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Relation Between Levels of Fibroblast Growth Factor 23 and the Risk of Ischemic Stroke

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Abstract

Background: **Fibroblast growth factor 23 (FGF23) is a hormone secreted by osteocytes that regulates the homeostasis of phosphates by inducing phosphaturia and inhibiting the development of calcitriol. Elevated FGF23 is linked with cardiovascular events and mortality. The role of FGF23 as a risk factor for ischemic stroke is unclear.** ***Aim:*** **The study aimed to evaluate the levels of FGF23 and the risk of ischemic stroke.** ***Subjects and Methods:*** **This case-control study included 44 adult ischemic stroke patients and 44 healthy controls. The levels of FGF23 were estimated using the Enzyme-Linked Immune Sorbent Assay (ELISA) method.** ***Results:*** **FGF23 levels were significantly higher in ischemic stroke patients compared to the control group. Receiver operating characteristics (ROC) curve analysis showed high sensitivity (84.1%) and specificity (95.5%) in detecting ischemic stroke. Analysis of variance (ANOVA) test displayed a statistically significant relation between levels of FGF23 and the severity of stroke according to the National Institutes of Health Stroke Scale (NIHSS). There were no significant relations between FGF23 levels and carotid artery stenosis or the lesion location on magnetic resonance imaging (MRI) according to Oxford classification of stroke.** ***Conclusion:*** **FGF23 levels were significantly higher among ischemic stroke patients.**

Keywords: Cerebrovascular events, sensitivity, specificity, carotid artery stenosis

Introduction

Stroke is a medical emergency. The incidence is steeply increasing with age and in many countries with lower and middle incomes. It is increasing in combination with fewer healthy lifestyles. Stroke is the most severe clinical type of cerebrovascular disease, more than 99% of which is caused by arterial involvement and less than 1% by venous involvement in the form of cerebral venous thrombosis, leading to episodes of brain dysfunction, 85% of arterial causes are caused by infarction and 15% by hemorrhage(1). Fibroblast growth factor 23 (FGF23) is a bone-derived hormone which regulates homeostasis of vitamin D and phosphorus. Higher levels of FGF23 were associated with higher prevalence of cardiovascular and kidney disease independent of typical risk factors(2). Elevated FGF23 was associated with a higher risk of cardio-

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vascular mortality and combined stroke-including vascular outcomes but few studies investigated the stroke separately[3,4]. Those with elevated FGF23 had an increased risk of stroke in people with established heart disease. Still, results from population-based studies that include people without proven heart disease or chronic kidney disease are minimal and conflicted[5]. This study was conducted to assess the relationship between FGF23 levels and ischemic stroke risk and the possibility of using it as a screening test for stroke in high-risk populations to implement preventive measures.

Subjects and Methods

This case-control study was carried out in the Department of Neuropsychiatry, Suez Canal University Hospital, Ismailia, Egypt. Forty-four adult patients aged ≥ 18 of both sexes were included. Patients were diagnosed with ischemic stroke by clinical diagnosis by history and detailed neurological examination and radiographic diagnosis by computed tomography (CT) scanning and magnetic resonance imaging (MRI)[6]. Patients with significant cardiac, hepatic, renal, endocrinological, malignant, traumatic, surgical, chronic inflammatory disorders, fever or infectious conditions, and pregnancy were excluded. Another 44 age and sex-healthy subjects were included as a control group attending Suez Canal University Hospital for blood donation. The ethical committee of the Faculty of Medicine, Suez Canal University accepted the study. Before inclusion in this study, written, informed consent was obtained from all the participants. All the subjects were subjected to clinical evaluation including detailed history taking, comprehensive general and neurological examination, and assessment of the severity of ischemic stroke by using the National Institutes of Health Stroke Scale (NIHSS) score[7]. Neuroimaging: CT brain (Siemens, Balance Somatom, single-slice instrument, Germany) and MRI brain (Achieva, Philips Medical Systems, The Netherlands) were used to assess whether the acute stroke was consistent with a demonstrable lesion. We assessed the site of the lesion according to The Oxford Stroke Classification which classifies stroke based on the initial symptoms[8]. Carotid artery stenosis was studied by high-resolution B-mode ultrasonography using (Philips HD11) device with a linear probe (7 MHZ). The degree of stenosis was measured as the percentage of the difference between the original vessel lumen diameter/area, and the residual lumen diameter/area at the maximum stenosis site, based on the European Carotid Surgery Trial criteria[9]. An assay of FGF23 levels was performed using kits based on the standard sandwich enzyme-linked immune sorbent assay (ELISA) method. The purified anti-FGF23 antibodies were precoated on a 96-well plate, and the anti-FGF23 antibody conjugated by the horse radish peroxidase was used as antibodies for detection[10].

Statistical Analysis

Data were analyzed using IBM Statistical Package of Social Sciences (SPSS) software version 20.0**.** **(**Armonk, NY, IBM Corp**)**[11]. Qualitative data were described using numbers and percentages. Quantitative data were described using median, range, mean, and standard deviation (SD). Man-Whitney U and analysis of variance test were used to examine the significance between variables. A *P*-value of 0.05 was considered significant.

Results

This study included 44 ischemic stroke patients with a mean age of 57.1±10.4 years,

23 males (52.3%) and 21 females (47.7%). The FGF23 levels in patients (median 40.0; range 21.0-240.0 pg/ml) were higher than in controls (median 18.0; range 10.0-31.0 pg/ml) and the difference was statistically highly significant (p<0.001) (Table 1).

