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Serum levels of follicle-stimulating hormone, luteinizing hormone, and testosterone in patients with ischemic stroke

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Abstract

Objective: Although sex hormones impart many effects on the cardiovascular system, few studies have analyzed the relationship between these hormones and ischemic stroke. We aimed to assess the serum levels of follicular stimulating hormone (FSH), luteinizing hormone (LH), and testosterone (Tn) among patients who had developed ischemic strokes.

Methods: This case-controlled study was conducted at the Rizgary teaching hospital, Erbil, Iraq, from December 1, 2018, to October 31, 2019. Fifty patients, who developed completed ischemic stroke were consecutively enrolled (patients' group). This group was age-matched and gender-matched with another group of 40 healthy individuals, who had no stroke in the past. Serum levels of FSH, LH, and Tn were performed on days 1-4 of hospital admission. In both genders, these values were compared and analyzed.

Results: No statistically significant difference was found among the levels of serum FSH and Tn in both groups and genders (P-value=0.257 and P-value=0.835, respectively). Although there was no statistically significant difference among the levels of serum LH between patients and control groups in males, but there was a statistically significant difference among women (P-value=0.033) in both groups.

Conclusion: Serum LH levels among women who had developed ischemic stroke demonstrated a statistically significant difference when compared to non-stroke, age-matched and gender-matched female individuals in the control group. Whether this difference is clinically significant or not, further analytic studies are required to clarify its effect.

Key words: Ischemic stroke, FSH, LH, testosterone, sex hormones

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Introduction:

The role of endogenous sex hormones in elderly men and women is not yet clear. With aging, serum hormone levels decline in both sexes, with women experiencing a rapid decline after menopause and men having a more gradual decrease with age; male patients are on average younger than females when they got their first stroke.1It is unclear whether lower serum levels of endogenous sex hormones are related to an increased risk of stroke; some hospital-based studies have reported decreased levels of testosterone in men with coronary artery disease and acute ischemic stroke.2Women typically experience lower rates of vascular disease and atherosclerosis-related ischemic stroke than males. This epidemiological advantage is lost by the perimenopausal years, emphasizing that female reproductive hormones play some role in this sex difference.2Epidemiological studies on the role of endogenous sex hormones and ischemic heart disease in men are conflicting. Several case-control studies have shown decreased levels of endogenous testosterone in male survivors of myocardial infarction, whereas, in two prospective studies, testosterone levels in men who subsequently died from cardiovascular disease were normal.2,3

Patients and methods:

This case-controlled study was conducted at the Rizgary teaching hospital, Erbil, Iraq, from December 1, 2018, to October 31, 2019. Fifty patients, who developed completed ischemic stroke were consecutively enrolled (patients' group). This group was age-matched and gender-matched with another group of 40 healthy, who had no stroke in the past. Serum levels of FSH, LH, and Tn were performed on the 1st 4 days of hospital admission. In both genders, these values were compared and analyzed.

Initial workup and inclusion criteria:

Patients should have developed a completed form of ischemic stroke of any type to be included in the patients' group.[4] All patients in the stroke group (n=50) had undergone brain CT scan and/or brain MRI within 24 hours of their presentation. The control group (n=40) underwent elective non-contrast brain CT scan. All patients (n=90) should have no history of hormonal replacement therapy.

Patients and individuals in both groups were assessed and managed by different neurologists and neurology residents. Hypertension was ascertained if the patient had a history of hypertension or systolic blood pressure >140 mmHg or diastolic blood pressure >90 mm Hg. The patient was considered diabetic if he had a history of diabetes or had a random blood glucose level of more than 200 mg/dl or a recent fasting blood glucose level of more than 126 mg/dl on 2 occasions. Dyslipidemia was defined if one or more of the following had been detected: serum total cholesterol >240 mg/dL, serum triglycerides (TG) >200 mg/dl, low-density lipoprotein (LDL) >160 mg/dl, and/or high-density lipoprotein (HDL) <40 mg/dl.[5-7]

Laboratory tests:

All participants (n=90) underwent an extensive battery of investigations: complete blood counts, ESR, blood glucose level, serum lipid profile, urea and

electrolytes, liver function tests, serum TSH, electrocardiography, trans-thoracic echocardiography, and carotid Doppler/Duplex ultrasonography. Serum levels of FSH, LH and Tn were assessed in both groups (n=90). In the patients' group, venous blood samples were obtained between day 0 to 4 of stroke; all samples were obtained between 9-11 AM and stored at 2-8 ^{o}C.

