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The role of serum testosterone and TBI in the in-patient rehabilitation setting

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Abstract

Objectives: To explore the relationship between serum testosterone levels, age, length of stay, admission, discharge and changes in functional capacity over time among patients with traumatic brain injury treated in a rehabilitation hospital.

Design: This study used a nonrandomized chart review of 54 males, consecutively admitted to a brain injury rehabilitation hospital.

Methods: The charts of 54 males consecutively admitted to a brain injury rehabilitation unit between the periods of December 2004 and May 2005 were included in this study. Individuals were included in this study if they were 18 years of age or older, had suffered a traumatic brain injury, undergone admission and discharge, functional independence measure (FIM) testing and had received a serum testosterone level check within one to seven days from admission.

Main outcome and results: The main outcome measure of this study was the FIM changes over time, as compared with admission testosterone levels. Low serum testosterone levels on admission to the in-patient rehabilitation unit were associated with longer lengths of stay, lower average admission FIM scores, less improvement in FIM scores, and a lower FIM efficiency. Although not statistically significant, individuals presenting to our unit with low testosterone levels, on average, stayed 26 days longer than did those with normal levels. Age and the presence of multi-trauma did not appear to be factors associated with serum testosterone levels. Changes in discharge cognitive FIM scores between the two groups approached statistical significance ($p = 0.06$).

Conclusion: This pilot study suggests that testosterone levels may be important in the recovery of patients with traumatic brain injury, treated at an in-patient rehabilitation hospital.

Keywords: *Brain injury, rehabilitation, testosterone, traumatic brain injury, acquired brain injury*

Background

Hypotestosteronemia had been reported in 28–79% of males with traumatic brain injury (TBI) in sub-acute and chronic hospitals [1–3] and 16–100% of individuals suffering SCIs [4]. The exact mechanism of Hypotestosteronemia in TBI has been debated, although it is believed to be related to dysregulation of the hypothalamic-pituitary axis. Injury severity and physiological stressors, GCS on presentation and the presence of a basal skull fracture have all been implicated in the etiology of Hypotestosteronemia. To date, no clear association has been demonstrated.

To date, there have been no studies exploring the relationship between testosterone levels in TBI and outcome in the acute rehabilitation setting. As previous studies have demonstrated that low testosterone is associated with affect, muscle response to exercise and cognitive function, we hypothesized that individuals with Hypotestosteronemia on admission would have a longer length of stay and lower FIM efficiency when compared with their normo-testosterone counterparts.

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Methods

This study is a non-randomized retrospective chart review of consecutive males admitted to a traumatic brain injury unit for acute rehabilitation. A total of 54 males qualified for our study (28 in the Hypotestosteronemia group and 26 in the normo-testosteronemia group). Males were included in the study if they had a history of TBI, were 18 years or older, had serum testosterone levels drawn within 7 days of admission and had both admission and discharge FIM testing. FIM score was selected as the primary measure of functional outcome because of its accessibility and use in accredited rehabilitation hospitals.

The electronic records of eligible study participants were reviewed. Individuals were stratified to the Hypotestosteronemia group if they had serum testosterone levels less than 270 ng/dl based on a normal range of 270–1070 ng/dl. The date of initial injury, admission to the unit and discharge were recorded. In the case of interrupted stays, the total number of rehabilitation days was summed as the total rehab LOS. Additionally, the difference between the lowest admission FIM score and the final discharge FIM score was utilized to calculate the total change in FIM score and FIM efficiency (change in FIM divided by days hospitalized). To calculate the total time since injury the total number of acute care days and rehabilitation days were summed. One individual was excluded from the calculation of 'time from initial injury to discharge from rehabilitation' in the normo-testosterone group, as he was initially discharged to a SNF prior to his admission at our facility. Finally, the mechanism of injury (TBI vs. ABI) and the presence of a history of multiple traumas were reviewed. This study was reviewed and approved by the institutional review board of our facility.

Results

A total of 56 patients were reviewed for this study, with 28 in the low testosterone group and 26 in the normo-testosterone group. All of the individuals in the normo-testosterone group had serum testosterone levels less than the median testosterone value of 670 ng/dl for our lab and 22 of 26 individuals (85%) had values in the lower quartile of the normal range.

The demographic break down of each group was similar. The mean age was 46 years for the low testosterone group and 49 years for the normo-testosterone group ($p = 0.60$). Ages ranged from 17 to 87 years in the low testosterone group and 20 to 84 in the normo-testosterone group. There were similarities between each group in the ratio of TBI to ABI. Eight-six percent of individuals in the low testosterone and 81% of the normo-testosterone group's injuries resulted from a TBI with the remainder being classified as an ABI.

