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The predictive value of serum testosterone level on the functional outcomes after acute ischemic stroke in males

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ABSTRACT

Introduction: We aimed to evaluate the predictive value of sex hormone levels on 3-month functional outcomes after acute ischemic stroke (AIS) in males.

Materials and methods: A total of 110 male AIS patients were included in this prospective study. Serum levels of testosterone and estradiol were measured at admission. The National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS) were measured at admission and after 3 months. A mRS score $\geq$3 was considered as a poor functional outcome.

Results: The median age of the 110 subjects was 62.0 [23.3] years (range 35–93 years). Univariate logistic regression revealed that bioavailable testosterone, free testosterone, age, NIHSS at admission, mRS at admission, and prior ischemic stroke were associated with a poor functional outcome (mRS score $\geq$3) at 3 months. In multivariate analysis, only age, NIHSS at admission, and mRS at admission were independent predictors.

Conclusions: After controlling the covariates, bioavailable and free testosterone levels are not associated with the 3-month mRS in male patients with AIS. Age, NIHSS at admission, and mRS at admission are robust predictors for the functional outcomes.

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KEYWORDS
Testosterone; ischemic stroke; functional outcome; recovery; predictor

Introduction

Stroke is a leading cause of death and long-term disability globally. While mortality rates have decreased worldwide over the past two decades, the absolute number of stroke events and stroke survivors are still high and continue to increase [1]. Stroke causes a substantial burden to patients, family members, and the health care system. In order to optimize rehabilitation programs and to more efficiently allocate healthcare resources, it is necessary to identify the prognostic factors of disease development and patient functional outcomes [2]. In addition, some of these factors may be involved in the mechanism of recovery from acute stroke, and may serve as potential therapeutic targets if they are adjustable. To date, several clinical parameters, such as age, baseline stroke severity, infarct volume and location, and pre-stroke physical function have been shown to predict the functional outcome after acute ischemic stroke (AIS) [3–8]. Despite this, there has been persistent enthusiasm in finding new prognostic factors of such a prevalent and devastating disorder.

Low testosterone is associated with several cardiovascular risk factors, such as diabetes [9], dyslipidemia [10], and obesity [11]. Testosterone deficiency is associated with an increase in pro-inflammatory cytokines and some biomarkers for atherosclerosis [12–14]. Epidemiological studies have demonstrated that low testosterone increases the incidence of AIS [15–18]. Low testosterone has also been reported in patients who have suffered from stroke [19,20]. Testosterone deficiency is associated with some neuropsychiatric diseases, such as depression [21]. Testosterone was shown to protect neurons against ischemia in animal studies [22], and it was also shown that testosterone enhances functional recovery after brain ischemia in male rats, which was probably mediated via the promotion of antioxidant defenses, brain-derived neurotrophic factor, and neurogenesis [23]. Moreover, it was recently demonstrated that testosterone replacement therapy improves glycemic control and endothelial function in men with type 2 diabetes [24,25], and reduces obesity in hypogonadal men with erectile

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dysfunction [26]. Yassin et al. [27] suggest a lifelong treatment to continuously control these cardiometabolic parameters. While the true effect of testosterone supplement on the prevention of cardiovascular events is still to be determined, current evidence and expert opinions support a beneficial effect [28]. On the other hand, estrogen has also been shown to be neuroprotective in animal models [29]. These findings suggest that testosterone and/or estrogen may affect patient functional outcomes after AIS.

Compared with the high number of studies investigating the association between testosterone and coronary heart disease, its association with cerebrovascular diseases in humans has been less studied. Moreover, human studies regarding the effect of testosterone on stroke outcomes are scarce. The current study aimed to investigate whether the level of endogenous testosterone at the onset of AIS affected the disease severity and the functional outcomes after 3 months in male patients.

Materials and methods

Study subjects

The present prospective study enrolled 110 male patients with AIS who presented to a tertiary medical center between June 2015 and August 2017. All patients were admitted within 24 h of experiencing a new focal or global neurological event. The diagnosis of AIS was performed by the treating neurologist, with the assistance of appropriate diagnostic modules (e.g. MRI or CT scan). All patients diagnosed of acute ischemic stroke were enrolled in the current study. Patients were excluded from the study if any of the following applied: (1) patients who underwent either intravenous or intra-arterial thrombolysis; (2) those who died within 3 months of the event; (3) those who were not willing to participate the study. The study protocol was approved by the institutional review board (approval no. CGH-P103074). Written informed consent was obtained from all participants.