Table 1. Fibroblast growth factor 23 levels (pg/ml) among the studied groups

	Patients (n=44)	**Controls** (n=44)	Sig. test	*p*-value
Range	21.0-240.0	10.0-31.0	52.50	<0.0001*
Median	40.0	18.0		

**Significant at p-value ≤ .05, Mann-Whitney U test was used.*

Table 2. Relation between the fibroblast growth factor 23 and the different risk factors for ischemic stroke among the patients (n=44)

Variables	**n**	**Fibroblast growth factor 23**		**Sig. test**	**p**
		Range	**Median**		
Ischemic heart disease					
No	38	21.0-240.0	40.0	77.0	0.203
Yes	6	39.0-130.0	45.50		
Recurrent stroke					
No	31	21.0-160.0	40.0	154.50	0.224
Yes	13	24.0-240.0	44.0		
Carotid stenosis					
Significant	11	21.0-49.0	40.0	150.0	0.391
Insignificant	33	21.0-240.0	40.0		
Smoking					
No	33	21.0-160.0	40.0	158.50	0.531
Yes	11	25.0-240.0	40.0		
Hypertension					
No	16	21.0-74.0	40.0	192.0	0.433
Yes	28	21.0-240.0	41.0		

**Significant at p ≤ 0.05, Mann-Whitney U test was used.*

There was a non-statistically significant difference between the FGF23 levels and patient history of ischemic heart disease, recurrent stroke, degree of carotid artery stenosis, smoking, or hypertension (p = 0.203, 0.224, 0.391, 0.531, and 0.433, respectively) (Table 2). Moreover, there were non-statistically significant differences between FGF23 levels either with the stroke severity based on NIHSS or the location of the MRI lesion according to the Oxford classification of stroke (Tables 3 and 4). The Receiver Operating Characteristics (ROC) indicated a significantly high area under the curve (0.973, p <0.001). The sensitivity and specificity at a cut-off point > 24 pg/ml of FGF23 levels were 84.09% and 95.45%, respectively (Table 5).

Discussion

According to our results, FGF23 levels were higher in ischemic stroke patients when compared to the control group with a highly significant statistical difference. This was in accordance with Wright and his colleagues[3] who confirmed that the levels of FGF23 were higher in patients with ischemic stroke. Only a few studies were carried out to assess the

relationship between FGF23 levels and risk of ischemic stroke. Wright and co-authors, 2014[3], showed that elevated FGF23 was a risk factor for ischemic stroke independent of chronic kidney disease, and Panwar and his colleagues (2015)[12] showed that higher levels of FGF23 were associated with increased risk of ischemic stroke. In the current study, there was a non-significant statistical difference in the relationship between ischemic heart disease and FGF23 levels, which agrees with Taylor and his colleagues[13] who reported no association between FGF23 and ischemic heart disease risk.

Table 3. Relation between fibroblast growth factor 23 and the severity of stroke among the patients (n=44)

Severity of stroke (NIHSS)	n	Fibroblast growth factor 23		Sig. test	p
		Range	Median		
Minor	13	21.0-75.0	40.0	3.240	0.356
Moderate	12	24.0-160.0	48.0		
Moderate to severe	11	21.0-74.0	40.0		
Severe	8	21.0-240.0	44.0		

*NIHSS: National Institutes of Health Stroke Scale, *Significant at p ≤ 0.05, Analysis of variance (ANOVA) test was used.*

Table 4. Comparison between fibroblast growth factor 23 levels and the site of the lesion in brain imaging

Site of stroke	n	Fibroblast growth factor 23		Sig. test	p
		Range	Median		
Total anterior circulation	6	40-49	42.5	3.240	0.356
Partial anterior circulation	23	21-240	40.0		
Lacunars stroke	3	40-73	40.0		
Posterior circulation	12	21-49	42.0		

**Significant at p ≤ 0.05, Analysis of variance (ANOVA) test was used.*

In addition, there was a non-significant statistical difference in the relationship between smoking and FGF23 levels. This finding disagrees with Panwar and his colleagues[12] who reported that FGF23 has a significant statistical difference in the relationship between smoking and FGF23 levels. Our results showed that there was a non-significant statistical difference between hypertension and FGF23; which was consistent with the results of Panwar and his colleagues[12]. There was a non-significant statistical difference between significant carotid stenosis and level of FGF23 in the patients' group that disagreed with Shah and his colleagues (2015)[14] who reported that there was a significant statistical difference between significant carotid artery stenosis and levels of FGF23.

Table 5. Receiver Operating Characteristics (ROC) for fibroblast growth factor 23 levels to predict the patients versus the controls.

	Cutoff	Sensitivity	Specificity	PPV	NPV
Fibroblast growth factor 23	>24 pg/ml	84.09%	95.45%	94.9%	85.7%

PPV: positive predictive value, NPV: negative predictive value.

When the ROC curve was constructed in the current study, it was found that the area under the curve was 0.973%. The sensitivity and specificity are 84.09% and 95.45% at a cut-off point >24 pg/ml of FGF23 level. In another study, the ROC curve for the relation between FGF23 level and risk of ischemic stroke[9], a cut-off value of 90 pg/ml with a sensitivity of 72% and a specificity was 90% with a *p*-value of 0.006 was set.

Conclusion

This study concluded that there is an association between higher risk of ischemic stroke in patients with elevated FGF23.

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