Higher Serum Fibroblast Growth Factor-23 Levels and the Risk of Stroke and Its Subtypes: Evidence From a Meta-Analysis of Prospective Studies

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Background: Epidemiologic studies have indicated conflicting associations of fibroblast growth factor-23 (FGF23) with the risk of stroke. To this end, a meta-analysis of prospective studies was conducted to assess the association. *Methods:* Relevant studies were identified by searching PubMed and Embase databases to March 23, 2018. Relative risks (RRs) with 95% confidence intervals (CIs) were combined with the fixed-effects model or random-effects model according to the degree of heterogeneity. Moreover, stratified analyses and sensitivity analysis were carried out for further analysis. *Results:* Seven prospective studies involving 1988 stroke events among 18048 participants were eligible for our meta-analysis. The combined RRs for total stroke were 1.29 (95% CI: 1.10, 1.52) for the highest versus lowest category of FGF23, with low heterogeneity among studies ($P_{heterogeneity} = 0.38$, $I^2 = 6.1\%$). Stratified analyses showed that the combined RRs for ischemic stroke (IS) and hemorrhagic stroke (HS) risk were 1.12 (95% CI: 0.92, 1.37) and 2.63 (95% CI: 1.61, 4.30), respectively. In the stratification by geographic areas, the association between higher FGF23 and stroke was similar with studies performed in the United States (RR = 1.24, 95%CI: 1.03, 1.49) and Europe (RR = 1.88, 95%CI: 0.77, 4.55); however, only the results in the United States were statistically significant. Sensitivity analysis indicated the combined results were robust. *Conclusions:* Our meta-analysis showed that higher FGF23 levels were associated with an increased risk of stroke. The positive association consistently existed in HS rather than in IS. Further studies are required to confirm these causal associations and to investigate the mechanisms.
Key Words: Fibroblast growth factor-23—stroke—ischemic stroke—hemorrhagic stroke—meta-analysis

Introduction

Fibroblast growth factor-23 (FGF23), a bone-secreted hormone, has been reported to increase urinary phosphate excretion while inhibit vitamin D activation occurring in the renal proximal tubule.[1] Apart from correlation with chronic kidney disease (CKD),[1] elevated FGF23 has also been associated with a higher risk of cardiovascular disease (CVD) incidence and mortality.[2,3] Besides, biological evidence has implicated the connection between elevated FGF23 and CVD. For example, laboratory data indicated that serum FGF23 levels were elevated in experimental myocardial infarction (MI) models.[4] Moreover, FGF23 was also observed to directly induce cardiac hypertrophy in experimental models.[5]

Stroke is the second leading cause of death globally, and the most common cause of disability in adults.[6] Therefore, preventing stroke should be a vital public health priority in the present society.[7] In spite of several well-established traditional risk factors for stroke, inducing age, smoking, hypertension, atrial fibrillation, it is still

important to further explore novel risk factors for stroke. In recent years, a probable association has been proposed between elevated FGF23 and stroke risk in some original observational studies[8-14]; however, the magnitude of the findings and conclusions are inconsistent.

Recently, Xiao[2] and Jiang[3] reported that higher serum FGF23 concentrations were associated with an increased risk of stroke in meta-analyses. However, both included studies were incomplete. Furthermore, stroke outcomes were merely considered as secondary endpoints, and there were no stratified analyses referring to study or population characteristics and stroke subtypes. Notably, emerging data indicated the difference between the associations of FGF23 and stroke subtypes [ischemic stroke (IS) and hemorrhagic stroke (HS)].[8,9,11] In consideration of the different pathophysiology progress of IS and HS,[15] it is of great significance to investigate the subtype differences in the FGF23−stroke associations. In order to fill these gaps, we systematically and comprehensively evaluated the association between FGF23 and the occurrence of first stroke by performing an updated meta-analysis of prospective studies.

Materials and Methods

Literature Search and Study Selection

This study was conducted in accordance with the guidelines of the "Meta-Analysis of Observational Studies in Epidemiology Group." [16] We conducted a systematic search of PubMed, Embase databases for relevant prospective studies with the final update on March 23, 2018. The following MeSH terms or key words were used in our search strategy: ((((Fibroblast Growth Factor-23) OR FGF23)) AND (((((cerebrovascular disease) OR stroke) OR intracerebral hemorrhage) OR subarachnoid hemorrhage)) AND ((((((prospective) OR cohort) OR nested) OR follow-up) OR longitudinal) OR duration). Additionally, the bibliographies of retrieved articles were also manually scrutinized to identify any further studies. Of note, there was no language restriction in this study.

Study Selection

The studies were considered if they met the following criteria: (1) the study was of prospective design; (2) the exposure of interest was serum FGF23; (3) the outcome of interest was stroke incidence or mortality; and the adjusted relative risk (RR) or hazard ratio (HR) with 95% confidence intervals (CIs) was provided; (4) the adjusted RR or HR with corresponding 95%CI was for at least two categories of FGF23. In the case of multiple publications reported from the same study population, the most recent one with the largest events were selected in this meta-analysis.

Data Extraction and Quality Assessment

The following data were extracted from each eligible study using a standardized data collection form: the last name of first author, publication year, study design, study location; duration time, study population, the number of stroke patients and participants, methods for FGF23 measurement, categorized FGF23 concentrations with maximally adjusted risk estimates of stroke and corresponding 95%CI, and the covariate cofounders controlled for in the statistical analysis.

The quality of prospective studies was assessed using the Newcastle−Ottawa Scale (NOS).[17] A quality score was calculated on the basis of three major components of included studies: 0-4 stars for the selection of the study groups, 0-2 stars for the comparability, and 0-3 stars for the ascertainment of the outcome. A higher score indicated a better methodological quality. Literature search, study selection, data extraction, and quality assessment were performed independently by two authors (X.-Y.Y. and Z.-Y.W.). And any disagreement was resolved by consensus.

Statistical Analysis

The RRs were commonly used to measure the relationship between FGF23 and stroke incidence. The ORs and HRs were considered as approximations of RRs. For one study,[14] it separately presented stroke risk estimates among participants with or without CKD; therefore, the results were pooled by using a fixed-effects model, which
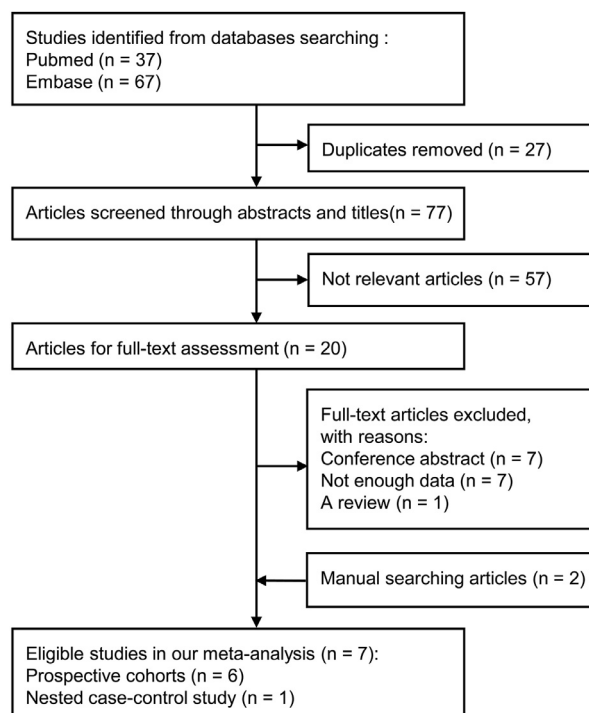

Figure 1. *Flow diagram of the searching process.*