

Journal of Nephrologist



Does fibroblast growth factor 23 correlates with volume status in hemodialysis patients?

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ARTICLE INFO

Article type:
Original Article

Article history:
Received: 4 November 2018
Accepted: 9 January 2019
Published online: 29 January 2019

Keywords:
Fibroblast growth factor 23
Hemodialysis
Volume status
Overload
Bio-impedance analysis
Chronic kidney disease

ABSTRACT

Introduction: Volume overload is a known risk factor for cardiovascular disease and stroke in hemodialysis patients. The use of fibroblast growth factor 23 (FGF23) as a volume overload marker has been validated in multiple studies.

Objectives: This is a prospective cross-sectional study considering the association between FGF23 and bioimpedance-measured volume overload in hemodialysis patients.

Patients and Methods: Bioimpedance analysis was performed on 43 hemodialysis patients at the end of hemodialysis to evaluate the remaining volume overload and serum FGF23 was measured before hemodialysis.

Results: The results indicated no significant correlation between mean serum FGF23 levels and volume overload in hemodialysis patients ($P=0.824$).

Conclusion: Although this study did not show any association between volume overload and FGF23, further studies are needed to define the role of FGF23 as a volume overload marker.

Implication for health policy/practice/research/medical education:

In this study, we aimed to assess the correlation between FGF-23 and overload in hemodialysis patients. We found fibroblast growth factor 23 (FGF23) has not any significant association with overload in hemodialysis patients.

Please cite this paper as: Minoo F, Alamdari A, Karimi H. Does fibroblast growth factor 23 correlates with volume status in hemodialysis patients?. J Nephrologist. 2019;8(4):e35. DOI: 10.15171/jnp.2019.35.

Introduction

End-stage kidney disease can occur due to different etiologies such as diabetes mellitus and hypertension and even specific conditions like microalbuminuria, obesity or glomerulonephritis (1). Cardiovascular disease and stroke are the principal causes of morbidity and mortality in hemodialysis patients (2). Studies have indicated that hypertension is the major cause of cardiovascular and cerebrovascular adverse events in hemodialysis patients which, in turn, has been linked to chronic volume overload in these patients (3,4). Therefore, fluid management is an essential component of successful dialysis prescription (5). Ideally, fluid removal during dialysis treatment should result in dry weight (DW) which is the lowest weight a patient can tolerate without developing symptoms and hypotension (2,6). Traditionally, DW is determined clinically based on patient's blood pressure, presence

of edema, and patient tolerance to the chosen weight (7). However, clinical assessment lacks sensitivity and specificity (8), thus necessitating more objective tools to determine DW (2). Although several objective methods such as biochemical markers (2), vena cava diameter (9), lung sonography (10), and blood volume monitoring (11) have been used for DW assessment, however, there is no single standard method. Further, cost and complexity also limit using these methods (2).

Among various methods, bioimpedance analysis (BIA) is non-invasive, low cost, and accurate tool for determining DW which is increasingly being used in many dialysis centers (5). It is performed by nursing staff at bedside within minutes. Total body water (TBW), extracellular water (ECW), and intracellular water (ICW) are determined via this tool. This method, combined with clinical evaluation, can provide valuable information

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about fluid management in hemodialysis patients (12,13).

At present, biochemical markers such as atrial natriuretic peptide (ANP) and brain natriuretic marker (BNP) have been studied as an overload marker, but the results were contradictory (14-16). Recently, it has been proposed that fibroblast growth factor 23 (FGF23), which is the most powerful predictor of cardiovascular mortality, increases following hypervolemia (17). FGF23 is a phosphaturic hormone produced by osteocytes and increases in early stages of chronic kidney disease (CKD) to maintain phosphate balance (18,19).

Objectives

The aim of this study was to evaluate the relationship between the remaining volume overload after hemodialysis and mean serum FGF23.

