INTRODUCTION

Intracerebral hemorrhage (ICH), which accounts for 10%–15% of all stroke cases, has poor prognosis and limited treatment options [1]. Very few circulating biomarkers are known to be associated with the risk of ICH.

The osteogenic hormone fibroblast growth factor 23 (FGF23) is an important regulator of phosphate and calcium homeostasis [2]. It directly suppresses phosphate reabsorption in the kidney and lowers levels of vitamin D and parathyroid hormone (PTH). In turn, FGF23 synthesis is stimulated by high levels of serum phosphate, vitamin D, PTH and calcium [2]. Fibroblast growth factor 23 is primarily known as a marker of chronic kidney disease [2]. However, FGF23 is also an emerging risk factor for different cardiovascular diseases in the general population. Studies have found FGF23 to be associated with left ventricular
cardiac hypertrophy, incident coronary heart disease and major adverse cardiovascular events (a composite of myocardial infarction, stroke and all-cause mortality) [3–5].

A meta-analysis from 2018 concluded that FGF23 is associated with incident all-cause stroke [6]. FGF23 levels were significantly associated with hemorrhagic but not ischaemic stroke [6]. Di Giuseppe et al. found that FGF23 was associated with hemorrhagic stroke, defined as a joint outcome of ICH and subarachnoid hemorrhage [7], but there was no significant association between FGF23 and hemorrhagic stroke in a study by Panwar et al. [8]. A previous study from the Malmö Diet and Cancer Study (MDCS) found that FGF23 was associated with subarachnoid hemorrhage [9]. In another study, including 26 ICH cases, Wright et al. found a significant association between FGF23 and incident ICH [10]. Hence, although FGF23 has been associated with stroke in previous studies, the relationships with subtypes of hemorrhagic stroke still need to be clarified.

The purpose of the present study was to examine the relationship between baseline plasma levels of FGF23 and incident ICH, including subgroup analyses of ICH with different locations and outcomes.

MATERIALS AND METHODS

Study population and baseline examination

Between 1991 and 1996, all men aged 46–73 years and all women aged 45–73 years residing in the city of Malmö, Sweden, were invited to participate in the Malmö Diet and Cancer Study (MDCS), a population-based cohort study intended to investigate the association between diet and health outcomes [11]. In total, 28,449 individuals participated, corresponding to 41% of the eligible population. The baseline examination consisted of a self-administered questionnaire, blood samples and a physical examination performed by a nurse. Blood pressure was measured using a mercury-column sphygmomanometer in the supine position after 10 min of rest. Plasma was separated and frozen to −80°C within 1 h. Apolipoproteins A1 and B were measured using an immunonephelometric assay.

Current smoking was defined as regular or occasional smoking. The cut-off for high alcohol intake was >40 g/day for men and >30 g/day for women. Subjects who had self-reported diabetes mellitus, used anti-diabetic drugs or had been diagnosed with diabetes in national or local patient registers were classified as diabetic.

Incidence of ICH

MDCS subjects were followed until first ICH, death, emigration or end of follow-up in December 2010. To identify incident cases of ICH in the MDCS, linkage with the local stroke register of Malmö and the Swedish Hospital Discharge Register and Causes of Death Register (International Classification of Diseases 9th edition code 431 and 10th edition I61.0–9) was used [11]. The ICH diagnosis was validated by review of hospital records and confirmed when computed tomography, magnetic resonance imaging or autopsy showed parenchymal hemorrhage, and secondary causes such as trauma, arterio-venous malformation, hemorrhagic infarction, intravenous thrombolysis or tumor were not present based on available workup. The ICH cases were also classified by location as lobar (cortical or subcortical white matter) or non-lobar (basal ganglia, internal capsule, periventricular white matter, brain stem or cerebellum) by a neuroradiologist. Four ICH cases that occurred outside of Malmö could not be validated in medical records but were still included in the analyses.

The hemorrhage volume was measured using the formula ABC/2 [12]. Data on self-assessed functional outcome 3 months after ICH were retrieved from the Swedish Stroke Register (Riksstroke), and translated into the modified Rankin Scale (mRS), as described previously [13]. The mRS is a seven-step assessment tool used to grade global disability after stroke, where 0 indicates no symptoms, 3 corresponds to moderate disability and 6 is the score for fatal cases [14].

Cases and controls

Cases were defined as subjects with first ever ICH after the baseline examination. Up to December 2010, 246 ICH cases were identified. Subjects with missing plasma samples or laboratory errors (n = 25) or missing information about blood pressure (n = 1) were excluded, leaving 220 cases (82 lobar, 101 non-lobar, 37 with undefined location); 244 controls were randomly selected from the MDCS, matched to cases based on sex, 5-year age group and follow-up time (incidence density sampling method).