Serum FSH, LH, and Ts were measured by electrochemiluminescence immunoassay analyzer (ECLIA)with "Elecsys and cobas e 411" immunoassay analyzers; the kits were manufactured by Roche Diagnostic GmbH.

The FSH's normal reference range for menopausal women is25.8-134.8 mIU/ml while values for pre-menopausal women were as follows: follicular phase is 3.5-12.5 mIU/ml, ovulation phase is 4.7-21.5 mIU/ml, and luteal phase 1.7-7.7 mIU/ml. For males, the normal reference range is 1.5-12.4 mIU/ml.

The LH's normal reference range for menopausal women is 7.7-58.5 mIU/ml while such values for pre-menopausal women are as follows: follicular phase is 2.3-12.6 mIU/ml, ovulation phase is 14.0-95.6 mIU/ml, and luteal phase is 1.0-11.4 mIU/ml). The normal reference range in males is 1.7-12.4 mIU/ml.

The testosterone's normal reference range in men is 2.8-8.0ng/ml while in women is 0.06-

Statistical Analyses:

The data were analyzed by an independent statistician using Statistical Package for Social Sciences version 19.0. The Chi-square test of association was used to compare proportions. Fisher's exact test was used in the analysis of contingency tables. The Student's t-test was used to compare the means values of the two groups. The Binary logistic regression analysis was used when values were dependent variables in both groups, and factors that were significantly associated (via Chi-square) with stroke were entered as independent variables into the model. A P-value of ≤ 0.05 was considered statistically significant.

Results:

A total of 90 patients were enrolled in the study; 50 in the patients' (stroke) group and 40 in the control group. The mean age is 65.28 (± standard deviation of 10.367 years). In the control group, 25 (out of 50) patients were in the age group of 60-69 years, and 13 patients were above the age of 70 years(table 1).

Table 1: Risk factors for ischemic stroke in the patients' group (n=50).

Risk factors	Patients,n (%)	P-value[§]
Hypertension	30 (60%)	<0.001
Diabetes Mellitus	21 (42%)	0.001
Dyslipidemia	14 (28 %)	<0.001
Smoking	5 (10%)	1.0 *
Previous stroke	5 (10%)	0.063 *
IHD	6 (12%)	0.032 *
Atrial Fibrillation	3 (6.1%)	0.249 *

*UsingFisher's exact test.
[§]P-value ≤0.05 is statistically significant

Women comprised most of the patients, in terms of gender, and dominated both groups. Sixty-seven females were involved in this study; 39 in the patients' group and 28 in the control group. One woman only in the patients' group was pre-menopausal; she was in the follicular phase of her menstrual cycle. Three women were pre-menopausal in the control group (2 were in their follicular phase while the other was in her luteal phase of the cycle).There was no statistical difference in terms of menopause among both groups (P-value=0.30). A total of 23 men were enrolled; 11 in the patients' group and 12 in the control group. The normal reference range of FSH, LH, and Tnwas measured according to age and gender and in women according to the phase of the menstrual cycle.

Hypertension was the commonest risk factor for stroke; hypertension was present in 60% of stroke patients while it was found in 5% of the control group (P-value <0.001).Diabetes mellitus ranked 2nd and was detected in 42 % of stroke patients and 10 % of the control group (P-value=0.001) (Table 2). Table 5 shows the values of FSH, LH, and Tn in all patients (n=90).

Serum FSH:

Table 2: Descriptive statistics of the ages of the patients and the control group combined (n=90).

