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The Association of Serum Testosterone Levels With Recurrence and Mortality After Acute Ischemic Stroke in Males

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Abstract

The current study aimed to investigate whether low testosterone predicted the recurrence and clinical outcomes after acute ischemic stroke (AIS) in males. From June 2015 through August 2017, the study prospectively enrolled 110 male AIS patients. All received detailed evaluations at admission and were followed for at least 1 year. The cumulative incidence, overall survival, length of hospital stay, and the percentage of previous stroke were compared between subjects with testosterone $<$440 ng/dl and $>$440 ng/dl. The median age was 62 years (range, 35–93 years). The median serum testosterone at admission was 438 [203] ng/dl (range, 44–816 ng/dl); 55 patients (50%) had testosterone $<$440 ng/dl and were considered as low testosterone. The median follow-up was 23 months. During the period, 12 recurrences and 10 deaths occurred. The 1-year and 3-year cumulative recurrence rate were 8.3% and 11.9%, respectively; the 1-year and 3-year overall survival were 96.3% and 84.6%, respectively. The cumulative recurrence rates were similar between the two testosterone groups (log-rank test, $p = .88$). Low testosterone was associated with poor survival with marginal significance (log-rank test, $p = .079$). Men with low testosterone had a higher percentage of previous stroke (29.1% versus 12.7%, $p = .035$). The mean lengths of hospital stay were similar between the two testosterone groups (16.6 $\pm$ 15.8 days versus 14.0 $\pm$ 10.6, $p = .31$). Total testosterone at admission fails to predict stroke recurrence. However, men with low testosterone at admission are more likely to have previous stroke and may have a higher all-cause mortality rate after AIS.

Keywords

testosterone, stroke, recurrence, mortality, cardiovascular disease

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Stroke is the leading cause of death and chronic disability all over the world (Lozano et al., 2012), and the epidemiological data identified that the number of new events continues to increase in the past two decades (Feigin et al., 2014). A substantial percentage, around 6% to 12%, of patients with recent ischemic stroke would have a second episode in the following 1 year (Amarenco et al., 2018; Bergström et al., 2017; Dhamoon, Sciacca, Rundek, Sacco, & Elkind, 2006). For better risk stratification and optimal management, it is importance to identify the predicting factors for the recurrent ischemic stroke. More importantly, predictors may also serve as therapeutic targets if they are involved in the mechanisms of cerebrovascular diseases and can be treated or modified. Atherosclerosis is the major cause of acute ischemic stroke (AIS) and has been well recognized as a strong predictor for recurrence of cerebrovascular events

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(Amarenco et al., 1996; Serena, Segura, Roquer, Garcia-Gil, & Castillo, 2015). To Identify and to control the risk factors for atherosclerosis has long been considered the main strategy of stroke prevention (Tsivgoulis, Safouris, Kim, & Alexandrov, 2018).

Low testosterone is associated with multiple risk factors for atherosclerosis, such as obesity, diabetes, hypertension, and dyslipidemia (Corona, Monami, et al., 2011; Ho et al., 2015). Low testosterone is associated with increased systemic inflammation (Liao et al., 2016) and endothelial dysfunction (Corona, Bianchini, Sforza, Vignozzi, & Maggi, 2015), both of which contribute to atherosclerosis. Epidemiological studies demonstrated that low testosterone independently predicts the development of atherosclerosis (Hak et al., 2002; Hougaku et al., 2006). Several meta-analyses have confirmed that low testosterone increases the risk of major cardiovascular events as well as the mortality due to cardiovascular diseases and all causes (Corona et al., 2018a; Ruige, Mahmoud, De Bacquer, & Kaufman, 2011). A recent meta-analysis further demonstrated that testosterone therapy may have a beneficial effect on cardiovascular mortality in select subjects (Corona et al., 2018b). With the recognition of the association of serum testosterone with vascular health, the current study tested the hypothesis that low testosterone could negatively affect the clinical outcomes after AIS in male patients. The current study primarily aimed to investigate whether serum testosterone levels at admission predict the subsequent recurrence of ischemic stroke. In addition, the current study evaluated whether testosterone level was associated with mortality, the length of hospital stay, and history of previous stroke.