Fibroblast growth factor 23

Plasma from cases and controls was aliquoted to 96-well plates before analysis of FGF23 in 2015. Plasma levels of FGF23 were analyzed using the Proseek Multiplex CVD I assay, with polyclonal antibodies that recognize both intact and C-terminal FGF23. The concentrations were expressed in arbitrary units on the log2 scale [15]. The intra-assay and inter-assay coefficients of variation were 9% and 21%, respectively. FGF23 showed a positively skewed distribution. Therefore, levels are presented as median and interquartile range, and log-transformed values were used in all statistical analyses.

Statistical analyses

Differences in baseline characteristics between ICH cases and controls were evaluated using Student’s t test and the chi-squared test. Distributions of baseline characteristics by quartiles of FGF23 were studied with trend tests (using the Stata command nptrend, an extension of the Wilcoxon rank-sum test, for continuous variables, and the Mantel–Haenszel test for categorical variables).
Conditional logistic regression, stratified on the 96-well plate to account for any differences between batches, was used to analyze the association of FGF23 with ICH. FGF23 was analyzed on the log₂ scale, and the odds ratios therefore represent the increased odds per doubled concentration of FGF23. All analyses were adjusted for age and sex. A second model also included systolic blood pressure, use of blood pressure lowering drugs, use of oral anticoagulants, smoking, high alcohol intake, body mass index, diabetes mellitus, living alone and levels of apolipoprotein B.

Two methods were used to adjust for the potential confounding effect of impaired renal function. First, a sensitivity analysis was performed after exclusion of all individuals with an inpatient or outpatient hospital diagnosis of chronic kidney disease (International Classification of Diseases 9th edition codes 585, 586 or International Classification of Diseases 10th edition codes N18, N19) any time before the baseline examination or during the follow-up period. Secondly, a multiple imputation of estimated glomerular filtration rate (eGFR) values was performed and eGFR was included in the multivariable-adjusted regression models. The imputation was based on 5061 eGFR values (combined creatinine and cystatin C formula) [16] from the MDCS-Cardiovascular sub-cohort that was randomly selected amongst individuals examined between 1991 and 1994. The imputation model was based on all variables used in the analyses of the association of FGF23 with incident ICH, the outcome variable itself (incident ICH) and other variables that could correlate with kidney function (height, waist circumference, hemoglobin and white blood cell count). Twenty imputed datasets were created assuming missingness at random [17].

Subgroup analyses of the association of FGF23 with lobar and non-lobar ICH, as well as ICH with large volume (>40 ml, defined a priori), poor functional outcome (mRS 3–6) and fatal outcome within 28 days were performed. Missing data were handled using listwise deletion.

*p values <0.05 were considered statistically significant. Stata version 12.0 was used for statistical analyses.

RESULTS

Baseline characteristics of ICH cases and controls are presented in Table 1. ICH cases had higher blood pressure and higher levels of FGF23, and were more likely to smoke, use warfarin and have high alcohol intake. Table 2 shows baseline characteristics by quartiles of FGF23. Subjects in the higher quartiles were older, more likely to use blood pressure lowering drugs, and had higher systolic blood pressure and body mass index and lower eGFR. The highest quartile also tended to include a higher proportion of women, smokers and individuals with diabetes.

Of the 220 ICH cases in the present study, 68 cases were fatal at 28 days. Out of 166 cases with data on hemorrhage volume, 41 had volume >40 ml. Of the 171 ICH cases with available data on mRS, 135 had mRS scores of 3–6 after 3 months.