Patients and Methods

Patients

This prospective cross-sectional study was conducted at the dialysis center of the Imam Khomeini hospital complex, affiliated to Tehran University of Medical Sciences, Tehran, Iran. Forty-three patients, who were on stable hemodialysis treatment thrice a week for at least 3 months and were 18-80 years of age, enrolled in this study. Patients were excluded from the study if they had psychiatric disorders, pregnancy and lactation, hypoalbuminemia, and local extremity edema, or if they refused to participate. In addition, patients with cardiac pacemakers, implanted electrical pumps, and implanted hip or knee joint were excluded from the study. All participants were provided written informed consent forms before enrollment. Demographic data and patients' laboratory data were collected from the medical records. All patients were dialyzed with high flux dialyzers appropriate for body surface area. Blood pressure measurements were obtained by dialysis unit staff in standard conditions before and after hemodialysis.

Bioimpedance analysis (InBody S10) was performed at the end of hemodialysis to evaluate the remaining volume overload while patients were in the supine position with electrodes placed on their wrists and ankles.

Venous blood samples were taken for FGF23 measurement from all of the patients at the start of dialysis session, after which plasma samples were frozen at -70°C until analysis. Serum FGF-23 levels were measured by ELISA kits (from BIOTECH company made in China, pg/mL).

Ethical issues

Study-related data was delivered to subjects and informed consent was provided before the study. The research followed the Tenets of the Declaration of Helsinki. The

Ethics Committee of Tehran University Medical Sciences approved this study (ethical cod # 29580, grant number # 940314629580). This study was conducted as the thesis of Hamed Karimi in the department of internal medicine of Tehran University Medical Sciences.

Statistical analysis

Data were analyzed using SPSS version 16 software for descriptive statistics. Student's t-test and chi-square test were used for continuous and categorical variables, respectively. The correlation was studied by assessing Pearson's coefficient of correlation. A multivariate logistic regression model was employed to investigate the association between FGF23 and other variables. Statistical significance (P value) was set at below the 5% level.

Results

A total of 43 adult patients with the mean age of 56.72 ± 11.58 years were included in this study. The mean systolic and diastolic blood pressure after hemodialysis was 130.58 ± 21.4 mm Hg and 77.15 ± 8.74 mm Hg, respectively. The average fluid overload of patients determined by BIA was 0.560 ± 0.93 liter at the end of dialysis (Figure 1). The mean serum FGF23 level of patients was 1010.92 ± 463.84 pg/mL. Although there was a negative correlation between FGF23 levels and fluid overload, it was not significant ($P=0.824$). No significant correlation was found between FGF23 levels and age, gender, and high blood pressure. In addition, there was no difference between males and females in terms of dialysis time, blood pressure, fluid overload, FGF23, and Kt/V. Additionally, Age, gender, blood pressure, and Kt/V had no effects on the correlation between FGF23 and fluid overload according to co-variance analysis (Table 1).

Discussion

FGF23 has recently been recognized as a volume overload

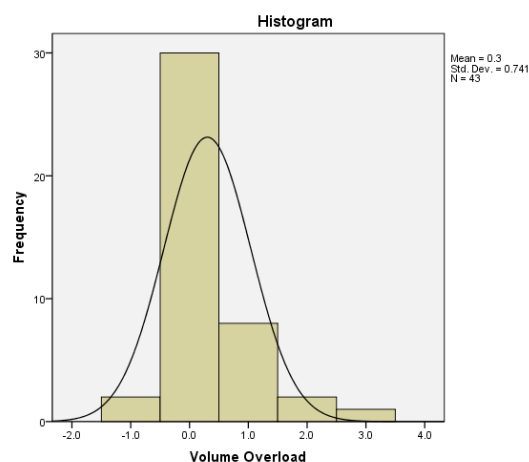


Figure 1. Frequency of bioimpedance measured volume overload in hemodialysis patients.

marker in hemodialysis population (17-20). However, our study did not find any significant relationship between FGF23 levels and volume overload.

