG: Severe Patient Group; NIHSS1: The NIHSS at Admission; NIHSS2: The NIHSS of 14 days after Admission; SCT: Serum Concentration of Testosterone; NIHSS: National Institutes of Health Stroke Scale

Introduction

Male sex is an important risk factor for stroke [1] as well as ischemic heart disease [2]. Testosterone has many physiological actions in muscles bones, hematopoietic system, brain, reproductive and sexual organs, adipose tissue. Within these areas it stimulates muscle growth and maintenance bone development while inhibiting bone resorption, the production of red blood cells to increase hemoglobin, libido, enhanced mood and cognition, erectile function and lipolysis [3]. In men, androgens have both pro-and anti-thrombotic effects [4]. It is therefore conceivable that endogenous sex hormones play a role in the pathogenesis of these atherothrombotic diseases. Ischaemic stroke is a major cause of morbidity and mortality in elderly men. Our main objective was to examine whether testosterone (T) was associated with incident ischaemic stroke in elderly men [5]. This review describes the state of our knowledge of androgen-related contributions to neurological injury and recovery following cerebral ischemia that occurs following stroke. Experimental studies examining the effects of castration, androgenic agonists and antagonists and aging provide valuable insights into the role of androgens in clinical outcome following cerebrovascular events [6]. Despite several scientific and technological advances, there is no single neuroprotective treatment that can reverse the brain damage after acute ischemic stroke (AIS). Cerebral ischemia caused by loss of blood supply to the brain during cardiac arrest or stroke are major causes of death and disability. Acute ischemic stroke remains a major global cause of death, permanent disability and dementia [7]. The role of androgens in male stroke is understudied and important to pursue given that male sex is a well-known risk factor for human stroke [8]. We review recent advances in our understanding of androgens in the context of ischemic cell death and neuroprotection. We also highlight some possible molecular mechanisms by which androgens impact ischemic outcomes [8]. Biological sex is an important factor in predicting vulnerability of the brain to an ischemic insult, with males being at higher risk for cardio-cerebrovascular events than females of the same age [6]. Cerebral stroke continues to be a major cause of death and the leading cause of long-term disability in developed countries. Evidence reviewed here suggests that gender influences various aspects of the clinical spectrum of ischemic stroke, in terms of influencing how a patients present with ischemic stroke through to how they respond to treatment [9]. Severity was assessed on the Scale of NIHSS and infarct size by computed tomographic scan. We designed two groups, the control group composed of 100 male control subjects, the patient group contained 100 male AIS patients, the assessment of neurological deficit was performed with the NIHSS In total, 100 male stroke patients admitted to our department were enrolled in the study (mean age 76, range 60 - 80 years, from stroke onset: 1 - 14 hours).

Of patients with acute cerebral infarction in patients with neurological deficits of the extent of the use of National Institutes of Health Stroke Scale (NIHSS) assessed. All Patients were also evaluated using the NIHSS at admission and 14 days after admission. The serum level of testosterone in 100 male patients and 100 healthy persons was determined. Inclusion criteria were male sex and aged 60 - 80 years. Exclusion criteria included pre-existing stroke. Data were collected on healthy elderly people who had total plasma testosterone checked in 2015. All the patients were scored by score of The National Institutes of Health Stroke Scale (NIHSS). According to the degree of nerve function defect (NIHSS), the subjects were divided into mild (0~ 5), moderate (6~15), severe (> 15) three groups. and compared with among groups. Blood samples from patients were drawn a mean of 1days after stroke onset and also 14 days after admission in 100 patients.

Statistical analyses

Data were presented as mean ± standard deviation (SD) and compared with among the groups. Correlations between testosterone and NHISS were evaluated using Spearman's rank-order correlation coefficients. Continuous variables between the two groups were performed using the Student t test. Multiple mean comparison was analyzed by the one-way analysis of variance (ANOVA) followed by post hoc LSD test. Statistical analysis was performed using the SPSS statistical software for Windows version 11.5 (SPSS, Inc., Chicago, IL, USA).

We performed additional subgroup analyses focusing on testosterone and NIHSS. Statistical analysis was performed using SPSS software 11.5 (SPSS, Chicago, IL, USA) using the two-sample t test. Results were expressed as the mean ± SD. A value of P less than 0.05 was considered statistically significant. Correlation between testosterone and NIHSS and other parameters (height, body mass) was performed using the Pearson's test, linear regression analysis and one-way analysis of variance. By contrast, levels of testosterone were not associated with height, weight. Written consent was obtained from all participants.