|                      | Controls | All ICH   | p    |
|----------------------|----------|-----------|------|
| n                    | 244      | 220       |      |
| Age, years           | 62 (7)   | 62 (7)    | 0.88 |
| Men, n (%)           | 119 (49) | 105 (48)  | 0.82 |
| Systolic blood pressure, mmHg | 146 (21) | 153 (20)  | 0.0012 |
| Diastolic blood pressure, mmHg | 87 (11)  | 90 (11)   | 0.0028 |
| Blood pressure medication, n (%) | 55 (23)  | 56 (25)   | 0.46 |
| Body mass index, kg/m² | 25.8 (3.9) | 26.0 (4.2) | 0.56 |
| Diabetes, n (%)      | 14 (6)   | 14 (6)    | 0.78 |
| Smoking, n (%)       | 49 (20)  | 70 (32)   | 0.0038 |
| High alcohol consumption, n (%) | 6 (2)    | 14 (6)    | 0.039 |
| Use of warfarin, n (%) | 2 (1)    | 8 (4)     | 0.037 |
| Apolipoprotein B, mg/dl | 108.6 (24.5) | 106.7 (25.8) | 0.44 |
| Apolipoprotein A1, mg/dl | 153.9 (27.6) | 153.9 (28.5) | 1.00 |
| Use of lipid-lowering drugs, n (%) | 3 (1)    | 7 (3)     | 0.15 |
| Living alone, n (%)  | 60 (25)  | 63 (29)   | 0.32 |
| Estimated glomerular filtration rate, ml/min/1.73 m² | 85.1 (14.7) | 85.4 (14.8) | 0.50 |
| Fibroblast growth factor 23, NPX, median (interquartile range) | 2.47 (0.77) | 2.69 (0.95) | 0.002 |

Note: Numbers are mean (standard deviation) unless otherwise stated. Abbreviations: ICH, intracerebral hemorrhage; NPX, normalized protein expression, arbitrary units on the log₂ scale.
Higher FGF23 was associated with all ICH, lobar ICH, non-lobar ICH, fatal ICH, ICH with large volume and ICH with poor functional outcome (Table 3). Odds ratios (ORs) were similar for all subgroups. Results remained relatively unchanged after multivariable adjustment, both with and without adjustment for eGFR. No evidence was found of a nonlinear association between FGF23 and all ICH when evaluating a quadratic term of FGF23 in the fully adjusted model. In a sensitivity analysis that excluded individuals with prevalent (n = 1) or incident (n = 21) chronic kidney disease, ORs remained similar for all ICH (OR 1.87, 95% CI 1.23–2.83, p = 0.003), non-lobar ICH (OR 2.21, 95% CI 1.34–3.65, p = 0.002), ICH with large volume (OR 2.26, 95% CI 1.19–4.30, p = 0.013) and ICH with poor functional outcome (OR 1.85, 95% CI 1.14–3.02, p = 0.012). The associations of FGF23 with lobar ICH (OR 1.55, 95% CI 0.85–2.82, p = 0.152) and fatal ICH (OR 1.75, 95% CI 0.94–3.24, p = 0.075) were slightly attenuated.

**DISCUSSION**

Understanding the pathogenesis behind ICH and identifying risk factors is essential to reduce the death and disability caused by this devastating form of stroke. This prospective, population-based nested case–control study investigated the association of plasma levels of FGF23 with incident ICH. FGF23 was significantly associated with all ICH, lobar ICH, non-lobar ICH, fatal ICH, ICH with large volume and ICH with poor functional outcome, even after adjustment for potential ICH risk factors and eGFR.

**TABLE 2** Baseline characteristics by quartiles of fibroblast growth factor 23

|                | Q1   | Q2   | Q3   | Q4   | p<text>_trend_</text> |
|----------------|------|------|------|------|------------------------|
| Age, years     | 59 (6)| 62 (6)| 62 (7)| 64 (8)| <0.001                 |
| Men, n (%)     | 61 (53)| 57 (49)| 60 (52)| 46 (40)| 0.081                 |
| Systolic blood pressure, mmHg | 147 (19)| 148 (23)| 149 (20)| 152 (21)| 0.041                 |
| Diastolic blood pressure, mmHg | 89 (11)| 88 (11)| 87 (11)| 88 (11)| 0.82                  |
| Blood pressure medication, n (%) | 19 (16)| 18 (16)| 36 (31)| 38 (33)| <0.001                 |
| Body mass index, kg/m² | 25 (4)| 26 (3)| 26 (4)| 26 (4)| 0.017                  |
| Diabetes, n (%) | 7 (6)| 5 (4)| 5 (4)| 11 (9)| 0.30                   |
| Smoking, n (%)  | 24 (21)| 30 (26)| 29 (25)| 36 (31)| 0.097                  |
| High alcohol intake, n (%) | 3 (3)| 5 (4)| 9 (8)| 3 (3)| 0.68                   |
| Oral anticoagulants, n (%) | 3 (3)| 1 (1)| 1 (1)| 5 (4)| 0.39                   |
| Apolipoprotein B, mg/dl | 106 (26)| 106 (25)| 107 (26)| 111 (24)| 0.093                 |
| Apolipoprotein A1, mg/dl | 157 (28)| 155 (27)| 153 (30)| 151 (27)| 0.079                 |
| Use of lipid-lowering drugs, n (%) | 1 (1)| 1 (1)| 5 (4)| 3 (3)| 0.15                   |
| Living alone, n (%) | 23 (20)| 38 (33)| 31 (27)| 31 (27)| 0.47                   |
| Estimated glomerular filtration rate, ml/min/1.73 m² | 88.5 (14.5)| 85.5 (14.2)| 85.4 (15.0)| 81.6 (14.3)| 0.013                 |

Note: Numbers are mean (standard deviation) unless otherwise stated.