Variables	Age	Testosterone*	FSH*	LH*
Mean	61.36	0.93381	34.64462	17.36743
Median	62.00	0.28000	29.00000	13.46000
Standard Deviation	10.884	1.397589	32.271505	15.808488
Minimum	25	0.040	2.090	1.220
Maximum	99	5.660	144.320	69.440

*See text for the normal reference ranges in both genders.

Overall, in the patients' group, 18 % of the patients show low (below normal) serum FSH levels while 12.5 % of the control group has low values (P-value=0.257). Seventy-six percent of the patients' group and 87.5% of the control group demonstrate normal serum FSH levels. Only 6 % of the patients' group show high (above normal) values of serum FSH; none of the individuals in the control group have high levels (table 3). No statistical difference was found when both groups were compared (P-value=0.257).

Table 3: Comparison of serum FSH levels between the patients (n=50) and the control group (n=40)

FSH		Patients n (%)	Control n (%)	Total	P-value *
FSH'sserum level	Low	9	5	14	0.257
		18.0%	12.5%	15.6%	
	Normal	38	35	73	
		76.0%	87.5%	81.1%	
	High	3	0	3	
		6.0%	0%	3.3%	
Total		50	40	90	
		100.0%	100.0%	100.0%	

* Using Fisher's exact test. P-value ≤0.05 is statistically significant.

Women: In the patients' group, 23.1 % had low (below normal) levels of serum FSH, 71.8 % had normal levels, and 5.1% demonstrated high (above normal) levels of FSH. In the control group, 17.9% had low (below normal) levels of FSH, 82.1% show normal FSH, and none of them demonstrated low (below normal) levels of FSH (P-value=0.606) (Table 4).

Table 4: Comparison of serum FSH levels between the patients and the control group in women.

FSH		Patients n (%)	Control n (%)	Total	P-value *
FSH's serum level	Low	9	5	14	0.606
		23.1%	17.9%	20.9%	
	Normal	28	23	51	
		71.8%	82.1%	76.1%	
	High	2	0	2	
		5.1%	0%	3.0%	
Total		39	28	67	
		100.0%	100.0%	100.0%	

* UsingFisher's exact test. P-value ≤0.05 is statistically significant.

Men: In men, 90.9 % of the patients 'group show normal serum levels of FSH while 9.1% show high (above normal) FSH levels. All individuals in the control group 100 % demonstrated normal levels (P-value=0.478) (Table 5). No statistical difference was found between both groups.

Serum LH:

Table 5: Comparison of serum FSH levels between the patients and the control group in men.

FSH		Patients n (%)	Control n (%)	Total	P-value*
FSH's serum level	Normal	10	12	22	0.478
		90.9%	100.0%	95.7%	
	High	1	0	1	
		9.1%	0%	4.3%	
Total		11	12	23	
		100.0%	100.0%	100.0%	

* UsingFisher's exact test. P-value ≤0.05 is statistically significant.

A difference in serum LH levels between the patients 'group and the control group was found. In patients' group, 16% showed a low level of LH (5% of the control group had sub-normal levels) and 74% of the patients' group had normal levels of LH (95 % of the control group had normal serum values). Only 10 % of patients' group demonstrated elevated levels of LH (zero percent in the control group had high values) (table 6).

Table 6: Comparison of serum LH levels between the patients (n=50) and the control group (n=40).

LH		patients n (%)	Control n (%)	Total	P-value*
LH's serum level	Low	8	2	10	0.017
		16.0%	5.0%	11.1%	
	Normal	37	38	75	
		74.0%	95.0%	83.3%	
	High	5	0	5	
		10.0%	0%	5.6%	
Total		50	40	90	
		100.0%	100.0%	100.0%	

* Using Fisher's exact test. P-value ≤0.05 is statistically significant.

In women,20.5% of the patients' group showed low levels (7.1% of the control group had low values) and 66.7% of the patients 'group showed normal levels of LH (92.9% of the control group had normal levels). About 12.8 % of the patients' group showed low levels of LH (none of the individuals in the control group had low levels)(P-value=0.033) (Table 7).

Table 7:Comparison of serum LH levels between the patients and the control group in women.

