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EDITORIAL

Fibroblast Growth Factor: Will This Hormone Be the Hemoglobin A1c for Managing Phosphorus Balance in Chronic Kidney Disease?

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What Is Fibroblast Growth Factor (FGF)?

Fibroblast growth factor 23 (FGF23) is a bone-derived hormone that regulates phosphorus and vitamin D metabolism by increasing the rate of urinary excretion of phosphate and by inhibiting the renal production of 1,25-dihydroxyvitamin D.[1] In patients with chronic kidney disease (CKD), circulating FGF23 levels rise progressively as a physiological adaption to compensate for persistent phosphate retention and increased total body phosphorus.[2,3] Elevated phosphate levels and depressed 1,25-dihydroxyvitamin D levels are associated with increased mortality among patients with CKD. Recently, increased FGF23 levels have been associated with mortality, left ventricular hypertrophy, endothelial dysfunction, and progression of CKD independent of serum phosphate levels.[4] Fibroblast growth factor 23 is emerging as an attractive biomarker for identifying which patients with CKD might benefit most from aggressive management of their hyperphosphatemia.[5] It is currently not known whether FGF23 exerts direct end organ toxicity, such as in the heart, vessels, and kidneys, or whether it is a marker for damage.[6]

How Does FGF Affect Phosphorus Levels?

A sustained increase in dietary phosphorus intake stimulates FGF23 secretion that increases phosphaturia and decreases synthesis of 1,25-vitamin D. A hormone that induces phosphaturia is know as a phosphatonin.[7] Fibroblast growth factor 23 synergizes with parathyroid hormone to increase renal phosphate excretion by reducing expression of renal sodium-phosphate cotransporters in the proximal tubules.[8] A sustained reduction in phosphorus intake lowers FGF23 secretion, which enhances tubular phosphorus resorption and increases 1,25-vitamin D production. The binding and action of FGF23 require the presence of Klotho, which is a transmembrane protein expressed in renal tubules that binds to multiple fibroblast growth factor receptors and functions as a coreceptor for FGF23.[9] Elevated levels of FGF23 are associated with bone fracture healing and this substance is a promising candidate as an indicator for healing processes prone to reunion versus nonunion.[10] Excessive production of FGF23 may play an important role in impaired mineralization plus renal phosphate-wasting syndrome associated with Fibrous Dysplasia and McCune Albright Syndrome.[11] Furthermore, defects in either FGF23 or Klotho are associated with phosphate retention, as well as an accelerated aging syndrome. Klotho has been referred to as an antiaging gene.[12] The early senescence phenotypes in Klotho-deficient or FGF23-deficient mice can be avoided by treating the hyperphosphatemia, which suggests that phosphate retention may accelerate aging. This observation ties in with epidemiologic data, thus demonstrating that hyperphosphatemia is invariably present among patients with end-stage renal disease and may be associated independently with increased risk of all-cause mortality, accelerated cardiovascular calcification, and cardiovascular mortality.[13,14]

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Abbreviations: (CKD) chronic kidney disease, (FGF) fibroblast growth factor, (FGF23) fibroblast growth factor 23, (HbA1c) hemoglobin A1c

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Why Is FGF Being Compared to Hemoglobin A1c?

An elevated serum FGF23 level has been proposed to represent a biomarker of greater time-averaged phosphorus exposure that is superior to an isolated serum phosphate level, analogous to the superiority of hemoglobin A1c (HbA1c) as a measure of overall glycemic control compared with an isolated glucose level.[4] Phosphorus levels, like glucose levels, can vary throughout the day. Fibroblast growth factor 23 appears to be a potential long-term indicator of phosphorus balance that is even better than serum phosphate levels themselves. Fibroblast growth factor 23 screening might be used to determine which normophosphatemic CKD patients could benefit from phosphorus binders. This therapy, which lowers the phosphorus burden in normophosphatemic CKD, could be added to current therapy that is limited to dietary phosphate restriction.[15]

What Problems Might Need to Be Solved for FGF to Be Adopted as a Surrogate Marker for Phosphatemia?