Initial evaluation and follow-up

Baseline demographics and biochemical data were obtained from the patient on their admission for AIS. The demographic data included age, body mass index (BMI), hypertension, diabetes mellitus, atrial fibrillation, hyperlipidemia, coronary arterial disease, previous stroke, and smoking habit. The baseline biochemical data included routine blood chemistry and hormone levels, including testosterone, estradiol, and sex hormone binding globulin. The levels of bioavailable and free testosterone were calculated using Vermeulen's formula [30]. The initial stroke severity and the functional status were assessed using the National Institute of Health Stroke Scale (NIHSS) and the Modified Rankin Scale (mRS).

All patients received standard medical care according to the current guidelines [31] and the physicians' expertise. Patients were discharged when their clinical condition was considered appropriate and they then underwent regular follow-ups at the outpatient clinic. At 3 months after the stroke, a second evaluation using the NIHSS and mRS was performed.

Statistics

The continuous variables are expressed as the median [interquartile range], and the categorical variables are expressed as a count (percentage). The serum levels of each sex hormone were categorized into three groups by tertile. The Kruskal–Wallis test was used to detect differences among the tertiles of each sex hormone. A mRS score $\geq$3 was considered to represent a poor functional outcome. Logistic regression was performed to assess the association of each sex hormone and other factors (age, comorbidities, NIHSS at admission, and mRS at admission) with the poor outcome (mRS $\geq$3). The procedure also yielded the odds ratio (OR) and 95% confidence interval (CI) for mRS $\geq$3. Multivariate analyses were performed with models listed as below: Model 1 adjusted for age; Model 2 adjusted for age and NIHSS at admission; Model 3 adjusted for age and mRS at admission; Model 4 adjusted for age, NIHSS at admission, and mRS at admission. A p value of <0.05 was considered to indicate a statistically significant difference. All statistical analyses were performed using SPSS 22.0 (IBM Corp., Armonk, NY).

Results

The median age of the 110 subjects was 62.0 [23.3] years (range 35–93 years). At admission, the median total testosterone, bioavailable testosterone, free testosterone, and estradiol were 438 [203] ng/dL, 139 [72.1] ng/dL, 6.6 [3.0] ng/dL, and 39.4 [20.0] pg/mL. The median NIHSS and mRS at admission were 4.0 [4.0] and 2.0 [1.8], respectively, and they were 1.0 [2.0] and 1.0 [2.3] at 3 months. The comorbidities and baseline NIHSS and mRS of the whole cohort and the comparisons among the tertiles of each sex hormones are listed in Table 1.

Table 2 compares the NIHSS and mRS at 3 months among the tertiles of each sex hormone. The median

Table 1. Characteristics and initial neurological status of the 110 male patients with acute ischemic stroke.