LH		Patients n (%)	Control n (%)	Total	P-value*
LH's serum level	Low	8	2	10	0.033
		20.5%	7.1%	14.9%	
	Normal	26	26	52	
		66.7%	92.9%	77.6%	
	High	5	0	5	
		12.8%	0%	7.5%	
Total		39	28	67	
		100.0%	100.0%	100.0%	

*P-value ≤0.05 is statistically significant.

In men, all patients and controls showed normal levels of serum LH; there was no difference between 2 groups (table 8).

Table 8: comparison of serum LH levels between the patients and the control group in men.

LH		patients n (%)	Control n (%)	Total	P-value
LH's serum level	Normal	11	12	23	NA*
		100.0%	100.0%	100.0%	
Total		11	12	23	
		100.0%	100.0%	100.0%	

*NA, not applicable.

Testosterone:

There was no statistical difference in the level of testosterone between the two groups. In the patients' group, 14% had low levels of serum testosterone (12.5% of the control group had low levels) and 86% of the patients' group and 87% of the control groups demonstrated normal levels (P-value=0.835) (Table 9)

Table 9: Comparison of serum testosterone levels between patients (n=50) and the control group (n=40).

Testosterone		Patients n (%)	Control n (%)	Total	P-value*
Testosterone's serum level	Low	7	5	12	0.835
		14.0%	12.5%	13.3%	
	Normal	43	35	78	
		86.0%	87.5%	86.7%	
Total		50	40	90	
		100.0%	100.0%	100.0%	

*P-value ≤0.05 is statistically significant.

In men, we found no statistical differences between both groups. About 36% of the patients' group and 41.1% of the control group showed low levels of testosterone. Around 63.6% of the patients' group and 58.3% of the control group showed normal levels (P-value=1.0)(Table (10).

Table 10:Comparison of serum testosterone levels between the patients and the control group in men.

		Patients n (%)	Control n (%)	Total	P-value *
Testosterone's serum level	Low	4	5	9	1
		36.4%	41.7%	39.1%	
	Normal	7	7	14	
		63.6%	58.3%	60.9%	
Total		11	12	23	
		100.0%	100.0%	100.0%	

*By Fisher's Exact Test. P-value ≤0.05 is statistically significant.

In females, 7.7% of the patients' group showed a low level of testosterone while 92.3% showed a normal level. All individuals (100%) in the control group showed normal levels of serum testosterone (P-value=0.25) (Table 11).

Table11: Comparison of serum testosterone levels between the patients and the control group in women.

Testosterone		**Patients n (%)**	**Control n (%)**	Total	P-value*
Testosterone's serum level	Low	3	0	3	0.25916
		7.7%	0%	4.5%	
	Normal	36	28	64	
		92.3%	100.0%	95.5%	
Total		39	28	67	
		100.0%	100.0%	100.0%	

* P-value ≤0.05 is statistically significant.

Discussion:

Follicle-stimulating hormone (FSH) is a glycoprotein gonadotropin secreted by the anterior pituitary in response to gonadotropin-releasing hormone (GnRH), which is released by the hypothalamus, the same pituitary cell also secretes luteinizing hormone (LH). FSH and LH are composed of alpha and beta subunits, the specific beta subunit confers the unique biologic activity, FSH and LH bind to receptors in the testis and ovary and regulate gonadal function by promoting sex steroid production and gametogenesis.[8,9]

FSH binds with receptors in the Sertoli cells and stimulates spermatogenesis. LH stimulates the production of testosterone in Leydig cells, which in turn may act on the Sertoli and peritubular cells of the seminiferous tubules and stimulates spermatogenesis. The gonadotropins (LH and FSH) are pulsatile-released from the anterior pituitary gland and acts via the hypothalamo-hypophysio-gonadal axis which stimulates gonadal endocrine function and gametogenesis in males. This activity leads to proper spermatogenesis and male sexual responses. Suppression of this axis leads to a reduction of sperm count, semen quality, impairment of erection, and finally infertility.[8,9]