Most importantly, it will be necessary to demonstrate that lowering elevated levels of this hormone actually is associated with improved outcomes. Such studies are proposed to validate any proposed biomarker as being mechanistically linked to a disease. In this case, studies would use elevated FGF23 levels to monitor increased body phosphorus and follow this analyte during phosphorus lowering therapy. Subjects would be predialysis patients early in their course of kidney disease who do not typically receive phosphorus binders. This type of study, which used HbA1c levels to lower the glycemic burden, is how the Diabetes Control and Complications Trial (biomarker validation study) established HbA1c as a marker for microvascular disease. In that study the risk for development and progression of chronic microvascular complications was found to be closely related to the degree of glycemic control, as measured by HbA1c. Even this landmark study showed that HbA1c was a surrogate marker rather than a direct marker. Because it could take decades for a study to demonstrate benefit to HbA1c-directed intensive therapy, the diabetes scientific community has accepted this surrogate marker as a valid marker of glycemic burden.[16] It is not known which other substances in addition to phosphorus affect FGF23 levels, and it is not established whether FGF23 itself is toxic and responsible for the adverse outcomes in CKD or whether elevated levels of this substance are a by-product of renal damage.

What Problems Does Hemoglobin A1c Have That Might Also Affect the Adoption of FGF as a Biomarker?

The diabetes community accepts HbA1c as a valid marker of glycemic load, and the nephrology community is now considering adopting FGF23 as their own integrated test for the body burden of a dangerous analyte, namely phosphorus. A variety of factors in addition to blood glucose levels can affect HbA1c measurements. Clinical chemists are studying HbA1c measurements in terms of the accuracy of currently utilized measurement equipment and interference from various biological and environmental factors. Based on their findings, any future candidates under consideration to be designated as integrated measure analytes will likely be scrutinized carefully before they are adopted.

Six factors that can affect HbA1c measurements include: (1) accuracy problems with the assay; (2) hemoglobinopathies; (3) biologic variation; (4) demographic factors; (5) smoking history; and (6) ambient temperature. A reference measurement system within the concept of metrological traceability is now accepted internationally as a valid analytic anchor thanks to the work of the National Glycohemoglobin Standardization Program and the International Federation of Clinical Chemistry.[17] The accuracy of HbA1c measurements can be affected adversely by the presence of hemoglobin variants or elevated levels of fetal hemoglobin. The most common hemoglobin variants are HbS, HbE, HbC, and HbD. The effect of each variant or elevated fetal hemoglobin must be considered with any measurement method.[18] Hemoglobin A1c is subject to biological variation because of differences in either red cell turnover in people who are hematologically normal or in the relationship between plasma glucose and red blood cell glucose concentration to which hemoglobin is exposed directly.[19] The reference range for HbA1c is affected by the age, race, and gender of patients with diabetes.[20] Smoking increases the HbA1c value because of the increased permeability of glucose across the red cell membrane into the cell, which can increase the HbA1c level.[21] Hemoglobin A1c levels are higher in cooler months and lower in warmer months in both Northern and Southern Hemispheres. In a country with minimal monthly temperature variation, there is only minimal variation in HbA1c values through the year.[22] It is likely that the interpretation of FGF23 levels will be affected by one or more of these six factors or possibly by other factors that have not yet been reported to affect HbA1c levels.

Is Hemoglobin A1c Worthy of Emulation by Other Biomarkers That Reflect Total Body Burden?

Hemoglobin A1c is a useful analyte for monitoring mean levels of glycemia over a 2- to 3-month period. Concentrations of this analyte are linked mechanistically to glucose levels. Increased HbA1c levels are associated with an increased risk of diabetic microvascular complications. Both observational and randomized trials have demonstrated a link between lowering HbA1c levels and improved outcomes. Confounding factors that can affect HbA1c levels are recognized. For FGF23 or other biomarker analytes reflecting total body burden of any substance to attain this level of acceptance in CKD or other diseases, more information will be needed. In the case of FGF23, observational studies have linked elevated levels of this substance with end organ damage, but it remains to be seen whether modifying levels of this substance will be associated with improved outcomes. At this point in time, HbA1c remains the gold standard for monitoring long-term integrated levels of potentially dangerous analytes. Other candidate measures of long-term burden of other substances will need to be evaluated with the same rigor that HbA1c has been studied.

