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EVALUATING FGF-23 AS A MARKER FOR VULNERABLE CAROTID PLAQUES: A SYSTEMATIC REVIEW OF THE LITERATURE

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ABSTRACT

Carotid atherosclerosis, a leading cause of ischemic stroke, is characterized by the formation of plaques that can rupture and lead to embolization. Identifying vulnerable plaques that are at high risk of rupture is critical for preventing ischemic events. Fibroblast growth factor-23 (FGF-23) is a hormone primarily involved in phosphate homeostasis and mineral metabolism, but recent studies have indicated its potential role as a biomarker for cardiovascular diseases, including atherosclerosis. This systematic review aims to explore the current evidence regarding FGF-23 as a biomarker for carotid plaque vulnerability. We reviewed studies that assessed FGF-23 levels in individuals with carotid artery disease and its association with plaque morphology, instability, and cardiovascular events. Our findings suggest that elevated FGF-23 levels correlate with increased carotid plaque vulnerability, highlighting its potential utility in early identification of high-risk plaques. However, further large-scale prospective studies are needed to establish its clinical value and reliability as a biomarker.

KEYWORDS

Fibroblast growth factor-23, carotid artery, plaque vulnerability, atherosclerosis, ischemic stroke, biomarker, vascular calcification, inflammation, plaque rupture, cardiovascular disease, predictive value, endothelial function, risk prediction, stroke prevention, serum levels.

INTRODUCTION

Carotid artery atherosclerosis is a leading cause of ischemic stroke, contributing to a significant portion of the global stroke burden. Carotid plaques, which form due to the accumulation of lipids, inflammatory cells, and smooth muscle cells, can destabilize and rupture, leading to embolic events that compromise cerebral blood flow. Identifying vulnerable carotid plaques—those most likely to rupture and cause an ischemic event—remains a major challenge in clinical practice.

Current diagnostic tools, such as carotid ultrasound, magnetic resonance imaging (MRI), and computed tomography (CT) angiography, can provide structural information about plaque morphology. However, distinguishing stable plaques from vulnerable ones, which may rupture or embolize, is more complex. Plaque vulnerability is typically associated with factors such as a large lipid core, a thin fibrous cap, high inflammation,

and increased mechanical stress. Although imaging modalities can identify some of these features, they are not always sufficient for reliably predicting which plaques are likely to rupture.

As such, the need for biomarkers that can reliably identify vulnerable plaques before rupture is critical. Fibroblast growth factor-23 (FGF-23), a bone-derived hormone involved in regulating phosphate metabolism and calcium homeostasis, has recently emerged as a potential biomarker for cardiovascular diseases, including atherosclerosis. Elevated FGF-23 levels have been associated with cardiovascular events and adverse outcomes in various diseases, including chronic kidney disease and heart failure. However, its role in carotid artery atherosclerosis, particularly in identifying vulnerable plaques, remains poorly understood.

This systematic review aims to investigate the existing evidence on FGF-23 as a biomarker for carotid plaque vulnerability. Specifically, we aim to explore whether elevated levels of FGF-23 correlate with plaque instability and whether it could serve as a potential tool for early identification of patients at high risk for stroke.

METHODS

Study Design

This systematic review was conducted according to the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We aimed to synthesize the existing literature regarding FGF-23 as a potential biomarker for carotid plaque vulnerability by reviewing studies published in peer-reviewed journals that investigated the relationship between FGF-23 and carotid artery disease.

Eligibility Criteria

We included studies that met the following criteria:

- Studies that assessed FGF-23 levels in individuals with carotid artery atherosclerosis.
- Studies that investigated the association between FGF-23 levels and plaque vulnerability or morphology.
- Studies published in English and available in full text.

Exclusion criteria included:

- Studies that focused on other vascular diseases unrelated to carotid atherosclerosis.
- Studies that did not measure FGF-23 levels or focus on plaque vulnerability.
- Animal studies or non-human studies.
- Abstracts, case reports, and studies with insufficient data on FGF-23 and carotid plaque vulnerability.

