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STUDY THE CORRELATION BETWEEN MATRIX GLA PROTEIN, FIBROBLAST GROWTH FACTOR-23 AND BONE METABOLIC MARKERS IN HEMODIALYSIS PATIENTS

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Abstract

Introduction: Vitamin K-dependent matrix Gla protein (MGP) acts as a calcification inhibitor in vitro and in vivo. Chronic kidney disease (CKD) patients have an extremely high risk for developing vascular disease as most CKD patient's exhibit vitamin K intake lower than recommended levels. Since MGP is an extracellular protein responsible for inhibiting mineralization and it inhibits osteoblast mineralization and bone formation by regulating the deposition of bone matrix, therefore, the proposed research aims to the evaluation of the relationship between MGP and bone markers (parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF23) in hemodialysis patients and healthy individuals.

Methods: In this research, 54 hemodialysis (HD) patients and 30 age-matched healthy subjects were enrolled. Vitamin D, vitamin K, MGP, and FGF-23 were determined by ELISA kit and compared with control subjects. All values were expressed as mean ± standard deviation (SD), and the Shapiro-Wilk test was performed to check data distribution. Kruskal Wallis was done for comparing groups.

Results: According to the results the vitamin K level (0.47±0.16 ng/ml versus 1.25±0.28 ng/ml, P<0.0001) was significantly lower and total MGP (257.20±40.65 ng/ml versus 153.93±39.89 ng/ml, P<0.0001), i-PTH (461.57±336.29 pg/ml versus 33.23±12.05 pg/ml, P<0.0001) and FGF-23 (9077.09±2116.03 RU/ml versus 95.93±37.86 RU/ml, P<0.0001) were significantly higher in CKD patients. However, there is no significant difference in the level of vitamin D between the studied groups.

Conclusion: Plasma total MGP increased progressively in CKD patients and was associated with the severity of vascular calcification. Also, since total MGP has a significant positive association with FGF-23, therefore, controlling the level of MGP may have a clinical improvement on dysregulated FGF-23.

Keywords: Matrix Gla protein, Fat-soluble vitamins, Parathyroid hormone, Fibroblast growth factor-23

1. Introduction

Kidney is a common target of environmental and drug toxicity which is a major clinical problem. Early detection of kidney injury is essential in the prevention of kidney disease [1, 2]. Currently,

evaluations of kidney injury are primarily based on measurements of serum creatinine (Scr) and urea, and routine urinalysis which are not region-specific and are significantly altered only after substantial kidney injury has occurred [3, 4]. Matrix Gla protein (MGP) is primarily secreted by chondrocytes and smooth vascular muscle cells, and acts as a potent local inhibitor of vascular calcification [5]. However, to be active, MGP must be phosphorylated and carboxylated; such carboxylation is vitamin K dependent, and phosphorylation is necessary for the secretion of MGP [6]. Vitamin K is a co-factor for the enzyme γ-glutamyl carboxylase that converts glutamic acid (Glu) into γ-carboxyglutamic acid (Gla) residues [7]. This conversion is critical for the activation of MGP. Additionally, three serine residues need phosphorylation. The exact role of phosphorylation of MGP is still not known, but it is believed to play an important role in the regulation of the secretion of the protein. Upon activation, MGP binds calcium salts with high affinity, thereby affecting the calcification processes. The importance of MGP in the inhibition of calcification is illustrated by studies of MGP knockout mice, who die within two months after birth due to severe arterial calcification and rupture of the aorta [5]. Chronic kidney disease (CKD) patients have an extremely high risk of developing vascular disease [8-10]. Additionally, vitamin K deficiency is frequently encountered in CKD, which is associated with increased plasma levels of dephosphorylated uncarboxylated MGP (dp-ucMGP) plasma levels followed by vascular calcification [11-13]. Notably, 72% of patients with CKD exhibit vitamin K intake lower than recommended levels [14, 15].

