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Effects of Testosterone Levels on Functional Recovery with Rehabilitation in Stroke Patients

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Abstract

The effects of testosterone on functional recovery in stroke patients have not previously been studied. The purpose of the study was to determine the effects of pre-rehabilitation serum testosterone levels on functional recovery in male stroke patients. In total, 111 male stroke patients admitted to our department were enrolled in the study (age: 74 ± 10 years, days from stroke onset: 36 ± 14 days). Serum concentration of free testosterone (Free-T) was measured upon admission. Patients were also evaluated using the Functional Independence Measure (FIM) at admission and discharge. The main outcome variable was FIM at discharge. Correlations between Free-T and FIM were evaluated using Spearman's rank-order correlation coefficients. We performed multivariate linear regression analysis to assess the effects of testosterone on functional outcome with adjustment for patient background variables. In addition, we added a subgroup analysis based on age. The average Free-T serum concentration was 4.7 ± 1.7 pg/ml. There was a significant positive correlation between Free-T and discharge FIM. The multivariate linear regression model showed that Free-T concentration was significantly associated with FIM at discharge ($\beta = 0.09$; $P = 0.01$). In the subgroup analysis, Free-T had significant association with discharge FIM only in patients under 76 years old ($\beta = 0.24$; $P < 0.001$). Our data suggest that serum Free-T levels have a positive effect for discharge FIM in male stroke patients.

Key words: rehabilitation, stroke, testosterone, recovery

Introduction

Serum testosterone levels fall gradually with age.[1)] Testosterone deficiency is associated with low physical function,[2)] diminished activities of daily living (ADL),[3)] lack of motivation, easy fatigability, and memory deterioration.[4)] Testosterone supplementation is well known to improve muscle strength,[5)] physical function[6)] in humans, and neuroprotection against brain injury in rat models.[7)]

Prevalence of late-onset hypogonadism (LOH, also referred to as age-associated testosterone deficiency) syndrome increases 30% in 70-year-olds and 50% in 80-year-olds.[8)] Many post-stroke rehabilitation patients are elderly who may have potential age-related testosterone deficiencies. In addition, brain damage can cause abnormalities in hormone profiles. Low levels of testosterone have been reported in patients who had suffered from stroke.[9)]

Serum testosterone levels likely affect the functional outcome of post-stroke rehabilitation patients. However, there have been no previous studies about the relationship between testosterone levels and functional outcome of stroke rehabilitation patients. The purpose of this study was to clarify the effects of serum testosterone level on functional recovery in male patients post-stroke.

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Methods

I. Subjects

The subjects were male stroke (cerebral hemorrhage or infarction) patients undergoing post-stroke rehabilitation hospitalized at our Department of Rehabilitation Medicine. They were recruited over a two-year period starting from April 1, 2011. Inclusion criteria were as follows: (1) 40–90 years old, (2) 10–60 days since stroke onset, (3) hospital stay of 20–180 days. We excluded patients who had recent history of hormonal agents, antidepressants, or diuretics. The study was approved by the Ethics Committee of our university's School of Medicine.

II. Measurement of hormonal profiles

Within three days of hospitalization, serum levels of free testosterone (Free-T) was measured early in the morning. Free-T was measured in 32 patients at discharge. Free-T concentration was determined by a commercial laboratory using a sensitive radioimmunoassay (SRL Inc., Tokyo). The normal range of Free-T for males aged ≥ 70 years is 4.5–13.8 pg/ml. Luteinizing hormone and follicle-stimulating hormone were measured in 20 patients randomly.

III. Functional evaluation

The ward nurse assessed the ADL using the Functional Independence Measure (FIM)[10] at admission (FIMa) and discharge (FIMd). FIM is a functional assessment scale with a minimum score of 18 (complete dependence) and a maximum score of 126 (complete independence). The difference between FIMa and FIMd, FIM gain, was also calculated. FIMd was adopted as our primary clinical outcome.