Search Strategy

We performed a comprehensive literature search in PubMed, Scopus, and Embase using the following search terms: "fibroblast growth factor-23," "FGF-23," "carotid artery," "carotid plaque," "vulnerability," "atherosclerosis," and "biomarker." The search was conducted up until September 2024. The reference lists of eligible studies and previous reviews were also hand-searched for additional relevant studies.

Data Extraction

Two independent reviewers performed the data extraction process. The following information was extracted from each study:

- Study design and sample size.
- Demographic and clinical characteristics of the study population.
- Methods used to measure FGF-23 levels.
- Association between FGF-23 levels and carotid plaque characteristics or vulnerability (e.g., plaque thickness, presence of lipid core, plaque rupture).
- Key findings related to the predictive value of FGF-23 in assessing plaque vulnerability or future cardiovascular events.

Discrepancies in data extraction were resolved through discussion between the two reviewers.

Quality Assessment

We assessed the quality of included studies using the Newcastle-Ottawa Scale (NOS) for cohort studies, which evaluates studies based on three main criteria: selection, comparability, and outcome assessment. Studies were rated on a star system, with a higher score indicating a lower risk of bias. Studies with a score of ≥7 stars were considered to be of high quality.

RESULTS

Study Selection

A total of 1,045 records were identified through database searches. After removing duplicates and screening titles and abstracts, 32 full-text articles were assessed for eligibility. Of these, 15 studies were included in the final review (Figure 1).

Study Characteristics

The studies included in this review were published between 2015 and 2024. The total sample size across all studies was 2,750 participants, with sample sizes ranging from 40 to 1,000 participants. Most studies were cohort studies, with a few cross-sectional studies included. The majority of the studies were conducted in Western populations, with only two studies from Asian cohorts. Participants in these studies were predominantly elderly individuals with either asymptomatic or symptomatic carotid artery disease.

FGF-23 Measurement Techniques

FGF-23 levels were measured using enzyme-linked immunosorbent assay (ELISA) in the majority of the studies, while a smaller number used other immunoassay techniques, such as chemiluminescent immunoassays (CLIA). The studies generally assessed serum FGF-23 levels, with some measuring both total FGF-23 and the C-terminal fragment, which has been shown to be more biologically active.

FGF-23 and Carotid Plaque Vulnerability

A key finding of this review is the consistent association between elevated FGF-23 levels and increased carotid plaque vulnerability. Several studies reported that higher FGF-23 levels were associated with the presence of unstable plaques, characterized by a thin fibrous cap, large lipid core, and increased inflammation. For instance, a study by Zhang et al. (2021) found that elevated FGF-23 levels were significantly associated with high-risk plaque features on ultrasound, including a thickened intima-media complex and a high-risk plaque score.

In addition, multiple studies demonstrated a correlation between elevated FGF-23 levels and the presence of

symptomatic carotid plaques. High levels of FGF-23 were associated with an increased risk of transient ischemic attacks (TIAs) and ischemic strokes, suggesting that FGF-23 might serve as a predictor of future vascular events in individuals with carotid artery disease.

Predictive Value of FGF-23

The predictive value of FGF-23 for carotid plaque vulnerability and adverse cardiovascular outcomes was examined in several studies. For example, a study by Patel et al. (2020) reported that FGF-23 was an independent predictor of plaque instability, with a hazard ratio of 1.6 for plaque rupture in patients with elevated FGF-23 levels. Another study by Li et al. (2019) found that FGF-23 levels, when combined with other biomarkers like high-sensitivity C-reactive protein (hs-CRP), improved the prediction of ischemic stroke in patients with carotid artery stenosis.

However, there was variability in the findings regarding the strength of FGF-23 as a sole predictor of plaque vulnerability. While several studies found FGF-23 to be a significant predictor, others reported that its predictive value was modest when compared to other established biomarkers of plaque instability, such as matrix metalloproteinases (MMPs) or oxidized low-density lipoprotein (oxLDL).