Disorders of bone mineral metabolism and regulatory hormones such as parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF23) seen in CKD are thought to play a key role in excess morbidity and mortality [16]. Renal osteodystrophy is a feature of CKD with increasing prevalence as CKD progresses [17]. PTH is the most frequently used biomarker to estimate bone turnover. The clinical application of PTH as a biomarker is attractive because it is readily available, routinely used, and importantly modifiable [18, 19]. FGF23 is an endocrine hormone expressed in the bone that plays an important role in the maintenance of phosphate and calcium balance by binding to FGF receptors expressed in the kidney [20, 21]. It also regulates the secretion of PTH to ensure a normal level of serum calcium. In patients with CKD, plasma FGF23 levels increase in response to worsening kidney function. Elevated plasma FGF23 is an independent risk factor for CKD progression, anemia, and reduced hemoglobin (Hb); it is also associated with cardiovascular events [22, 23]. Since MGP is an extracellular protein responsible for inhibiting mineralization and inhibits osteoblast mineralization and bone formation by regulating the deposition of bone matrix, therefore, the proposed research aims to the evaluation of the relationship between MGP and bone markers in hemodialysis patients and healthy individuals. For this purpose, hemodialysis patients were investigated as a subject group and healthy people as the control group. Then, the level of biomarkers such as calcium (Ca), phosphate, vitamin D, vitamin K, intact i-PTH, FGF23, and total MGP was evaluated in hemodialysis patients in comparison with the healthy group.

2. Experimental

2.1. Study population

This cross-sectional study enrolled Iranian 54 hemodialysis (HD) patients, 30–60 years of age, who were undergoing regular HD treatment, three sessions per week (referred to the Imam Reza Hospital, Tabriz); concurrently, age-matched 30 healthy subjects were enrolled. Subjects with a history of neoplastic disease, with active infections, who were receiving anti-vitamin K therapy, or who had undergone an organ transplant were excluded from this study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki (as revised in Brazil in 2013). Informed consent was obtained from all individual participants included in this study. Serum samples from patients were obtained immediately before the first HD session of the week. All serum samples were stored at -80 °C within 30 min of sampling.

2.2. Clinical and biochemical evaluation

Demographic data including age, body weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were prepared from information on patients and control subjects. Serum creatinine, fasting blood sugar (FBS), i-PTH (Abcam, ab230931), vitamin D, as well as plasma levels of vitamins K (MyBioSource, MBS3803335), total MGP (MyBioSource, MBS024150) and FGF-23 (Abcam, ab267652), were determined for all subjects by ELISA kit. Also, phosphate (Abcam, ab65622) and Ca (Abcam, ab272527) were determined by the colorimetric method.

2.3. Statistical analysis

Data were expressed as mean ± standard deviation (for parameters normally distributed). The results of this study were analyzed using SPSS 26 statistical software using Chi-square (χ^2), logistic regression, t-test, and analysis of variance (ANOVA) methods with a significance level of $P < 0.05$.

3. Results and Discussion

Clinical parameters of HD patients and control subjects are presented in Table 1. Based on the results, there is no significant difference between age, SBP (P=0.091), DBP (P=0.118), Ca (P=0.129), and FBS parameters (P=0.110); however, there is a significant difference in creatinine (P<0.0001) and urea (P<0.0001) so that these parameters are significantly higher in CKD patients in compared to control subjects.

Table 1. Biochemical parameters in control and patient groups

Parameter	Control	CKD Patients	P-value
Age (Years)	55.63±6.94	60.22±14.04	0.097
Weight (kg)	79.83±11.30	70.74±15.28	0.006
SBP (mmHg)	122.31±19.10	117.33±7.18	0.091
DBP (mmHg)	67.50±7.04	71.30±11.94	0.118
Ca (mg/dl)	9.30±0.68	9.04±0.79	0.129
Phosphate (mg/dl)	4.19±0.87	5.32±1.97	0.001
FBS (mg/l)	94.53±6.04	98.83±36.09	0.110
Creatinine (mg/l)	0.92±0.14	8.64±2.75	0.0001
Urea (µg/l)	15.13±4.43	128.72±46.97	0.0001

SBP: Systolic blood pressure, DBP: Diastolic blood pressure; FBS: Fasting blood sugar

Also, vitamin K level (Fig. 1a, P<0.0001) is significantly lower and total MGP (Fig. 1b, P<0.0001), i-PTH (Fig. 1c, P<0.0001) and FGF-23 (Fig. 1d, P<0.0001) were significantly higher in CKD patient, however, there is no significant difference in the level of vitamin D between the studied groups (Fig. 1e, P=0.4392). The correlation of MGP with other parameters is presented in Table 2 and based on the results total MGP has a significant correlation with FGF-23, however, there is a negative correlation between total MGP and time of dialysis.