		Total testosterone				Bioavailable testosterone				Free testosterone				Estradiol			
	All	1st tertile	2nd tertile	3rd tertile	*p*	1st tertile	2nd tertile	3rd tertile	*p*	1st tertile	2nd tertile	3rd tertile	*p*	1st tertile	2nd tertile	3rd tertile	*p*
Age (years)	62.0 [23.3]	65.5 [21.3]	63.0 [20.5]	56.0 [22.0]	0.03	75.0 [25.3]	65.0 [16.5]	54.0 [14.5]	<0.001	75.0 [22.0]	65.0 [17.0]	53.0 [13.5]	<0.001	62.0 [23.0]	60.5 [17.3]	65.0 [25.0]	0.70
BMI (kg/m^2)	25.5 [5.1]	25.0 [3.6]	26.7 [6.0]	22.9 [5.1]	0.01	23.5 [4.9]	25.7 [5.5]	26.5 [4.5]	0.01	23.2 [4.7]	25.7 [5.4]	26.4 [3.7]	<0.01	24.8 [4.1]	26.8 [5.0]	23.3 [5.5]	0.02
Obesity (%)	55 (50.0)	22 (61.1)	18 (48.6)	15 (40.5)	0.21	14 (38.9)	24 (64.9)	17 (45.9)	0.07	15 (41.7)	21 (56.8)	19 (51.4)	0.43	17 (45.9)	20 (52.6)	18 (51.4)	0.83
Smoking (%)	47 (42.7)	14 (30.9)	15 (40.5)	18 (48.6)	0.66	13 (36.1)	17 (45.9)	17 (45.9	0.62	14 (38.9	17 (45.9)	16 (43.2	0.83	13 (35.1	18 (47.4	16 (4.7)	0.51
Hypertension (%)	89 (80.9)	31 (86.1)	29 (78.4)	29 (78.4)	0.63	29 (80.6)	33 (89.2)	27 (73.0)	0.21	31 (86.1)	32 (86.5)	26 (70.3)	0.13	30 (81.1)	30 (78.9)	29 (82.9)	0.91
Diabetes mellitus (%)	53 (48.2)	16 (44.4)	21 (56.8)	16 (43.2)	0.44	16 (44.4)	22 (59.5)	15 (40.5)	0.23	16 (44.4)	19 (51.4)	18 (48.6)	0.84	21 (56.8)	16 (42.7)	16 (45.7)	0.42
Hyperlipidemia (%)	54 (49.1)	12 (33.3)	24 (64.9)	18 (48.6)	0.03	14 (38.9)	21 (56.8)	19 (51.4)	0.30	12 (33.3)	20 (54.1)	22 (59.5)	0.06	19 (51.4)	19 (50.0)	16 (45.7)	0.88
Metabolic syndrome (%)	60 (54.6)	17 (50.0)	24 (66.7)	19 (54.3)	0.34	16 (47.1)	25 (71.4)	19 (52.8)	0.10	16 (48.5)	23 (63.9)	21 (58.3)	0.43	22 (62.9)	19 (50.0)	19 (59.4)	0.52
Prior ischemic stroke (%)	22 (20.0)	11 (31.4)	7 (18.9)	5 (13.5)	0.16	7 (19.4)	9 (25.0)	7 (18.9)	0.78	8 (22.2)	8 (22.2)	7 (18.9)	0.92	10 (27.0)	7 (18.4)	6 (17.6)	0.55
Atrial fibrillation (%)	8 (7.3)	3 (8.3)	2 (5.4)	3 (8.1)	0.87	4 (11.1)	2 (5.4)	2 (5.4)	0.56	4 (11.1)	3 (8.1)	1 (2.7)	0.37	0 (0)	3 (7.9)	5 (14.3)	0.07
Coronary heart disease (%)	10 (9.1)	1 (2.8)	4 (10.8)	5 (13.5)	0.25	2 (5.6)	3 (8.1)	5 (13.5)	0.48	3 (8.3)	2 (5.4)	5 (13.5)	0.47	5 (13.5)	2 (5.3)	3 (8.6)	0.46
Uremia (%)	3 (2.7)	2 (5.6)	1 (2.7)	0 (0)	0.35	2 (5.6)	0 (0)	1 (2.7)	0.35	2 (5.6)	1 (2.7)	0 (0)	0.35	1 (2.7)	2 (5.3	0 (0)	0.39
NIHSS (admission)	4.0 [4.0]	4.0 [4.0]	5.0 [4.0]	4.0 [4.0]	0.58	4.0 [4.0]	4.5 [3.0]	3.5 [4.0]	0.39	4.0 [4.0]	4.0 [3.8]	4.0 [4.0]	0.46	5.0 [4.0]	3.0 [3.0]	4.0 [4.0]	0.22
mRS (admission)	2.0 [1.8]	2.0 [2.0]	2.0 [2.0]	2.0 [1.0]	0.32	3.0 [1.0]	2.0 [2.5]	2.0 [2.0]	0.16	2.5 [1.0]	2.0 [1.8]	2.0 [2.0]	0.27	2.0 [1.8]	2.0 [2.0]	2.0 [1.0]	0.46

Total testosterone (ng/dL): 1st tertile <375; 2nd tertile 375–500; 3rd tertile >500.
Bioavailable testosterone (ng/dL): 1st tertile <121; 2nd tertile 121–163; 3rd tertile >163.
Free testosterone (ng/dL): 1st tertile <5.8; 2nd tertile 5.8–7.5; 3rd tertile >7.5.
Estradiol (pg/mL): 1st tertile <33.3; 2nd tertile 33.3–46.4; 3rd tertile >46.4.