References:

1. Gutiérrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, Smith K, Lee H, Thadhani R, Jüppner H, Wolf M. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. N Engl J Med. 2008:359(6):584-92.
2. Komaba H, Fukagawa M. FGF23: a key player in mineral and bone disorder in CKD. Nefrología. 2009;29(5):392-6.
3. Park SY, Jeong KH, Moon JY, Lee SH, Ihm CG, Rhee SY, Woo JT, Oh IH, Lee TW. The relationship between circulating fibroblast growth factor 23 and bone metabolism factors in Korean hemodialysis patients. Clin Exp Nephrol. 2010. [Epub ahead of print.]
4. Wolf M. Fibroblast growth factor 23 and the future of phosphorus management. Curr Opin Nephrol Hypertens. 2009;18(6):463-8.
5. Zisman AL, Wolf M. Recent advances in the rapidly evolving field of fibroblast growth factor 23 in chronic kidney disease. Curr Opin Nephrol Hypertens. 2010. [Epub ahead of print.]
6. Peiskerová M, Kalousová M, Kratochvílová M, Dusilová-Sulková S, Uhrová J, Bandúr S, Malbohan IM, Zima T, Tesar V. Fibroblast growth factor 23 and matrix-metalloproteinases in patients with chronic kidney disease: are they associated with cardiovascular disease? Kidney Blood Press Res. 2009;32(4):276-83. Epub 2009 Oct 1.
7. Tsagalis G, Psimenou E, Manios E, Laggouranis A. Fibroblast growth factor 23 (FGF23) and the kidney. Int J Artif Organs. 2009;32:232-9.
8. Bergwitz C, Jüppner H. Regulation of phosphate homeostasis by PTH, vitamin D, and FGF23. Annu Rev Med. 2010;61:91-104.
9. Kuro-O M. Overview of the FGF23-Klotho axis. Pediatr Nephrol. 2009 Jul 22.
10. Goebel S, Lienau J, Rammoser U, Seefried L, Wintgens KF, Seufert J, Duda G, Jakob F, Ebert R. FGF23 is a putative marker for bone healing and regeneration. J Orthop Res. 2009;27:1141-6.
11. Riminucci M, Collins MT, Fedarko NS, Cherman N, Corsi A, White KE, Waguespack S, Gupta A, Hannon T, Econs MJ, Bianco P, Gehron Robey P. FGF-23 in fibrous dysplasia of bone and its relationship to renal phosphate wasting. J Clin Invest. 2003;112(5):683–92.
12. Wang Y, Sun Z. Current understanding of klotho. Ageing Res Rev. 2009;8(1):43-51.
13. Qunibi WY. Consequences of hyperphosphatemia in patients with end-stage renal disease (ESRD). Kidney Int Suppl. 2004;(90):S8-12.
14. Giachelli CM. The emerging role of phosphate in vascular calcification. Kidney Int. 2009;75(9):890–7.
15. Oliveira RB, Cancela AL, Graciolli FG, Dos Reis LM, Draibe SA, Cuppari L, Carvalho AB, Jorgetti V, Canziani ME, Moysés RM. Control of PTH and FGF23 in normophosphatemic CKD patients: a new target in CKD-MBD therapy? Clin J Am Soc Nephrol. 2009 Nov 12.
16. Krishnamurti U, Steffes MW. Glycohemoglobin: a primary predictor of the development or reversal of complications of diabetes mellitus. Clin Chem. 2001;47(7):1157-65.
17. Weykamp C, Garry J, Mosca A. A review of the challenge in measuring hemoglobin A1c. J Diabetes Sci Technol. 2009;3(3):439-45.
18. Little R, Roberts W. Review of variant hemoglobins interfering with hemoglobin A1c measurement. J Diabetes Sci Technol. 2009;3(3):446-51.
19. Leslie RD, Cohen RM. Biologic variability in plasma glucose, hemoglobin A1c, and advanced glycation end products associated with diabetes complications. J Diabetes Sci Technol. 2009;3(4):635-43.
20. Higgins T, Cembrowski G, Tran D, Lim E, Chan J. Influence of variables on hemoglobin A1c values and nonheterogeneity of hemoglobin A1c reference ranges. J Diabetes Sci Technol. 2009;3(4):644-8.
21. Nilsson PM, Gudbjörnsdottir S, Eliasson B, Cederholm C; Steering Committee of the Swedish National Diabetes Register. Smoking is associated with increased HbA1c values and micro-albuminuria in patients with diabetes--data from the National Diabetes Register in Sweden. Diabetes Metab. 2004;30(3):261-8.
22. Higgins T, Saw S, Sikaris K, Cembrowski C, Lyon A, Khajuria A, Tran D. Seasonal variation in hemoglobin A1c: is it the same in both hemispheres? J Diabetes Sci Technol. 2009;3(4):668-71.