Comorbid injuries in the two groups were similar. Forty-six percent of the hypotestosterone arm ($n = 13$) and 42% of the normo-testosterone arm ($n = 11$) had one or more additional major injuries. The type and degree of injury was evenly distributed between each arm. In the low testosterone group there were eight skull fractures, four vertebral fractures, three upper extremity fractures, five lower extremity fractures and three rib/thorax fractures, and five organ injuries. In the normo-testosterone group there were eight skull fractures, six vertebral fractures, three upper extremity fracture, four lower extremity fractures and three rib/thorax fractures, and two organ injuries. Seven individuals in both groups had injuries at multiple sites.

The time from injury to admission to the rehabilitation hospital was lower for the low testosterone group (29 vs. 33 days). The low testosterone group had slightly lower admission FIM scores and longer rehabilitation lengths of stay (103 vs. 77 days). The total hospital stay was 22 days longer for the low testosterone group (138 vs. 116 days). This difference was not statistically significant.

On admission, individuals with Hypotestosteronemia had slightly lower total admission FIM score 34 vs. 43. At discharge the difference between the two groups in FIM was 71 and 89, respectively. The change in FIM scores was 35 for the low testosterone group and 46 for the normo-testosterone group. The mean discharge motor FIM was 50 for the low testosterone group and 64 for the normo-testosterone group. The change in motor FIM scores which was 27 and 35, respectively ($p = 0.08$).

The mean discharge cognitive FIM scores for the low testosterone group was 21 and the normo-testosterone group was 25. The admission to discharge cognitive FIM was 9 for the low testosterone group and 11 for the normal testosterone group ($p = 0.06$). FIM efficiency was 35% and 60% for the normal and low testosterone groups, respectively. Though clinically meaningful, this did not achieve statistical significance ($p = 0.17$).

Discussion

The role of testosterone in central and peripheral nerve injury is a relatively new area of inquiry. Testosterone levels have been shown to be low acutely following TBI. While some authors have noted a return to normal levels, the bulk of the published literature has shown that these levels

Table I. Group statistics.

Group statistics	Status	*N*	Mean	Std. deviation	Std. error mean	*p*-value
AGE	Mono	26	49.4	20.8	4.1	0.60
	Low	28	46.2	23.3	4.4	
Multiple trauma	Mono	26	0.4	0.5	0.1	0.77
	Low	28	0.5	0.5	0.1	
Length of stay	Mono	26	58.3	61.3	12.0	0.45
	Low	28	73.7	84.8	16.0	
Tot. LOS	Mono	26	77.0	72.1	14.1	0.27
	Low	28	103.2	98.7	18.6	
Adm FIM	Mono	26	42.8	28.6	5.6	0.30
	Low	28	35.4	23.9	4.5	
Dis FIM	Mono	26	88.7	32.9	6.5	0.07
	Low	28	70.8	38.2	7.2	
Delta FIM	Mono	26	45.9	29.6	5.8	0.17
	Low	28	35.4	26.0	4.9	
Ad Mt FIM	Mono	26	29.0	20.6	4.0	0.36
	Low	28	24.2	17.0	3.2	
Ds Mt FIM	Mono	26	63.6	25.9	5.1	0.08
	Low	28	50.3	29.4	5.6	
Ad Cg FIM	Mono	26	13.9	8.7	1.7	0.19
	Low	28	11.0	7.4	1.4	
Dis Cg FIM	Mono	26	25.2	8.1	1.6	0.06
	Low	28	20.5	9.8	1.9	
T. Inj-PMR	Mono	25	33.1	34.5	6.9	0.60
	Low	28	28.9	23.3	4.4	
T. Inj-DC	Mono	25	115.8	102.1	20.4	0.44
	Low	27	138.6	106.6	20.5	

Table II. Evaluation of FIM scores by study group.

	Status	*N*	Mean	Std. deviation	Std. error mean	*p*-value
Admission FIM	Normal	26	42.8	28.6	5.6	0.30
	Low	28	35.4	23.9	4.5	
Admission motor FIM	Normal	26	29.0	20.6	4.0	0.36
	Low	28	24.2	17.0	3.2	
Admission cognitive FIM	Normal	26	13.9	8.7	1.7	0.19
	Low	28	11.0	7.4	1.4	
Discharge FIM	Normal	26	88.7	32.9	6.5	0.07
	Low	28	70.8	38.2	7.2	
Discharge motor FIM	Normal	26	63.6	25.9	5.1	0.08
	Low	28	50.3	29.4	5.6	
Discharge cognitive FIM	Normal	26	25.2	8.1	1.6	0.06
	Low	28	20.5	9.8	1.9	

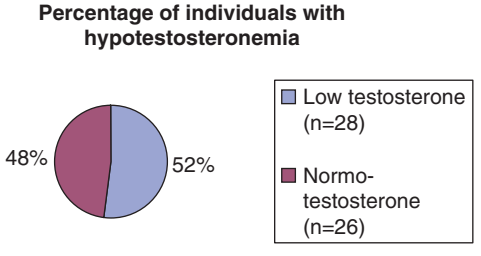

Figure 1. Percentage of individuals with hypotestosteronemia.