**TABLE 3** Odds ratio for intracerebral hemorrhage per doubling of fibroblast growth factor 23

|                | Age- and sex-adjusted OR (95% CI, p) | Multivariable-adjusted<sup>a</sup> without eGFR, OR (95% CI, p) | Multivariable-adjusted<sup>a</sup> with eGFR, OR (95% CI, p) |
|----------------|--------------------------------------|-------------------------------------------------|-------------------------------------------------|
| All ICH (n = 220) | 1.96 (1.36–2.82, <0.0001) | 1.84 (1.25–2.71, 0.002) | 1.85 (1.25–2.72, 0.002) |
| Lobar ICH (n = 82) | 1.93 (1.18–3.14, 0.008) | 1.73 (1.04–2.87, 0.035) | 1.73 (1.04–2.88, 0.036) |
| Non-lobar ICH (n = 101) | 2.01 (1.30–3.12, 0.002) | 2.13 (1.32–3.45, 0.002) | 2.14 (1.32–3.46, 0.002) |
| Fatal ICH (n = 68) | 2.09 (1.43–3.53, 0.006) | 1.88 (1.06–3.33, 0.03) | 1.92 (1.08–3.42, 0.027) |
| ICH with large volume (>40 ml, n = 41) | 1.77 (1.01–3.13, 0.048) | 2.18 (1.16–4.1, 0.016) | 2.21 (1.16–4.22, 0.017) |
| ICH with mRS 3–6 at 3 months (n = 135) | 2.01 (1.32–3.08, 0.001) | 1.94 (1.23–3.06, 0.005) | 1.94 (1.23–3.07, 0.005) |

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; OR, odds ratio.

<sup>a</sup>Age, sex, systolic blood pressure, blood pressure medication, body mass index, smoking, high alcohol intake, diabetes mellitus, use of oral anticoagulants, living alone and apolipoprotein B.
Some previous studies, but not all [8], suggest that higher FGF23 is associated with hemorrhagic stroke [6–10]. Wright et al. examined ICH as a separate outcome and found a significant association of FGF23 with ICH [10]. That study included 26 ICH cases, compared to 220 cases in the present study. Even though the underlying pathophysiology is considered to differ for lobar and non-lobar ICH [18], the association of FGF23 with lobar and non-lobar ICH has not been studied separately before. No studies of FGF23 in relation to ICH with large volume, fatal outcome or poor functional outcome are known.

In the Northern Manhattan Study, but not in the Framingham Heart Study, an association has also been found between FGF23 and cerebral white matter intensity volume [19,20]. An association of FGF23 with white matter hyperintensity volume could hypothetically be one link between FGF23 and risk of ICH, as white matter hyperintensities may express hypertensive small vessel disease, which is an important underlying pathology in ICH [18].

FGF23 is associated with several different cardiovascular outcomes, but it is unclear whether FGF23 plays a causal role in the pathogenesis of cardiovascular disease [3]. High FGF23 has been found to be associated with incident hypertension [21]. In mice, levels of FGF23 interact with the renin–angiotensin–aldosterone system in several ways: increasing FGF23 directly increases expression of the Na\(^+\)-Cl\(^-\) cotransporter in the kidney, thereby increasing plasma volume and contributing to increased blood pressure, and infusion of angiotensin upregulates FGF23 expression in mouse hearts [22,23]. However, the association of FGF23 with ICH in the present study was significant even after adjustment for systolic blood pressure and blood pressure medication at baseline. Hypothetically, FGF23 may increase the risk of ICH through being associated with future blood pressure increase.

FGF23 has also been found to be associated with endothelial dysfunction regardless of kidney function, and with arterial stiffness in subjects with eGFR <60 ml/min/1.73 m\(^2\) [24,25]. These are also mechanisms that potentially may be of importance for the pathology of small vessel disease and ICH.