FGF23 is a circulating, bone-derived factor. Its serum level rises in parallel with diminishing renal function and plays a critical role in the regulation of phosphorus and vitamin D metabolism (18). Serum levels of FGF23 can reach nearly 1000-fold above the normal range in CKD stage 4-5. This supra-physiologic levels of FGF23 can result in faster progression of moderate CKD and increased mortality in end-stage renal disease patients (21). Accelerated atherosclerosis and endothelial dysfunction secondary to increased FGF23 levels is the possible explanation for increased mortality in this population (22).

Several studies have concluded that FGF23 induces left ventricular hypertrophy (LVH) and is associated with cardiovascular disease in these patients (23-25). In addition, few studies have recently reported a definite relationship between hypervolemia and plasma FGF23 in hemodialysis patients (17,20). Recently, Unver et al (17) conducted a prospective study on 97 hemodialysis patients. They considered inter-dialytic volume overload (IVO) using pre-and post-dialysis weight as hypervolemia. They found a significant relationship with FGF23. Unver et al not only showed a correlation between hypervolemia and LVH in line with previous studies but also found that FGF23 concentration correlated with hypervolemia and LVH. According to their results, volume control and emitting overload can curb elevation of FGF23 levels and decrease ventricular hypertrophy.

Humalda et al (20) conducted an observational study on 109 prevalent hemodialysis patients. They investigated the relationship between FGF23, ultrafiltration volume (UFV), and copeptin. The results of this study suggested that FGF23 concentration strongly correlated with both UFV (ultra-filtrated volume; as functional markers of volume overload) and with biochemical markers of volume overload (copeptin). Indeed, UFV was identified as an independent determinant of FGF23 levels in hemodialysis patients. Further, they observed no relationship between FGF23 and structural markers of volume overload such as left ventricular mass index. The authors concluded that volume control could regulate mineral homeostasis.

In this study, we considered the relationship between FGF23 concentration and the remaining volume overload which was assessed by BIA at the end of dialysis. However, we did not find any correlation between FGF-23 and post-dialysis remained overload. The major limitations of our work included the small number of enrolled patients. In addition, mean volume overload was small (0.560 ± 0.93 L). In other words, our patients had low remained volume overload after hemodialysis. Probably, it has been the main

Table 1. Correlation between FGF23 and volume overload and other variables

| Variables | | FGF 23 | |
|-----------------|-------------------------|-------------------------|--------|
| Volume overload | Correlation coefficient | -0.035 | |
| | P value | 0.824 | |
| Dry weight | Correlation coefficient | -0.350 | |
| | P value | 0.804 | |
| Volume overload | Men | Correlation coefficient | -0.077 |
| | | P value | 0.703 |
| | Women | Correlation coefficient | 0.060 |
| | | P value | 0.826 |
| Volume overload | Yes | Correlation coefficient | 0.093 |
| | | P value | 0.658 |
| | No | Correlation coefficient | -0.183 |
| | | P value | 0.466 |
| Volume overload | Age≤50 years | Correlation coefficient | 0.120 |
| | | P value | 0.725 |
| | Age>50 years | Correlation coefficient | -0.101 |
| | | P value | 0.583 |

reason why we did not find any significant correlation as with previous studies.

Conclusion

Although we could not show any association between FGF23 and volume overload, further clinical studies in our center are necessary to clarify whether FGF23 is as an indicator of volume overload in hemodialysis patients or not.

Limitations of study

This was a pilot study requiring further investigations by other studies.

Authors' contribution

FSM and AA; idea and writing the manuscript. FSM; literature review. AA; critique and thought. HK; data gathering. FSM; statistical analysis. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

Funding/Support

This study was supported by Tehran University of Medical

Sciences (grant number 940314629580). The funding agency did not play any role in the planning, conducting, and reporting or decision-making to submit the paper for publication.

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