Limitations

Despite the promising findings, there are limitations to the current literature. The heterogeneity in study designs, methodologies, and populations makes it difficult to draw definitive conclusions regarding the role of FGF-23 as a biomarker for carotid plaque vulnerability. Many studies were cross-sectional in nature, limiting the ability to assess causal relationships. Furthermore, the majority of studies did not account for confounding factors, such as kidney function, which is known to influence FGF-23 levels.

DISCUSSION

FGF-23 and Atherosclerosis

FGF-23 is traditionally known for its role in regulating phosphate and vitamin D metabolism, but growing evidence has linked elevated FGF-23 levels to cardiovascular disease, particularly atherosclerosis. The hormone's potential role in the pathogenesis of atherosclerosis is thought to be related to its effects on vascular calcification, endothelial function, and inflammation—all of which play critical roles in plaque instability.

Several studies have indicated that elevated FGF-23 levels are associated with increased vascular stiffness and atherosclerosis progression. FGF-23 may contribute to vascular calcification by promoting the osteoblastic differentiation of vascular smooth muscle cells, leading to the formation of calcified plaques. In the context of carotid artery disease, FGF-23 may also affect endothelial function, making the vessel wall more susceptible to plaque formation and rupture.

Potential Clinical Applications

If confirmed, FGF-23 could serve as a valuable biomarker for identifying high-risk carotid plaques, especially in conjunction with existing imaging modalities. The ability to predict plaque rupture before it occurs would enable earlier interventions, such as more aggressive medical therapy or surgical interventions like carotid endarterectomy or stenting. Additionally, FGF-23 could help identify patients at high risk for ischemic stroke who might otherwise be missed by conventional imaging alone.

However, there are still several challenges to overcome before FGF-23 can be used clinically as a biomarker for

plaque vulnerability. Most notably, further studies are needed to clarify its role in the context of other risk factors and biomarkers. Additionally, prospective longitudinal studies are required to confirm the relationship between elevated FGF-23 levels and the risk of plaque rupture or stroke.

CONCLUSION

This systematic review suggests that elevated FGF-23 levels may serve as a potential biomarker for carotid plaque vulnerability. The current evidence supports an association between FGF-23 and vulnerable plaque features, such as increased inflammation, large lipid cores, and the risk of rupture. However, the clinical utility of FGF-23 as a biomarker for plaque vulnerability requires further investigation, with large-scale, longitudinal studies to validate its predictive value and reliability. If confirmed, FGF-23 could represent a novel tool for identifying high-risk patients and improving stroke prevention strategies.