Table 2. The association of male sex hormone levels with the 3-month functional outcomes.

	All	Total testosterone				Bioavailable testosterone				Free testosterone				Estradiol			
		1st tertile	2nd tertile	3rd tertile	*p*	1st tertile	2nd tertile	3rd tertile	*p*	1st tertile	2nd tertile	3rd tertile	*p*	1st tertile	2nd tertile	3rd tertile	*p*
NIHSS (3 months)	1.0 [2.0]	1.0 [2.0]	1.0 [2.0]	1.0 [2.0]	0.72	1.0 [2.0]	1.0 [2.5]	1.0 [2.0]	0.12	1.0 [2.0]	1.0 [2.5]	1.0 [2.0]	0.23	1.0 [2.0]	1.0 [2.0]	1.0 [2.0]	0.58
mRS (3 months)	1.0 [2.3]	1.0 [2.8]	1.0 [1.0]	1.0 [3.0]	0.94	1.5 [2.0]	1.0 [2.5]	1.0 [2.0]	0.05	1.0 [2.0]	1.0 [2.5]	1.0 [2.0]	0.31	1.0 [2.5]	1.0 [1.3]	2.0 [2.0]	0.56

Total testosterone (ng/dL): 1st tertile <375; 2nd tertile 375–500; 3rd tertile >500.
Bioavailable testosterone (ng/dL): 1st tertile <121; 2nd tertile 121–163; 3rd tertile >163.
Free testosterone (ng/dL): 1st tertile <5.8; 2nd tertile 5.8–7.5; 3rd tertile >7.5.
Estradiol (pg/mL): 1st tertile <33.3; 2nd tertile 33.3–46.4; 3rd tertile >46.4.

Table 3. Univariate logistic regression analysis determining the odds ratio of sex hormones for poor functional outcome (mRS ≥3) at 3 months.

	Odds ratio (95% CI)	*p* Value
Total testosterone		
1st tertile	1.08 (0.39, 3.03)	0.88
2nd tertile	0.52 (0.17, 1.63)	0.26
3rd tertile	REF	
Bioavailable testosterone		
1st tertile	5.91 (1.50, 23.30)	0.01
2nd tertile	4.80 (1.21, 18.96)	0.03
3rd tertile	REF	
Free testosterone		
1st tertile	3.78 (1.07, 13.32)	0.04
2nd tertile	3.49 (1.00, 12.24)	0.05
3rd tertile	REF	
Estradiol		
1st tertile	1.49 (0.51, 4.29)	0.47
2nd tertile	0.76 (0.24, 2.38)	0.64
3rd tertile	REF	

mRS at 3 months of first (<121 ng/dL), second (121–163 ng/dL), and third (>163 ng/dL) tertile of bioavailable testosterone of bioavailable testosterone were 1.5 [2.0], 1.0 [2.5], and 1.0 [2.0], respectively ($p = 0.05$).

Univariate logistic regression revealed that the lower and middle tertiles of bioavailable testosterone predicted a poor functional outcome (mRS score ≥3), with odds ratios of 5.91 (95%CI 1.50–23.30, $p = 0.01$) and 4.80 (95%CI 1.21–18.96, $p = 0.03$), respectively. The lower two tertiles of free testosterone also predicted a poor functional outcome, with odds ratios of 3.78 (95%CI 1.07–13.32, $p = 0.04$) and 3.49 (95%CI 1.00–12.24, $p = 0.05$), respectively. Neither total testosterone nor estradiol were associated with the mRS score (Table 3).