Result

Serum concentration of testosterone (SCT) was measured upon admission and 14 days after admission. Patients were also evaluated using National Institutes of Health Stroke Scale (NIHSS) at admission and 14 days after admission. In addition, we added a subgroup analysis based on illness severity. The average SCT serum concentration was 23.12 ± 4.24 nmol/L at admission and 19.24 ± 3.68 nmol/l at 14 days after admission. The multivariate linear regression model showed that T concentration was not significantly associated with the scale of NIHSS at admission and 14 days after admission. In the subgroup analysis, SCT had significant association with the scale of NIHSS only in severe patients ($P < 0.01$). There was statistically significant ($P < 0.05$) between control group and serum testosterone level of 14 days after admission. The testosterone level of cerebral ischemic group significantly lower than the average level of testosterone in control group, but there was no significant difference. There was no statistically significant between T1 and T2 in mild patient. The differences of testosterone serum level between moderate group and severe patients groups were not statistically significant ($P > 0.05$). The serum levels of testosterone in mild patients were higher than those in severe patients ($P < 0.05$). The differences of the testosterone serum level between moderate group and severe group were not statistically significant ($P > 0.05$). The serum level of testosterone in mild patient higher than in severe patients ($P < 0.01$), the serum levels of testosterone with deterioration patients were significantly decreased and in mild group was increased respectively. Basal ganglia cerebral infarction patients recover more quickly than the other groups cerebral infarction. Table 3 showed no difference between T1 and T2 in mild patient group and Moderate patient group. Correlation between testosterone and NIHSS and other parameters (height, body mass) was performed using the Pearson's test, linear regression analysis and one-way analysis of variance. By contrast, levels of testosterone were not associated with height, weight. NIHSS associated with testosterone showed a negative correlation. correlation coefficient r -0.335($P < 0.01$). There was statistically significant ($P < 0.05$) between control group and serum testosterone, levels of testosterone in patient group was negatively correlated with the score of neurological impairment.

Conclusion the testosterone level in the patients with cerebral infarction is maintained a relatively low level and the level of which is closely related to disease severity and prognosis.

	Testosterone (Admission)	Testosterone (14 days after admission)	P
Acute ischemic stroke	23.12 ± 4.24 nmol/L	19.24 ± 3.68 nmol/L	$P < 0.05$
Control Group	25.24 ± 4.67 nmol/L		

Table 1: *There was no difference between patients and control subjects in serum testosterone levels. No statistically significant correlation was found between level of testosterone at admission and level of testosterone at 14 days after admission. The testosterone level of cerebral ischemic group significantly lower than the average level of testosterone in control group, there was significant difference ($P < 0.05$).*

	Testosterone (Admission)	Testosterone 14 days after admission	NIHSS (Admission)	NIHSS 14 days after admission
BGCI (55)	25.12 ± 4.24	28 ± 5.15*	12.50 ± 5.16	8.50 ± 2.16+
BSI (21)	24.12 ± 4.14	23 ± 4.56*	14.50 ± 5.24	11.50 ± 5.45#
FTLI (16)	25.07 ± 4.34	26 ± 5.34*	9.25 ± 3.76	6.67 ± 2.76#
POLI (11)	20.12 ± 4.12	18 ± 3.89*	5.50 ± 2.10	4.68 ± 1.76#

Table 2: *Subgroup analysis data.*

*NIHSS: National Institutes of Health Stroke Scale; P < 0.05 was considered statistically significant. BGCI: Basal Ganglia Cerebral Infarction Subjects; BSI: Brain Stem Infarction; FTLI: The Frontal and Temporal Lobe Infarction; POLI: The Parietal and Occipital Lobe Infarction. There was no significant difference between testosterone at admission and testosterone after 14 days after admission in basal ganglia infarction brainstem infarction, frontal temporal lobe infarction, occipital lobe infarction respectively. Data were compared using the two-sample t-test and one-way analysis of variance. Data are expressed as the mean ± SD, n = 100. *compare with level of testosterone at admission in every group (p > 0.05). +compare with score of NIHSS at admission in BGCI group p < 0.05. #compare with score of NIHSS at admission in BSI, FTLI, POLI group respectively p > 0.05.*