In males, the testis sub-serves two principal functions: synthesis of testosterone by the interstitial Leydig cells under the control of luteinizing hormone (LH), and spermatogenesis by Sertoli cells under the control of follicle-stimulating hormone (FSH) (but also requiring adequate testosterone). Negative feedback suppression of LH is mediated principally by testosterone, while secretion of another hormone by the testis, inhibin, suppresses FSH. The axis can be assessed easily by a random blood sample for testosterone, LH and FSH. Testosterone is largely bound in plasma to sex hormone-binding globulin, and this can also be measured to calculate the "free androgen index" or the "bioavailable" testosterone. There is no equivalent of the menopause in men, although testosterone concentrations decline slowly from the fourth decade onwards.[10,11]

In females, the physiology is complicated by variations in function during the normal menstrual cycle. FSH produces growth and development of ovarian follicles during the first 14 days after the menses. This leads to a gradual increase in estradiol production from granulosa cells, which initially suppresses FSH secretion (negative feedback) but then, above a certain level, stimulates an increase in both the frequency and amplitude of gonadotrophin-releasing hormone (GnRH) pulses, resulting in a marked increase in LH secretion (positive feedback). The mid-cycle "surge" of LH induces ovulation. After the release of the ovum, the follicle differentiates into a corpus luteum which secretes progesterone. Withdrawal of progesterone results in menstrual bleeding. Circulating levels of estrogen and progesterone in pre-menopausal women are, therefore, critically dependent on the time of the cycle. The most useful 'test' of ovarian function is a careful menstrual history. Besides, ovulation can be confirmed by measuring plasma progesterone levels during the luteal phase ("Day 21 progesterone") or by tracking changes in estrogen and progesterone metabolites in urine specimens collected at weekly intervals. The cessation of menstruation (the menopause) occurs, in most developed countries, at a median age of 50.8 years. In the 5 years before there is a gradual increase in the number of anovulatory cycles; this is referred to as the climacteric. Estrogen and inhibin secretion fall and negative feedback results in the increased pituitary secretion of LH and FSH (typically to levels > 30 U/l).[12,13]

Many studies had been done to assess the relationship between the level of endogenous sex hormones and ischemic stroke. In both genders, the most common risk factor of ischemic stroke was hypertension, which was present in 60% of patients (P-value<0.001).Our finding is consistent with that of O'Donnell and colleagues. There were no differences in the mean age of stroke onset between men and women; the mean age of men was 65.6 years, while in women it was 65.1 years. These results indicate that our stroke patients are somewhat younger than those of Appelros colleagues, which showed that the mean age of men was 68.6 years and 72.9 years for women.[15]

In men, FSH levels revealed a slight difference between both groups. LH was normal in all men included in this study in both patients and the control group, and the study shows no difference between the two groups. The comparison of testosterone values in men of both groups shows no significant differences (P-value=1.0).This result is inconsistent with that of English and coworkers, who suggested that low concentrations of testosterone are associated with an increased risk of cardiovascular diseases in men.[16]We found no significant differences in the levels of FSH, LH, and testosterone between both groups.[17-20]

In women, a comparison of serum FSH levels between patients and controls showed no statistically significant difference (P-value=0.606).LH levels demonstrate an obvious difference between patients and controls and were statistically significant; 20.5% of patients showed elevated levels of LH and 12.8% of them showed sub-normal values (P-value=0.033).The results of testosterone comparison in both groups showed no significant difference (P-value=0.259).

In conclusion, comparing the results of serum FSH, LH (in males), and Tn among patients and their healthy counterparts demonstrated no statistically significant differences. However, LH levels in women showed a statistically significant

difference between the two groups (P-value=0.033).

Limitations:

1.The number of participants in both groups was relatively small.

2. There was a limited number of sex hormones assessment in our hospital per day. Also, free fractions of the sex hormones were not available in our hospital.

3. The targeted population was Kurdish ad all of them were residents of Erbil Governorate; no Arabs or other races were from the same or other governorates were enrolled.

Therefore, the results would have been different if the number of patients was larger, the sex hormones assessment was more available, and if other races/governorates were involved in the study.

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