Methods

Study Subjects

This is a single-center, prospective, observational study. The current study enrolled male AIS patients who presented to a tertiary medical center. All patients were admitted within 24 hr after the onset of a new focal or global neurological event. The diagnosis of AIS was made by the treating neurologist, with the assistance of magnetic resonance imaging (MRI) or computed tomographic (CT) scan. Those who received either intravenous or intra-arterial thrombolytic therapy were excluded from the study. The study protocol was approved by the institutional review board (CGH-P103074), and a written informed consent was obtained from each patient.

Initial Evaluation and Follow-Up

The study collected the demographic data, including age, body mass index (BMI), waist, smoking habit, and history of hypertension, diabetes mellitus, atrial fibrillation, hyperlipidemia, coronary arterial disease, and previous ischemic stroke. Blood samples for laboratory assessments were obtained in the first morning after admission (between 08:00 am and 10:00 am). The laboratory examinations included blood chemistry tests and total testosterone. It was previously demonstrated that total testosterone level $<$440 ng/dl is associated with increased Framingham 10-year cardiovascular disease risk in middle-aged and elderly men (Liao et al., 2016). Therefore, in the current study, total testosterone of $<$440 ng/dl was considered as low testosterone.

All patients received standard medical care based on the physicians' expertise and the current guidelines (Powers et al., 2015). Patients were discharged when the clinical conditions were considered appropriate. They then received regular follow-up at the outpatient clinic. All patients were followed for at least 1 year in the current study. The major information included stroke recurrence, time of recurrence, survival status, and cause of death.

Clinical Outcomes Assessment

The primary end point was the time to the recurrence of AIS. The second end point was the time to death. In the cross-sectional analyses, the study investigated the association of testosterone with the percentage of previous ischemic stroke as well as the length of hospital stay.

Statistics

The continuous variables are expressed as median [interquartile range], and the categorical variables are expressed as a count (percentage). Patients with the serum testosterone level $<$440 ng/dl were considered as low testosterone, and those with testosterone $>$440 ng/dl were considered as controls (Liao et al., 2016). Characteristics between the two groups were compared using Mann–Whitney U test or χ^2 test. Kaplan–Meier method was used to estimate the recurrence and mortality of the male AIS patients, grouped by the serum testosterone levels. The log-rank test was used to compare the recurrence and mortality between the two testosterone groups. The length of hospital stay was compared using Mann–Whitney U test, and the percentage of previous ischemic stroke was compared using χ^2 test. All statistic tests were two-sided, and a p value of $<$.05 was considered to indicate a statistically significant difference. All statistical analyses were performed using SPSS 22.0 (IBM Corp., Armonk, NY, USA).

Results

Patient Characteristics

From June 2015 through August 2017, a total of 110 male patients with AIS were enrolled in this study. The median

Table 1. Characteristics of the 110 Male Patients With Acute Ischemic Stroke.

	Total (n = 110)	<440 ng/dl (n = 55)	>440 ng/dl (n = 55)	p value
Age, years	62 [23]	66 [22]	58 [19]	.002
BMI, kg/m^2	25.5 [5.1]	25.7 [4.8]	25.5 [5.2]	.24
Obesity	55 (50.0%)	29 (52.7%)	26 (47.3%)	.57
Diabetes	53 (48.2%)	24 (43.6%)	29 (52.7%)	.34
Hypertension	89 (80.9%)	45 (81.8%)	44 (80.0%)	.81
Hyperlipidemia	54 (49.1%)	22 (40.0%)	32 (58.2%)	.06
Low HDL	40 (38.1%)	17 (32.1%)	23 (44.2%)	.20
Atrial fibrillation	8 (7.3%)	4 (7.3%)	4 (7.3%)	1.00
Smoking	47 (42.7%)	21 (38.2%)	26 (47.3%)	.34

Note. Continuous data are expressed as median [interquartile range]; categorical data are expressed as count (%). BMI = body mass index; HDL = high-density lipoprotein.