IV. Statistical analyses

Values are expressed as mean ± standard deviation (SD). Correlations between Free-T and FIMa, FIMd, and FIM gain were evaluated using Spearman's rank-order correlation coefficients. Multiple linear regression analysis with a stepwise approach was performed using FIMd as the dependent variable, and Free-T, length of hospital stay, stroke subtype, days from onset to admission, amount of exercise per day, FIMa, age, modified Rankin Scale before onset, modified Rankin Scale on admission, and stroke lesion side (right or left) and type [supratentorial (cortical) or supratentorial (subcortical) or subtentorial] as independent variables. We performed additional subgroup analyses focusing on FIMa and age adjusted with the significant covariates from the stepwise analyses. In the analyses, patients were separated into upper and lower groups based on median FIMa and median age. Statistical analyses were performed using SPSS software (ver. 15.0, SPSS Inc., Chicago, Illinois, USA). A *P*-value less than 0.05 was considered statistically significant.

Results

We recruited 111 male stroke patients in total. Table 1 lists the characteristics of the participating patients. The average age of patients was 74 years, and the mean Free-T concentration was 4.7 pg/ml. Luteinizing hormone and follicle-stimulating hormone levels in the randomly sampled 20 patients were within the normal range for their age group. There were no significant difference between admission Free-T level and discharge Free-T level in the 32 patients for whom the latter was sampled.

Table 1 Patient characteristics

	Patients (n = 111)
Age (years)	74.0 ± 9.5
Days from stroke onset (days)	35.6 ± 14.3
Length of stay (days)	66.8 ± 37.1
Stroke subtype (%)	
Cerebral infarction	82 (74)
Atherothrombotic infarction	27 (24)
Cardiogenic embolism	20 (18)
Lacunar infarction	25 (23)
Others	10 (9)
Cerebral hemorrhage	29 (26)
Putamen hemorrhage	14 (13)
Thalamic hemorrhage	10 (9)
Others	5 (5)
Lesion side (%)	
Right	63 (57)
Left	48 (43)
Lesion site (%)	
Supratentorial (cortical)	32 (29)
Supratentorial (subcortical)	54 (48)
Subtentorial	25 (23)
Free-T (pg/ml)	4.7 ± 1.7
Modified Rankin Scale before onset	0.29 ± 0.73
Modified Rankin Scale on admission	3.30 ± 1.46
Admission FIM	68.2 ± 26.9
Discharge FIM	85.9 ± 26.8
FIM gain	17.7 ± 15.9
Amount of exercise (minutes)	48.1 ± 16.2

Values are mean ± standard deviation (SD) or number (percentage) of patients. FIM: Functional Independence Measure, Free-T: free testosterone.

Table 2 lists the correlation coefficients for Free-T concentration versus FIMa, FIMd, and FIM gain: there were significant positive correlations for all three (r = 0.22, 0.40, and 0.32, respectively).

Table 3 shows the results of our multiple linear regression analysis model with a stepwise approach. Stroke subtype and amount of exercise were excluded from the model. Free-T concentration was identified as a significant predictor of FIMd (β = 0.09, *P* = 0.01, 95% confidence interval: 0.34–2.60).

Table 4 shows the results of subgroup analysis by FIMa. The median FIMa was 68, and we divided patients into a lower FIM group (< 68) and a higher FIM group (≥ 68). Free-T concentration was significantly associated with FIMd in both groups.

Table 2 Correlation coefficients between free testosterone and Functional Independence Measure

	Admission FIM	Discharge FIM	FIM gain
Free-T (pg/ml)	0.22 ($P = 0.023$)	0.40 ($P < 0.01$)	0.32 ($P < 0.01$)

FIM: Functional Independence Measure, Free-T: free testosterone.

Table 3 Multiple linear regression analysis model for prediction of discharge FIM

	B	SE	β	*P*	95% CI
Free-T (pg/ml)	1.47	0.57	0.09	0.01	0.34, 2.60
Modified Rankin Scale on admission	–5.76	1.08	–0.29	0.00	–7.91, –3.61
Admission FIM	0.63	0.06	0.63	0.00	0.52, 0.74
Age (years)	–0.35	0.11	–0.12	0.00	–0.56, –0.14
Length of hospital stay (days)	0.13	0.03	0.18	0.00	0.08, 0.18
Days from stroke onset (days)	–0.25	0.07	–0.14	0.00	–0.39, –0.12
Amount of exercise (minutes)	2.43	1.15	0.07	0.04	0.15, 4.70

R^2: 0.88, by ANOVA. B: regression coefficient, CI: confidence interval, FIM: Functional Independence Measure, Free-T: free testosterone, SE: standard error of regression coefficient, β: standard partial regression coefficient.