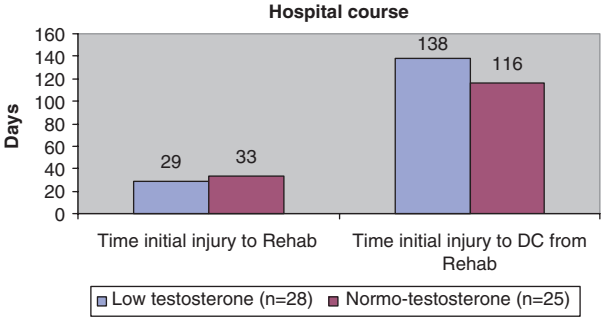

Figure 2. Time from injury to admission and discharge from rehabilitation.

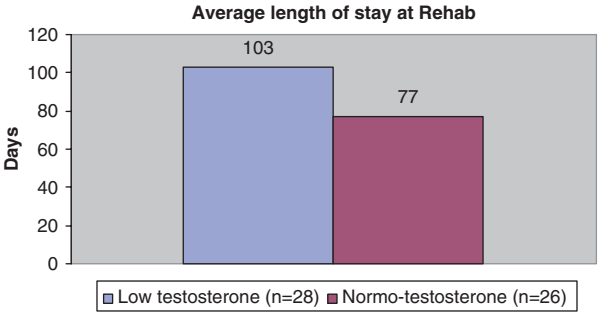

Figure 3. Average length of stay at rehabilitation hospital.

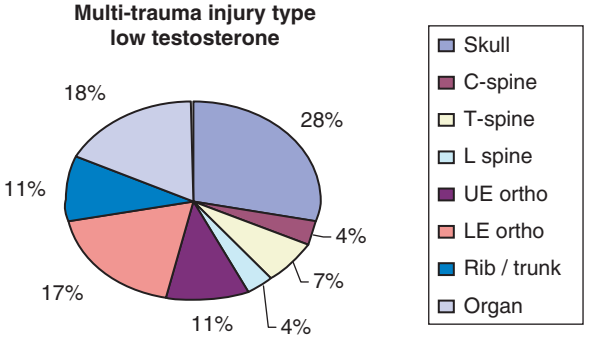

Figure 4. Multi-trauma injury type among those with low testosterone.

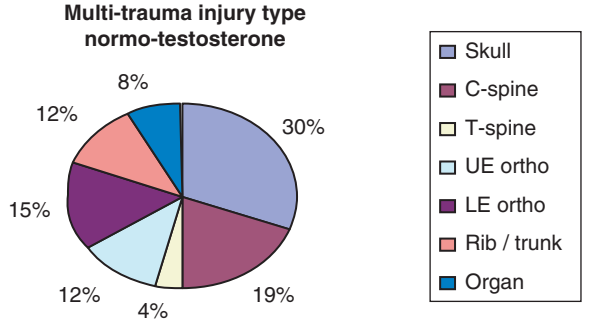

Figure 5. Multi-trauma type among those with normal testosterone.

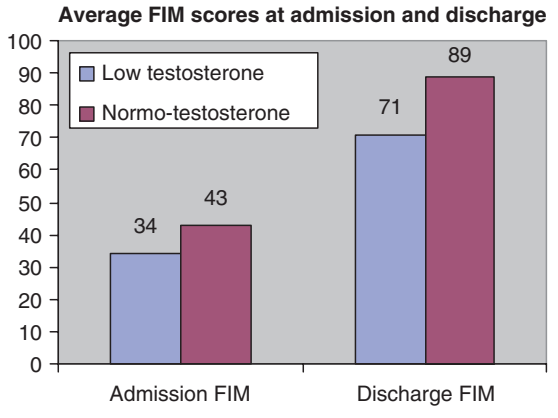

Figure 6. Average FIM scores at admission and discharge.

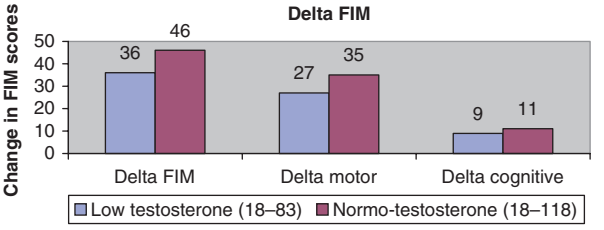

Figure 7. Changes in FIM scores while in rehabilitation.