Table 2. Odds Ratio and 95% Confidence Interval for Previous Stroke.

	OR	95% CI	p value
Testosterone			
<440 ng/dl	2.81*	[1.05, 7.52]	.039
>440 ng/dl	1	Reference	
Age, per 1 year	1.01	[0.98. 1.05]	.31
Diabetes mellitus			
DM (−)	1	Reference	
DM (+)	0.79	[0.31, 1.99]	.61
Obesity (waist >90 cm)			
Ob (−)	1	Reference	
Ob (+)	1.12	[0.45, 2.80]	.82
Hypertension			
HTN (−)	1	Reference	
HTN (+)	6.57	[0.83, 51.8]	.07
Hyperlipidemia			
Hyperlipidemia (−)	1	Reference	
Hyperlipidemia (+)	0.6	[0.24, 1.53]	.29
Atrial fibrillation			
Af (−)	1	Reference	
Af (+)	0.52	[0.06, 4.45]	.55
Smoking			
Smoking (−)	1	Reference	
Smoking (+)	0.66	[0.25, 1.71]	.39

Note. *After adjusting for age, the odds ratio of low testosterone (<440 ng/dl) was 2.66 (95% CI [0.95, 7.41], p = .062).

age was 62 [23] years (range, 35–93 years), and the median BMI was 25.5 [5.1] kg/m^2. The number (percentage) of subjects with central obesity (waist circumference >90 cm), diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation, and smoking were 55 (50.0%), 53 (48.2%), 89 (80.9%), 54 (49.1%), 8 (7.3%), and 47 (42.7%), respectively (Table 1).

The median serum testosterone at admission was 438 [203] ng/dl (range, 44 –816 ng/dl). Fifty-five patients (50%) had serum testosterone <440 ng/dl at admission and were categorized as low testosterone, while those with testosterone above this level were categorized as controls. Table 1 compares the demographic data between the two groups: The median age of the low testosterone group was significantly greater than that of the controls (66 [22] years versus 58 [19] years, p = .002), and the other demographic data were not significantly different between the two groups (Table 1).

The Association of Testosterone With Stroke Recurrence and Overall Survival

The longitudinal follow-up ended in August 2018, 1 year after the last enrollment. The median follow-up was 23 months (range, 3.4–39 months). During this period 12 recurrences occurred among the entire population. The Kaplan–Meier plot revealed that the cumulative AIS recurrence rate at 1 year and 3 years were 8.3% and 11.9%, respectively. The curves of cumulative incidence for recurrent ischemic stroke were not different between the low testosterone group and the control group (Figure 1 Left, log-rank test, p = .88).

There were 10 deaths during the follow-up period. Of the 10 patients, 4 died of cancer, 3 died of infection, 2 died of aging, and 1 died of aortic dissection. For the entire population, the 1-year and 3-year overall survival were 96.3% and 84.6%, respectively. The difference in survival between the two groups was marginally significant (Figure 1 Right, log-rank test, p = .079).

Association of Testosterone With Previous Stroke and Length of Hospital Stay

The percentage of subjects with history of previous ischemic stroke was significantly higher in the low testosterone group (29.1% versus 12.7%, p = .035). Logistic regression revealed low testosterone was significantly associated with previous ischemic stroke (odds ratio = 2.81, 95%