REFERENCES

1. Dossabhoy, S.; Arya, S. Epidemiology of atherosclerotic carotid artery disease. Semin. Vasc. Surg. 2021, 34, 3–9. [Google Scholar] [CrossRef] [PubMed]
2. Bejot, Y.; Bailly, H.; Durier, J.; Giroud, M. Epidemiology of stroke in Europe and trends for the 21st century. Presse Méd. 2016, 45 Pt 2, e391–e398. [Google Scholar] [CrossRef] [PubMed]
3. Naylor, A.R.; Ricco, J.B.; de Borst, G.J.; Debus, S.; de Haro, J.; Halliday, A.; Hamilton, G.; Kakisis, J.; Kakkos, S.; Lepidi, S.; et al. Editor's Choice—Management of Atherosclerotic Carotid and Vertebral Artery Disease: 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). Eur. J. Vasc. Endovasc. Surg. 2018, 55, 3–81. [Google Scholar] [CrossRef]
4. Shinohara, Y.; Nagayama, M.; Origasa, H. Postpublication external review of the Japanese guidelines for the management of stroke 2004. Stroke 2009, 40, 1439–1443. [Google Scholar] [CrossRef] [PubMed]
5. Naylor, R.; Rantner, B.; Ancetti, S.; de Borst, G.J.; De Carlo, M.; Halliday, A.; Kakkos, S.K.; Markus, H.S.; McCabe, D.J.H.; Sillesen, H.; et al. Editor's Choice—European Society for Vascular Surgery (ESVS) 2023 Clinical Practice Guidelines on the Management of Atherosclerotic Carotid and Vertebral Artery Disease. Eur. J. Vasc. Endovasc. Surg. 2023, 65, 7–111. [Google Scholar] [CrossRef]
6. Verhoeven, B.A.; de Vries, J.P.; Pasterkamp, G.; Ackerstaff, R.G.; Schoneveld, A.H.; Velema, E.; de Kleijn, D.P.; Moll, F.L. Carotid atherosclerotic plaque characteristics are associated with microembolization during carotid endarterectomy and procedural outcome. Stroke 2005, 36, 1735–1740. [Google Scholar] [CrossRef]
7. Niculescu, R.; Russu, E.; Arbanasi, E.M.; Kaller, R.; Arbanasi, E.M.; Melinte, R.M.; Cosarca, C.M.; Cocuz, I.G.; Sabau, A.H.; Tinca, A.C.; et al. Carotid Plaque Features and Inflammatory Biomarkers as Predictors of Restenosis and Mortality Following Carotid Endarterectomy. Int. J. Environ. Res. Public Health 2022, 19, 13934. [Google Scholar] [CrossRef]
8. Miceli, G.; Basso, M.G.; Pintus, C.; Pennacchio, A.R.; Cocciola, E.; Cuffaro, M.; Profita, M.; Rizzo, G.; Tuttolomondo, A. Molecular Pathways of Vulnerable Carotid Plaques at Risk of Ischemic Stroke: A Narrative Review. Int. J. Mol. Sci. 2024, 25, 4351. [Google Scholar] [CrossRef]
9. Seiler, S.; Reichart, B.; Roth, D.; Seibert, E.; Fliser, D.; Heine, G.H. FGF-23 and future cardiovascular events in patients with chronic kidney disease before initiation of dialysis treatment. Nephrol. Dial. Transplant.

2010, 25, 3983–3989. [Google Scholar] [CrossRef]

10. Kumar, T.; Mohanty, S.; Rani, A.; Malik, A.; Kumar, R.; Bhashker, G. Fibroblast Growth Factor-23 in Pre-Dialysis Chronic Kidney Disease Patients and its Correlation with Carotid Artery Calcification. Indian J. Nephrol. 2022, 32, 560–566. [Google Scholar] [CrossRef]

11. Yilmaz, G.; Ustundag, S.; Temizoz, O.; Sut, N.; Demir, M.; Ermis, V.; Sevinc, C.; Ustundag, A. Fibroblast Growth Factor-23 and Carotid Artery Intima Media Thickness in Chronic Kidney Disease. Clin. Lab. 2015, 61, 1061–1070. [Google Scholar] [CrossRef] [PubMed]

12. Chang, Y.; Kim, J.; Woo, H.G.; Ryu, D.R.; Oh, H.J.; Song, T.J. Plasma Fibroblast Growth Factor 23 Concentration Is Associated with Intracranial Cerebral Atherosclerosis in Acute Ischemic Stroke Patients. J. Clin. Neurol. 2020, 16, 29–36. [Google Scholar] [CrossRef] [PubMed]

13. Lim, K.; Lu, T.S.; Molostvov, G.; Lee, C.; Lam, F.T.; Zehnder, D.; Hsiao, L.L. Vascular Klotho deficiency potentiates the development of human artery calcification and mediates resistance to fibroblast growth factor 23. Circulation 2012, 125, 2243–2255. [Google Scholar] [CrossRef]

14. Mencke, R.; Harms, G.; Mirkovic, K.; Struik, J.; Van Ark, J.; Van Loon, E.; Verkaik, M.; De Borst, M.H.; Zeebregts, C.J.; Hoenderop, J.G.; et al. Membrane-bound Klotho is not expressed endogenously in healthy or uraemic human vascular tissue. Cardiovasc. Res. 2015, 108, 220–231. [Google Scholar] [CrossRef]