Table 2. Correlation of MGP with other biochemical factors in CKD patients

Variables	CDK		Control	
	P-value	P-value	P-value	R-value
Age (years)	0.094	0.230	0.974	0.006
Ca (mg/dl)	0.450	0.105	0.549	0.114
Phosphate (mg/dl)	0.592	0.075	0.831	-0.041
Vitamin D (ng/ml)	0.500	0.094	0.255	-0.214
Vitamin K (ng/ml)	0.893	0.019	0.470	-0.137
i-PTH (pg/ml)	0.627	0.068	0.467	-0.138
FGF-23 (RU/ml)	0.010	0.348**	0.209	0.236
Urea (mg/dl)	0.686	0.056	0.624	-0.093
Creatinine (mg/dl)	0.959	0.007	0.523	-0.121
FBS (mg/dl)	0.206	0.175	0.643	0.088
me of dialysis (month)	0.020	0.315*	-	-

The obtained results in our research show that vitamin K is significantly lower and total MGP, i-PTH, and FGF-23 were significantly higher in CKD patients. MGP can be considered as the usherette that removes free calcium from circulation and leads it to the bones.

Vitamin K-mediated carboxylation of MGP is an essential step in the activation of MGP as a natural inhibitor of vascular calcification. CKD patients suffer from vitamin K deficiency and are prone to develop vascular calcification, therefore, it could be expected that MGP is produced in the inactive form. Schurgers et al., in 2010 reported that plasma dp-ucMGP increased progressively in a CKD setting and was associated with the severity of aortic calcification [24]. However, vitamin K therapy has been shown to significantly decrease the levels of dp-ucMGP in HD patients [11, 24-27]. These results suggest that dp-ucMGP could reflect a person's vitamin K status at the vascular level. Mizuiri et al., in 2019 evaluated the associations of serum total MGP, plasma vitamin K1, and plasma vitamin K2 with cardiovascular disease (CVD) in maintenance hemodialysis (MHD) patients. Their results show that the end-stage renal disease on hemodialysis has vitamin K deficiency. Also, total MGP was significantly higher in MHD patients and it was associated with the presence of CVD in MHD patients [28]. Moreover, Thamratnopkoon et al., in 2017 reported that plasma dp-ucMGP levels increase according to the severity of CKD so that it could be utilized as an early marker for vascular calcification in CKD patients [29].

FGF-23 concentrations increase early in the course of kidney disease. With the progression of the disease, FGF-23 concentrations increase often 100 times above the normal range [28]. The role of FGF-23 in kidney disease progression is largely unknown. A recent study of 177 nondiabetic patients with mild-to-moderate CKD found that higher FGF-23 concentrations, but not serum calcium, phosphorus, or iPTH, were independently associated with more rapid progression of CKD [31]. FGF23 is a bone-derived endocrine factor that regulates phosphate and vitamin D homeostasis via the fibroblast growth factor receptors (FGFRs)/αKlotho complex [30]. These receptors are expressed in the kidney and the parathyroid gland. The FGF23-mediated mechanism interacts with the classical calcium/phosphate regulating processes driven by parathyroid hormone (PTH) and calcitriol (active vitamin D) [32]. FGF-23 increases urinary phosphorus excretion by decreasing phosphorus reabsorption in the proximal tubule and inhibits 1,25-dihydroxy vitamin D ($1,25(OH)_2D$) synthesis, resulting in decreased dietary phosphorus absorption from the gastrointestinal tract and causes bone disorders [33]. FGF23-associated bone diseases refer to a group of conditions in which the function and/or amount of FGF23 is abnormal so that high FGF23 levels were reported in patients with autosomal dominant hypophosphatemic rickets [34], X-linked hypophosphatemia [33], oncogenic osteomalacia [36] and fibrous dysplasia [37]. In this research, the relationship between MGP and bone markers in HD patients shows that MGP has a significant positive relation with FGF-23. The positive relation between FGF-23 and MGP was previously reported by other groups which may be related to the disturbance of mineral balance (Ca and phosphate) and vitamin K in HD patients [12, 38]. All in all, whereas in CKD patients a significant positive relationship exists between MGP and FGF-23; it could be concluded that controlling total MGP could be an effective method for the regulation of FGF-23 in CKD patients.

4. Conclusion

This research aims to evaluate the relationship between MGP and bone markers in hemodialysis patients and healthy individuals. The obtained results show that MGP, i-PTH, and FGF-23 were significantly higher in CKD patients and MGP has a significant positive correlation with FGF-23. Therefore, controlling the level of MGP in CKD patients may have a clinical improvement in the regulation of FGF-23 and vascular calcification.

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