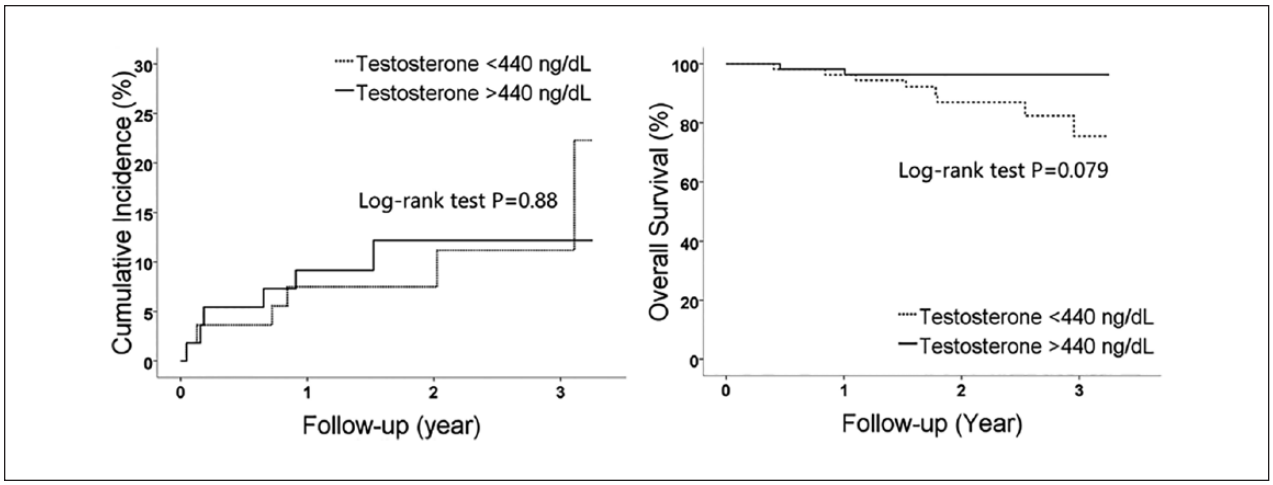

Figure 1. Kaplan–Meier plots for the cumulative incidence of stroke recurrence (left) and overall survival (right).

confidence interval [1.05, 7.52], $p = .039$, Table 2). The association remained marginally significant after controlling for age (odds ratio = 2.66, 95% CI [0.95, 7.41], $p = .062$, Table 2). The mean lengths of hospital stay were similar between the two testosterone groups (16.6 ± 15.8 days versus 14.0 ± 10.6, $p = .31$).

Discussion

The current study investigated the association of testosterone levels at admission with the clinical outcomes after AIS in males. The study did not observe an association of testosterone with subsequent recurrence after AIS. Low testosterone at admission might predict a worse overall survival. The cross-sectional analyses revealed that men with low testosterone had a 2.81-fold greater chance of previous stroke, and the association remained significant after adjusting for age.

There have been several studies investigating the relationship between testosterone and the incidence of ischemic stroke in the community-dwelling male population, and the results are inconsistent across all studies. In an analysis from the Health In Men Study including 3,443 men aged ≥70 years followed up for 3.5 years, men with total testosterone in the lowest quartile of values had a near twofold increase in the risk of stroke or transient ischemic attack after adjusting for age and other conventional cardiovascular risk factors (Yeap et al., 2009). Data from the Cardiovascular Health Study revealed a nonlinear positive association of dihydrotestosterone with the risk of ischemic stroke (Shores et al., 2014). In 2016 and 2018, three separate investigations from Denmark (Holmegard, Nordestgaard, Jensen, Tybjærg-Hansen, & Benn, 2016), Finland (Zeller et al., 2018), and the Netherlands (Glisic et al., 2018) confirmed that low testosterone increases the risk of ischemic stroke. On the contrary, analyses of data from the Atherosclerosis Risk in Communities study failed to confirm the association of endogenous testosterone with incident stroke or other atherosclerosis-related findings on brain MRI after controlling atherosclerosis risk factors in community-dwelling men (Srinath, Gottesman, Hill Golden, Carson, & Dobs, 2016). Three other studies reported no significant association of testosterone with ischemic stroke events (Abbott et al., 2007; Ohlsson et al., 2011; Soisson et al., 2013).