Univariate logistic regression also revealed that age (odds ratio 1.07, 95%CI 1.03–1.10, $p = 0.001$), NIHSS at admission (odds ratio 1.38, 95%CI 1.16–1.64, $p < 0.001$), mRS at admission (odds ratio 11.6, 95%CI 4.26–31.6, $p < 0.001$), and prior ischemic stroke (odds ratio 2.85, 95%CI 1.05–7.76, $p = 0.04$) were significantly associated with a mRS ≥3 at 3 months. The association of other comorbidities with the functional outcomes was not significant.

In multivariate analysis, both bioavailable and free testosterone were not associated with the mRS at 3 months in all the Models. On the other hand, age, NIHSS at admission, mRS at admission remained significantly associated with mRS in multivariate analysis (Table 4).

Discussion

The current study investigated the association between serum levels of male sex hormones and the disease

Table 4. Multivariate logistic regression analysis determining the odds ratio of sex hormones for poor functional outcome (mRS ≥3) at 3 months.

	Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Bioavailable testosterone								
1st tertile	2.55 (0.54, 11.9)	0.24	2.76 (0.45, 16.9)	0.27	2.01 (0.31, 13.0)	0.47	3.49 (0.45, 26.9)	0.23
2nd tertile	2.87 (0.68, 12.2)	0.15	2.85 (0.55, 14.8)	0.21	3.78 (0.52, 27.5)	0.19	4.44 (0.49, 40.1)	0.18
3rd tertile	REF		REF		REF		REF	
Free testosterone								
1st tertile	1.28 (0.29, 5.72)	0.75	0.85 (0.16, 4.56)	0.85	0.95 (0.14, 6.32)	0.96	1.23 (0.16, 9.69)	0.85
2nd tertile	1.95 (0.51, 7.48)	0.33	1.32 (0.31, 5.69)	0.71	3.44 (0.52, 22.6)	0.20	2.87 (0.40, 20.9)	0.30
3rd tertile	REF		REF		REF		REF	

severity and functional outcomes at 3 months after AIS in male patients. While univariate analysis revealed an association of low bioavailable testosterone or low free testosterone at admission with poor functional outcome at 3 months, the association did not remain significant in multivariate analysis. On the other hand, age, NIHSS at admission, and mRS at admission remained robust predictors for the functional outcomes.

In the literature, there have been very few human studies regarding the effect of testosterone on functional outcomes after stroke. A study consisting of 29 cerebral hemorrhages and 82 infarctions demonstrated that the free testosterone concentration at admission was positively correlated with the Functional Independence Measure at discharge [32]. Another recent study showed that long-term testosterone supplements significantly improved muscle strength, hypogonadal symptoms, and mental health 2–5 years after AIS [20]. To the best of our knowledge, the current study was the first to investigate the effect of endogenous testosterone on the functional outcome in a cohort exclusively consisting of AIS patients, and it contained the largest case number to date. Our findings suggested that the relationship between testosterone and functional outcomes at 3 months can be explained by other clinical factors, such as age, pre-stroke physical conditions, and at-admission stroke severity and physical morbidities. It has been demonstrated that the endogenous testosterone level does not improves to the predictive value of Framingham Risk Score for cardiovascular diseases (including stroke) in men [33]. Our findings also confirmed a recent study of Phan et al. [3], which intended to evaluate the impact of Charlson comorbidity index on prediction of functional outcomes after AIS. The authors found that a model incorporating age, gender, comorbidity, and NIHSS at 24 h had a high AUC of 0.9. In this model, NIHSS at 24 h is the most important factors, explaining 87.3% of the variance, follow by age (8.5%), comorbidity (3.7%), and male sex (0.5%). A more recent study also confirmed that both baseline NIHSS and the change in stroke severity after 24 h are important prognostic factors for the functional outcome [4]. On the other hand, it was also reported that pre-stroke physical conditions, as measured by pre-stroke mRS, predicts the functional outcome at the 90 d of AIS [8]. As previous studies have observed an inverse relationship between testosterone and baseline comorbidities or frailty [34,35], testosterone can be viewed as an approximate of the comorbidity index or the general physical condition. From this perspective, our results were generally in line with the previous studies [3], suggesting that testosterone level, comorbidities, and pre-stroke physical condition were relatively minor predictors, while age, initial NIHSS, and initial mRS robustly predicted the functional outcomes.