Table 4 Admission FIM subgroup analysis for prediction of discharge FIM

	Under-68 admission FIM (n = 56)			Over-68 admission FIM (n = 55)		
	β	*P*	95%CI	β	*P*	95% CI
Free-T (pg/ml)	0.18	0.01	0.74, 5.25	0.25	0.00	0.74, 2.46

CI: confidence interval, FIM: Functional Independence Measure, Free-T: free testosterone, β: standard partial regression coefficient.

Table 5 Age subgroup analysis for prediction of discharge FIM

	Under 76 years old (n = 55)			Over 76 years old (n = 56)		
	β	*P*	95%CI	β	*P*	95% CI
Free-T (pg/ml)	0.24	0.00	3.07, 6.94	0.08	0.15	–0.36, 2.25

CI: confidence interval, FIM: Functional Independence Measure, Free-T: free testosterone, β: standard partial regression coefficient.

Table 5 shows the results of subgroup analysis by age. Based on the median age (76 years), we divided patients into a younger group (< 76 years) and an older group (≥ 76 years). Free-T concentration had a significant association with FIMd only in the under-76 group (β = 0.24; $P < 0.001$); there was none for the over-76 group ($P = 0.15$).

Discussion

In the present study, we used multiple regression analysis to clarify the effect of Free-T on FIMd in male stroke patients. Our results showed that Free-T levels upon admission were significantly associated with FIMd after adjustment for all covariates. The subgroup analysis further specified the nature of this trend, suggesting it applied only to stroke patients under 76 years old.

Pan et al. suggested a potential therapeutic role for testosterone in stroke recovery using a rat model.[11] To our knowledge, however, there have been no previous studies investigating the relationship between testosterone and FIMd in stroke patients. The novelty of this study was focusing role of testosterone in a stroke recovery setting.

There have been no previous studies that linked stroke onset to decreased Free-T levels. It is possible that stroke damages the hypothalamic–pituitary–gonadal axis. On the other hand, Yeap et al. reported low testosterone levels have been linked to stroke risk.[12] The fact that many stroke patients exhibited decreased testosterone levels in our study is a reasonable observation, whichever causal direction is true.

Free-T level on admission correlated significantly with FIMa, FIMd, and FIM gain. In addition, Free-T level on admission correlated with FIMd even after adjustment with covariates. Severity of neurological deficits due to stroke may be related to testosterone concentrations, FIMd, and FIM gain. Several groups have elucidated positive effects of testosterone in improving psychosomatic function.[5,6] Testosterone therapy has also been reported to improve physical function in cardiac rehabilitation patients[13] and frail elderly patients.[14] These beneficial effects attributed to Free-T were probably helpful in patients' functional recovery. However, Free-T levels were not associated with FIMd in the over-76 group. Testosterone levels naturally decline with age, and so they were very low in our older patients. The importance of testosterone disappeared when Free-T levels decreased below a certain threshold.

According to past experimental findings, testosterone replacement therapy can potentially enhance rehabilitation effectiveness, including in post-stroke

rehabilitation.[15] However, based on the reported side effects of such supplementation, such as liver failure and polycythemia,[16] it is necessary to carefully monitor patients during treatment.

The present study had some limitations. First, since hormone levels were not measured at the time of stroke onset, the extent of the effect of the stroke itself on any hormonal abnormalities is unknown. Second, we did not perform hormone-loading tests in the present study; we suggest such testing should be conducted in the future. Third, bioavailable testosterone is difficult to measure in Japan technologically, and so we were only able to assess Free-T. However, Free-T is known to correlate well with bioavailable testosterone.[17] Thus, we suggest it is a viable alternative to use Free-T as an indicator for the prediction of bioavailable testosterone levels. Fourth, we did not measure baseline Free-T values before stroke onset.

In conclusion, our study demonstrated a significant relationship between Free-T serum levels and post-stroke functional recovery. These findings suggest the importance of Free-T in the functional recovery of older male stroke patients.

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Conflicts of Interest Disclosure

The authors have no conflicts of interest to declare.

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