To our knowledge, the current study was the first to look at the association of endogenous testosterone with the recurrence of ischemic stroke in males. The failure to observe a significant association reflects that the mechanisms underlying recurrent stroke may be complex and multifactorial (Hillen et al., 2003; Yamamoto & Bogousslavsky, 1998). Although several risk factors, such as age, hypertension, diabetes, and atrial fibrillation, were reported to be associated with the recurrence of ischemic stroke (Elneihoum, Göransson, Falke, & Janzon, 1998; Johnston et al., 2007; Lai, Alter, Friday, & Sobel, 1994), most stroke recurrences remain unexplained by conventional risk factors (Hillen et al., 2003). Analyses of data from the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial demonstrated that only about half of the recurrences were with the same mechanism as the previous stroke (Toni, Di Angelantonio, Di Mascio, Vinisko, & Bath, 2014). The alteration in stroke subtype between two stroke events was also demonstrated in other studies (Shin, Lee, & Bang, 2005). Results from these studies suggest that the mechanisms of cerebrovascular events are more complex than those of coronary heart disease. The involvement of multiple mechanisms also explains the reason why the current study failed to observe a significant relationship between testosterone and stroke recurrence.

While not demonstrating the predictive value of testosterone on the future recurrence of stroke, the current study did observe a significant association of testosterone with previous stroke. Multiple comorbidities and chronic disability are highly prevalent in those with previous stroke, and it is known that low testosterone can be a consequence of accumulating disease burden (Corona et al., 2016). It was demonstrated that men with chronic illness have lower serum testosterone levels than healthy men (Wu et al., 2008); luteinizing hormone levels fail to elevate in those with chronic illness, suggesting that the hypothalamic–pituitary–testicular axis is impaired (Wu et al., 2008). Several comorbidities associated with stroke, such as obesity and type 2 diabetes, are associated with increased concentrations of proinflammatory cytokines (Pastuszak, Kohn, Estis, & Lipshultz, 2017), which may disrupt the hypothalamus and result in lower testosterone levels (Igaz et al., 2006). Statin use is very common in stroke survivors, and statin has been reported to lower the testosterone level (Corona, Boddi, et al., 2010; Stanworth, Kapoor, Channer, & Jones, 2009).

The current study observed a marginally significant association of testosterone and the overall survival, and the majority of deaths in the current study were not related to cardiovascular or cerebrovascular diseases. This finding generally confirmed previous studies that low testosterone increases the risk of death due to all cause, cardiovascular disease, and cancer in the general population (Araujo et al., 2011; Corona, Monami, et al., 2010; Corona et al., 2018a; Corona, Rastrelli, et al., 2011; Khaw et al., 2007; Ruige et al., 2011). These results suggest that testosterone can be viewed as a marker for general health and a predictor for survival in either general male population or stroke survivors.

Regarding the strength of the current study, it was the first to investigate the association of endogenous testosterone with recurrence and mortality in men with AIS. However, there are some limitations. First, the relatively small sample size limits the power to detect a difference, and it may also lead to a *p* value of marginal significance. Second, the serum testosterone level was checked only once in the acute stage of ischemic stroke (at admission). It is not known how the testosterone level changes over time after AIS. It was recently reported that low testosterone levels are common in the acute phase of myocardial infarction in males, but the level appears to increase thereafter (Wang et al., 2018). Low testosterone at acute phase has been reported to predict the survival after acute myocardial infarction (Pesonen, Pussinen, & Huhtaniemi, 2016), which encouraged us to investigate the predictive value of testosterone level at acute phase of AIS, although further studies are still required. Third, as both intravenous and intra-arterial intervention significantly change the clinical course, we did not include these patients in the current study. This would lead to a limitation in the generalizability of the current study.

Conclusion

In the current study, total testosterone levels at admission failed to predict recurrence after AIS in male patients. Men with low testosterone at admission have a higher chance of previous stroke and may have a higher all-cause mortality rate.

Declaration of Conflicting Interests

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