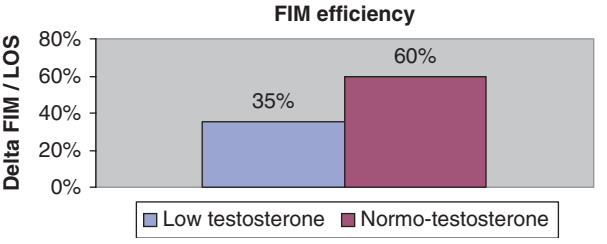

Figure 8. FIM change/time (FIM efficiency).

remain low in moderate and severe TBI. The relationship between injury severities as measured by GCS and testosterone levels has been more controversial. Fleischer [5] reported an inverse relationship between the severity of coma and blood testosterone levels. Cernak [6] studied testosterone levels in 31 patients with acute injuries. Among patients with mild injuries (GCS 13–15) testosterone levels normalized within 2 days post injury, while individuals with more severe injuries (GCS 4–6) testosterone levels remained low over a 7-day post trauma observation period.

There have been fewer studies exploring testosterone levels in patients recovering from TBI in the sub-acute setting. Our findings of low testosterone levels in 52% of our study population support the previously reported findings of 28% to 79% [1–3]. These data seem to support those from the previous literature suggesting a role of testosterone in the recovery patterns of patients with brain injuries.

Functionally, the low testosterone group began their rehabilitation process with a slightly lower admission FIM score (34 vs. 43); they made slower progress (FIM efficiency 35% vs. 60%), and completed their rehabilitation with lower FIM scores at the time of discharge (71 vs. 89). Differences in discharge FIM scores approached, but did not reach statistical significance, with a p-value of 0.07 (discharge cognitive FIM $p = 0.06$ and discharge motor FIM $p = 0.08$). This finding suggests that a low testosterone level at the time of admission to rehabilitation is associated with both motor and cognitive deficits in excess of those seen in matched normo-testosterone individuals.

Our finding of retarded motor recovery support Gregory's [7] findings in their rat model of lower extremity muscle fibre gains in rats with T9 cord transactions who were given testosterone. Other animal studies have suggested a neuroprotective role of testosterone in TBI and SCI. Separate studies, performed by Forger and Matsumoto [8, 9], demonstrated in the rat model that testosterone increased neuron somal size, neurotic growth, plasticity and synaptogenesis of motor neurons of the spinal nucleus of the bulbocavernosus. In the rat model, testosterone was shown to protect spinal cord neurons from glutamate-induced injury [7]. Additionally, Garcia-Estrada [10] suggested that gonadal hormones down-regulate reactive gliosis and astrocyte proliferation in the rat model. Exogenous testosterone administration, however, has been shown to improve spatial cognition and working memory in older individuals [11].

Differences in discharge cognitive FIM scores between the groups may indicate that testosterone plays a role in recovery from brain injury beyond motor gains alone. Our findings do suggest that low testosterone levels may impact cognitive recovery from TBI. This seems to support the improvements in spatial cognition and working memory in older adults seen by Janowsky [9] and in spatial and verbal memory in healthy older men demonstrated by Cherrier [12]. Though the patients in the low testosterone group received testosterone supplementation, the differences between the groups persisted. While no patients recovered to levels above those of normal it would have been instructive to review the recovery of the patient had the medical team not added testosterone as part of their clinical care.

Conclusion

This pilot study demonstrates that Hypotestosteronemia at the time of admission to an acute traumatic brain rehabilitation unit may be associated with a slightly lower admission FIM, longer length of stay and lower delta FIM and FIM efficiency. Although there were no statistically significant differences between the groups in LOS at our rehabilitation centre, the difference of 26 days does have clinical significance.

This study was limited, by its retrospective nature and low number of study subjects ($n = 54$). We also acknowledge that the average serum testosterone value recorded in the normo-testosterone group (384 ng/dl) fell into the bottom quarter of our lab's normal range (270–1070 ng/dl) with no values exceeding the mean lab value of healthy adult males. We believe that this may have blunted differences between the two groups. Despite these limitations, our finding that individuals with low testosterone appear to do much worse clinically, particularly in the area of cognitive recovery, justifies further research in this area. We believe further study of serum testosterone is needed to review its role for the management of males admitted for acute TBI rehabilitation. Testosterone supplementation in the acute and sub-acute period following TBI may play an important role in maximizing recovery. We acknowledge that further study is needed to confirm our preliminary findings.

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