FGF23 is regarded as a biomarker of renal function, and low eGFR may be associated with risk of ICH [26]. To account for a potential influence of kidney function or chronic kidney disease on the results, a sensitivity analysis was performed after excluding all individuals with an inpatient or outpatient diagnosis of chronic kidney disease any time during follow-up (n = 22). Furthermore, a multiple imputation of eGFR values was performed based on a randomly selected subgroup of >5000 individuals from the present cohort. The results were essentially unchanged in the sensitivity analysis and when adjusting for eGFR in the multivariable models. Therefore, it is unlikely that kidney function could explain the association between FGF23 and ICH in the present study. Results from the meta-analysis by Yao et al. also support that the association between FGF23 and stroke risk is independent of kidney function [6].

Our finding that subjects in the highest quartile of FGF23 were more likely to be female, smokers and diabetic is in line with previous studies [27]. Whilst the association of FGF23 with diabetes is unclear, some studies suggest an association of FGF23 with insulin resistance and insulin deficiency [28]. Subjects in the highest quartile of FGF23 were more likely to be smokers, and smoking may be a risk factor for ICH. However, in the present study, FGF23 was significantly associated with ICH after adjustment for diabetes, smoking and other potential confounders.

Hemorrhage volume is an important predictor of outcome after ICH [29], and the association between FGF23 and ICH with poor functional outcome is likely to be related to the association between FGF23 and ICH with large volume.

Further studies are needed to investigate potential mechanisms behind the association between FGF23 and ICH. A Mendelian randomization design to explore the relationship between FGF23 and ICH would be of great interest to assess potential causality and thereby better understand the pathophysiology of ICH.

**Strengths and limitations**

The prospective study design is a major strength of this study. In a nested case–control study, all ICH cases and controls come from the same population. This strongly reduces the risk of selection bias. The risk of loss to follow-up was also considered to be very small, since the inpatient and causes of death registers had national coverage during the entire follow-up period. Almost all ICH cases (98%) were validated by review of medical records and images.

ABC/2 is a widely used method for ICH volume measurement and has acceptable agreement with computed tomography-based planimetry [30]. However, ABC/2 does tend to overestimate the size of hemorrhages with large volume, lobar location and irregular shape [30].

Although measured eGFR values would be preferable compared to imputed values, it is reasonable to conclude that reduced kidney function is an unlikely reason for the relationship between FGF23 and ICH in the present study. There was no information on levels of phosphate, vitamin D or PTH, which is a limitation since FGF23 has a complex interplay with these variables [2]. However, in many previous studies on FGF23 and different cardiovascular outcomes, including hemorrhagic stroke, adjustment for serum phosphate, calcium, vitamin D and PTH had only small or no effect on the results [5,7,10,31]. Also, although these variables are strongly linked to kidney failure and to FGF23, they are not known risk factors for ICH in the general population [32]. In the sensitivity analysis excluding those with kidney failure, results were unchanged in our study.

Although many potential risk factors were adjusted for, residual confounding is still possible. Also, some risk factors could have changed during the follow-up period, including changes in risk factor management, for example blood pressure treatment and lifestyle changes. However, hypertension is still very prevalent in the general population. Also, any changes in risk factors over time would probably bias the results towards null.

Levels of FGF23 were only analyzed at one point in time. However, a random variation in FGF23 levels would most probably
bias the results towards null. Whilst the analysis method, immunoassay based on the proximity extension assay technique, performs well and has high sensitivity and specificity, the results are expressed as arbitrary units and cannot therefore be compared to absolute values. This is a limitation. However, the different methods for measuring FGF23 are still not standardized and comparable between studies that use different assays [33].

Summary

In this prospective, population-based study, levels of FGF23 were associated with incident ICH, and similarly with both lobar and non-lobar ICH. FGF23 was also associated with fatal ICH, ICH with large volume and ICH with poor functional outcome. Future studies evaluating a possible causal association, and the potential value of FGF23 in clinical risk prediction, would be of great interest.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Edith H Svensson: Data curation (equal); formal analysis (lead); investigation (equal); methodology (supporting); writing—original draft (lead). Martin Söderholm: Conceptualization (lead); data curation (equal); formal analysis (supporting); funding acquisition (lead); investigation (equal); methodology (lead); supervision (lead); writing—original draft (supporting).

ETHICAL APPROVAL

The Malmö Diet and Cancer Study and sub-projects were approved by the Lund University ethics committee (LU 51/90, 166/2007, 633/2009, 566/2013, 2016/452). Written informed consent was obtained from all participants.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available after application to the Malmö Diet and Cancer Study steering committee at Lund University, Sweden.

ORCID

Edith H. Svensson @ https://orcid.org/0000-0001-7720-3701

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