The strength of the current study was that this was the first to investigate the association of testosterone with the functional outcomes after AIS in males. However, there were still some limitations. First, the sample size was relative small, which limited the power to detect a difference. Second, the current study did not include those receiving intravenous and intra-arterial interventions because these interventions significantly change the clinical course and should be discussed separately. This limits the generalization of the results.

Conclusion

Bioavailable and free testosterone are associated with the 3-month mRS after AIS in male patients only in univariate analysis but not in multivariate analysis. Age, NIHSS at admission, and mRS at admission are robust predictors for the functional outcomes.

Ethics statement

The study protocol was approved by the institutional review board of Cathay General Hospital (CGH-P103074) and was performed in accordance with the

ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from the participants of this study.

Disclosure statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

[1] Feigin VL, Forouzanfar MH, Krishnamurthi R, et al. Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. Lancet. 2014;383:245–254.

[2] Wang J, Ning R, Wang Y. Plasma D-dimer level, the promising prognostic biomarker for the acute cerebral infarction patients. J Stroke Cerebrovasc Dis. 2016;25:2011–2015.

[3] Phan TG, Clissold BB, Ma H, et al. Predicting disability after ischemic stroke based on Comorbidity Index and stroke severity-from the Virtual International Stroke Trials Archive-Acute Collaboration. Front Neurol. 2017;8:192.

[4] Wouters A, Nysten C, Thijs V, et al. Prediction of outcome in patients with acute ischemic stroke based on initial severity and improvement in the first 24 h. Front Neurol. 2018;9:308.

[5] Cheng B, Forkert ND, Zavaglia M, et al. Influence of stroke infarct location on functional outcome measured by the modified Rankin scale. Stroke. 2014;45:1695–1702.

[6] Vogt G, Laage R, Shuaib A, et al. Initial lesion volume is an independent predictor of clinical stroke outcome at day 90: an analysis of the Virtual International Stroke Trials Archive (VISTA) database. Stroke. 2012;43:1266–1272.

[7] Ernst M, Boers AMM, Aigner A, et al. Association of computed tomography ischemic lesion location with functional outcome in acute large vessel occlusion ischemic stroke. Stroke. 2017;48:2426–2433.

[8] Quinn TJ, Taylor-Rowan M, Coyte A, et al. Pre-stroke modified *Rankin Scale: evaluation of validity, prognostic accuracy, and association with treatment. Front Neurol. 2017;8:275.

[9] Ho CH, Jaw FS, Wu CC, et al. The prevalence and the risk factors of testosterone deficiency in newly diagnosed and previously known type 2 diabetic men. J Sex Med. 2015;12:389–397.

[10] Chung TH, Kwon YJ, Lee YJ. High triglyceride to HDL cholesterol ratio is associated with low testosterone and sex hormone-binding globulin levels in Middle-aged and elderly men. *Aging Male*. 2018;1–5. doi:10.1080/13685538.2018.1501015

[11] Loncar G, Bozic B, Neskovic AN, et al. Androgen status in non-diabetic elderly men with heart failure. Aging Male. 2017;20:215–224.

[12] Liao PW, Wu CC, Chen KC, et al. Testosterone threshold for increased cardiovascular risk in middle-aged and elderly men: a locally weighted regression analysis. J Sex Med. 2016;13:1872–1880.

[13] Mohamad NV, Wong SK, Wan Hasan WN, et al. The relationship between circulating testosterone and inflammatory cytokines in men. *Aging Male*. 2018;1–12. doi:10.1080/13685538.2018.1482487

[14] Rezanezhad B, Borgquist R, Willenheimer R, et al. Association between serum levels of testosterone and biomarkers of subclinical atherosclerosis. Aging Male. 2018;21:182–186.

[15] Yeap BB, Hyde Z, Almeida OP, et al. Lower testosterone levels predict incident stroke and transient ischemic attack in older men. J Clin Endocrinol Metab. 2009;94:2353–2359.

[16] Ohlsson C, Barrett-Connor E, Bhasin S, et al. High serum testosterone is associated with reduced risk of cardiovascular events in elderly men. The MrOS (Osteoporotic Fractures in Men) study in Sweden. J Am Coll Cardiol. 2011;58:1674–1681.