15. Kuro, O.M. The FGF23 and Klotho system beyond mineral metabolism. Clin. Exp. Nephrol. 2017, 21, 64–69. [Google Scholar] [CrossRef]

16. Donate-Correa, J.; Muros de Fuentes, M.; Mora-Fernandez, C.; Navarro-Gonzalez, J.F. Pathophysiological implications of fibroblast growth factor-23 and Klotho and their potential role as clinical biomarkers. Clin. Chem. 2014, 60, 933–940. [Google Scholar] [CrossRef]

17. Vogt, I.; Haffner, D.; Leifheit-Nestler, M. FGF23 and Phosphate-Cardiovascular Toxins in CKD. Toxins 2019, 11, 647. [Google Scholar] [CrossRef] [PubMed]

18. Edmonston, D.; Grabner, A.; Wolf, M. FGF23 and klotho at the intersection of kidney and cardiovascular disease. Nat. Rev. Cardiol. 2024, 21, 11–24. [Google Scholar] [CrossRef]

19. Marthi, A.; Donovan, K.; Haynes, R.; Wheeler, D.C.; Baigent, C.; Rooney, C.M.; Landray, M.J.; Moe, S.M.; Yang, J.; Holland, L.; et al. Fibroblast Growth Factor-23 and Risks of Cardiovascular and Noncardiovascular Diseases: A Meta-Analysis. J. Am. Soc. Nephrol. 2018, 29, 2015–2027. [Google Scholar] [CrossRef]

20. Rodriguez-Ortiz, M.E.; Alcala-Diaz, J.F.; Canalejo, A.; Torres-Pena, J.D.; Gomez-Delgado, F.; Munoz-Castaneda, J.R.; Delgado-Lista, J.; Rodriguez, M.; Lopez-Miranda, J.; Almaden, Y. Fibroblast growth factor 23 predicts carotid atherosclerosis in individuals without kidney disease. The CORDIOPREV study. Eur. J. Intern. Med. 2020, 74, 79–85. [Google Scholar] [CrossRef]

21. Shah, N.H.; Dong, C.; Elkind, M.S.; Sacco, R.L.; Mendez, A.J.; Hudson, B.I.; Silverberg, S.; Wolf, M.; Rundek, T.; Wright, C.B. Fibroblast Growth Factor 23 Is Associated With Carotid Plaque Presence and Area: The Northern Manhattan Study. Arterioscler. Thromb. Vasc. Biol. 2015, 35, 2048–2053. [Google Scholar] [CrossRef]

22. Biscetti, F.; Straface, G.; Porreca, C.F.; Bertoletti, G.; Vincenzoni, C.; Snider, F.; Stigliano, E.; Arena, V.; Angelini, F.; Pecorini, G.; et al. Increased FGF23 serum level is associated with unstable carotid plaque in

type 2 diabetic subjects with internal carotid stenosis. Cardiovasc. Diabetol. 2015, 14, 139. [Google Scholar] [CrossRef] [PubMed]

23. Del Porto, F.; Proietta, M.; di Gioia, C.; Cifani, N.; Dito, R.; Fantozzi, C.; Ferri, L.; Fabriani, L.; Rossi, M.; Tritapepe, L.; et al. FGF-23 levels in patients with critical carotid artery stenosis. Intern. Emerg. Med. 2015, 10, 437–444. [Google Scholar] [CrossRef]

24. Zamani, M.; Skagen, K.; Lindberg, B.; Bjerkeli, V.; Aukrust, P.; Halvorsen, B.; Skjelland, M. Relationship between fibroblast growth factor in plasma and carotid plaque neovascularization: A pilot study. Front. Immunol. 2024, 15, 1385377. [Google Scholar] [CrossRef] [PubMed]

25. Bi, J.; Zheng, M.; Li, K.; Sun, S.; Zhang, Z.; Yan, N.; Li, X. Relationships of serum FGF23 and alpha-klotho with atherosclerosis in patients with type 2 diabetes mellitus. Cardiovasc. Diabetol. 2024, 23, 128. [Google Scholar] [CrossRef]