	Acute ischemic stroke		
	Mild patient group (57) (MPG)	Moderate patient group (28) (MDPG)	Severe patient group (15) (SPG)
T1	22.12 ± 3.24 nmol/L	26.12 ± 4.14 nmol/L	19.12 ± 4.01 nmol/L
T2	24.05 ± 3.18 #nmol/L	24.3 ± 3.98 #nmol/L	15.14 ± 3.84* nmol/L
p	P > 0.05	P > 0.05	P < 0.05

Table 3: *Shows the results of subgroup analysis by comparing with level of testosterone. Based on score of NIHSS, we divided patients into a mild patient group (0 - 5), moderate patient group (6-15) and severe patient group (> 15).*

T1: Level of testosterone at adimmison. T2 level of testosterone at 14 days after admission.
**compare with level of testosterone at admission in severe patient group p < 0.05. #compare with level of testosterone at admission in moderate patient group.*
MPG: Mild Patient Group; MDPG: Moderate Patient Group; SPG: Severe Patient Group.

	NIHSS1	NIHSS2	P
MPG	3.60 ± 1.09	2.13 ± 1.14*	P < 0.001
MDPG	9.47 ± 2.89	5.80 ± 2.86*	P < 0.001
SPG	20.53 ± 3.71	20.00 ± 3.64 #	P > 0.05

Table 4: *Shows the results of subgroup analysis by comparing with the score of NIHSS.*

**compare with NIHSS1 p < 0.001. # compare with NIHSS1 p > 0.05.*
There was no statistically significant between T1 and T2 in mild patient.
NIHSS1: The NIHSS at admission.
NIHSS2: The NIHSS of 14 days after admission.
**compare with NIHSS1 p < 0.001. # compare with NIHSS1 p > 0.05.*
MPG: Mild Patient Group; MDPG: Moderate Patient Group; SPG: Severe Patient Group; NIHSS1: The NIHSS at admission.

Discussion

The effects of testosterone on functional recovery in stroke patients have not previously been studied. Testosterone is more than a "male sex hormone". In aging males testosterone decreases approximately 0, 8 - 1% annually [10]. Male sex is a well-acknowledged risk factor for human stroke. It is an important contributor to the robust metabolic functioning of multiple bodily systems [11]. Testosterone has been implicated in cerebral physiology, though this is not without controversy. This study suggests that early exposure to gonadal hormones can have dramatic effects on the response to adult cerebrovascular injury [12]. Testosterone in severe patient group lower than the other two groups. The severe patient group has poor neural functional outcome. Testosterone levels to be low prior to disease severity, Clinical experiment show testosterone plays a significant role in promoting neural functional recovery. Serum testosterone levels likely affect the functional outcome of post-stroke rehabilitation patients [13]. Testosterone has been shown to improve cerebral perfusion, Serum testosterone levels fall gradually with age [14]. Extremely low endogenous testosterone concentrations were associated with high risk of ischemic stroke in men, a risk mediated in part by body mass index and hypertension [15]. The serum levels of testosterone at admission in Basal ganglia cerebral infarction were higher than those in other groups. the differences of the testosterone serum level were not statistically significant ($P > 0.05$). At admission in Basal ganglia cerebral infarction higher than the level 14 days after admission, there may be better in neurological recovery than the other groups It suggested that high level testosterone might be related to the neurological recovery. The serum level of testosterone in mild patient higher than in severe patients ($P < 0.01$), the fact that many stroke patients exhibited decreased testosterone levels in our study is a reasonable observation, whichever causal direction is true. Severity of neurological deficits due to stroke may be related to testosterone concentrations, Low SCT may be associated with an increased risk for stroke as it is associated with risk factors for stroke such as increased body mass index (BMI), diabetes, dyslipidemia, atherosclerosis, arterial stiffness, and atrial fibrillation. In an observational cohort of men with low testosterone levels, testosterone treatment was associated with decreased mortality compared with no testosterone treatment [16]. Testosterone supplementation is well known to improve muscle strength physical function in humans, and neuroprotection against brain injury in rat models [17]. The level of testosterone were affected by ischemic attack and the level of serum testosterone in severe patient group was decreased significantly. Thus, ischemia induced androgen loss may be as important as the steady level of androgens prior to the ischemic insult [8]. Rats receiving testosterone demonstrated a significant reduction in infarct volume and a significant increase in neurogenesis on 10^{th} day after focal cerebral ischemia. Our results for the first time showed a potential advantageous effect of testosterone after cerebral ischemia in male rats, which was probably mediated by promoting antioxidant defenses, BDNF levels and neurogenesis [18] ischemia-induced androgen loss may be as important as the steady level of androgens prior to the ischemic insult. The most probable cause that ischemic attack destroyed the blood test is barrier and reduced testosterone. Senile men with acute cerebral infarction have disorders of the hypothalamic-pituitary-ovary axis function and reduced testosterone but tend to normalize in convalescent stage of stroke. Table 3 showed no difference between T1 and T2 in mild patient group and Moderate patient group. The incidence of concurrent diseases, in severe patient group were significantly higher than the other group testosterone has a protective role in cerebral ischemic tissue and inhibits the inflammatory cascade reaction, which may be one of the neuroprotective role mechanisms. Further study is required to understand how androgens impact on ischemic injury [19]. Post-stroke rehabilitation patients are elderly who may have potential age-related testosterone deficiencies. Stroke is a leading cause of permanent disability and death. A complex series of biochemical and molecular mechanisms (e.g. the release of ROS/NOS, proapoptotic proteins and proinflammatory cytokine; neuronal depolarization, Ca^{2+} accumulation and so on) impair the neurologic functions of cerebral ischemia and stroke [20]. The treatment with androgens has a positive effect on risk factors of secondary ischemic stroke. It is an effective method for improvement of social adaptation of men survived after the stroke [21]. In addition, brain damage can cause abnormalities in hormone profiles. Low levels of testosterone have been reported in patients who had suffered from stroke. The lower blood testosterone level was associated with the higher risk of the development of atherosclerotic lesions of major arteries that allowed to estimate risks of ischemic stroke in middle-aged and elderly men [22]. By contrast, levels of testosterone were not associated with height, weight. Levels of testosterone was negatively correlated with the score of neurological impairment. Recent finding that androgens exhibit highly dose-dependent effects on ischemic outcomes in animals further complicates the issues that surround male sex steroids [23]. Yeap.,