[17] Soisson V, Brailly-Tabard S, Helmer C, et al. A J-shaped association between plasma testosterone and risk of ischemic arterial event in elderly men: the French 3C cohort study. Maturitas. 2013;75:282–288.

[18] Holmegard HN, Nordestgaard BG, Jensen GB, et al. Sex hormones and ischemic stroke: a prospective cohort study and meta-analyses. J Clin Endocrinol Metab. 2016;101:69–78.

[19] Jeppesen LL, Jorgensen HS, Nakayama H, et al. Decreased serum testosterone in men with acute ischemic stroke. Arterioscler Thromb Vasc Biol. 1996;16:749–754.

[20] Morgunov LY, Denisova IA, Rozhkova TI, et al. Hypogonadism and its treatment following ischaemic stroke in men with type 2 diabetes mellitus. *Aging Male*. 2018;1–10. doi:10.1080/13685538.2018.1487932

[21] Kulej-Lyko K, Majda J, von Haehling S, et al. Could gonadal and adrenal androgen deficiencies contribute to the depressive symptoms in men with systolic heart failure? Aging Male. 2016;19:221–230.

[22] Persky RW, Liu F, Xu Y, et al. Neonatal testosterone exposure protects adult male rats from stroke. Neuroendocrinology. 2013;97:271–282.

[23] Fanaei H, Karimian SM, Sadeghipour HR, et al. Testosterone enhances functional recovery after stroke through promotion of antioxidant defenses, BDNF levels and neurogenesis in male rats. Brain Res. 2014;1558:74–83.

[24] Groti K, Zuran I, Antonic B, et al. The impact of testosterone replacement therapy on glycemic control, vascular function, and components of the metabolic syndrome in obese hypogonadal men with type 2 diabetes. Aging Male. 2018;21:158–169.

[25] Khripun I, Vorobyev S, Belousov I, et al. Influence of testosterone substitution on glycemic control and endothelial markers in men with newly diagnosed functional hypogonadism and type 2 diabetes mellitus:

a randomized controlled trial. *Aging Male*. 2018:1–9. doi:10.1080/13685538.2018.1506918

[26] Salman M, Yassin DJ, Shoukfeh H, et al. Early weight loss predicts the reduction of obesity in men with erectile dysfunction and hypogonadism undergoing long-term testosterone replacement therapy. Aging Male. 2017;20:45–48.

[27] Yassin A, Nettleship JE, Talib RA, et al. Effects of testosterone replacement therapy withdrawal and re-treatment in hypogonadal elderly men upon obesity, voiding function and prostate safety parameters. Aging Male. 2016;19:64–69.

[28] Morgentaler A, Lunenfeld B. Testosterone and cardiovascular risk: world's experts take unprecedented action to correct misinformation. Aging Male. 2014;17:63–65.

[29] Suzuki S, Brown CM, Wise PM. Neuroprotective effects of estrogens following ischemic stroke. Front Neuroendocrinol. 2009;30:201–211.

[30] Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab. 1999;84:3666–3672.

[31] Powers WJ, Derdeyn CP, Biller J, et al. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2015;46:3020–3035.

[32] Momosaki R, Abo M, Watanabe S, et al. Effects of testosterone levels on functional recovery with rehabilitation in stroke patients. Neurol Med Chir(Tokyo). 2014;54:794–798.

[33] Hatami H, Parizadeh D, Bidhendi Yarandi R, et al. Endogenous testosterone does not improve prediction of incident cardiovascular disease in a community-based cohort of adult men: results from the Tehran Lipid and Glucose Study. *Aging Male*. 2018;1–8. doi:10.1080/13685538.2018.1466876

[34] Corona G, Maseroli E, Rastrelli G, et al. Is late-onset hypogonadotropic hypogonadism a specific age-dependent disease, or merely an epiphenomenon caused by accumulating disease-burden? Minerva Endocrinol. 2016;41:196–210.

[35] LeBlanc ES, Wang PY, Lee CG, et al. Higher testosterone levels are associated with less loss of lean body mass in older men. J Clin Endocrinol Metab. 2011;96:3855–3863.