et al. reported low testosterone levels have been linked to stroke risk. The fact that many stroke patients exhibited decreased testosterone levels in our study is a reasonable observation, whichever causal direction is true [24]. Low circulating testosterone levels have also been associated with higher stroke incidence and worse outcomes after stroke in men [25]. Testosterone administration increases infarct size after MCAO in male rats in part via exacerbation of glutamate neurotoxicity [26]. Our work suggests that that low testosterone levels are prone to stroke, Man with low testosterone levels are at increased risk of cerebral ischemia injury [8]. These results support the idea that testosterone affects the pathogenesis of ischemic stroke in men [27]. Basal ganglia cerebral infarction patients recover more quickly than the other groups cerebral infarction. Often the cause is unknown. there may be associated with more mild patients on basal ganglia region Testosterone deficiency is also associated with type-2 diabetes, the metabolic syndrome, coronary artery disease, stroke and transient ischemic attacks, and cardiovascular disease in general [3]. However, testosterone has also been shown to produce rapid vascular effects [19]. The serum level of testosterone in mild patient higher than in severe patients ($P < 0.01$), it is possible that stroke damages the hypothalamic–pituitary– gonadal axis. We propose that in elderly patients, high levels of circulating testosterone, could potentiate AIS-mediated neuropathology in the ischemic and penumbra areas [20]. Evidence suggests that patients with lower level of serum testosterone have worse outcomes than patients with higher level of serum testosterone. Our work suggests that higher levels of testosterone may have a protective role against the effect on neural functional recovery in patients who have undergone the acute ischemic stroke patients. NIHSS associated with testosterone showed a negative correlation. correlation coefficient r -0.335 ($P < 0.01$). T Levels of testosterone was negatively correlated with the score of neurological impairment. We conclude that testosterone exhibits dose-dependent and time-sensitive effects after ischemia.

Conclusions

Our experiments provided evidence that testosterone level in the patients with cerebral infarction is maintained a relatively low level and the level of which is closely related to disease severity and prognosis. These results support the idea that testosterone affects the pathogenesis of ischemic stroke in men.

Author Contributions

Jun Chen, Congyang Yan, Zheng Da, Feng Xi provided the data, Jun Chen conducted experiments and performed data analysis and Wrote a paper. Corresponding author Zhengping Zhai conceived and designed this study, and provided technical or material support and provided technical support. Shan Wu revised the manuscript.

Conflicts of Interest

None declared.

Ethical Approval

The experimental protocol was approved by the Institutional Human Study Committee of Lianshui County Peoples Hospital of Jiangsu Province China. All participants provided written informed consent. Written consent was obtained from all participants.

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