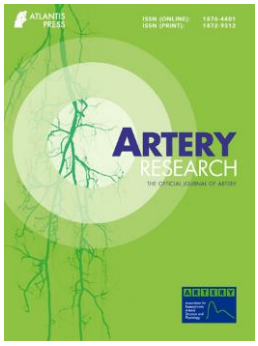

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SHORT COMMUNICATION

Correlation between fetuin-A and matrix Gla protein levels in human serum

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KEYWORDS
Fetuin-A;
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Osteoprotegerin;
Osteopontin;
Vascular calcification

Abstract *Background:* Vascular calcification is frequently found in hemodialysis patients. Fetuin-A is a well-characterized circulating inhibitor of calcification. Several other bone-associated proteins, such as the matrix Gla protein (MGP), osteoprotegerin (OPG), and osteopontin (OPN), are also presumed to inhibit vascular calcification. However, little is known about the relationship between fetuin-A and other calcification inhibitors. In this study, we examined the association of fetuin-A with MGP, OPG, and OPN.
Methods: We consecutively enrolled 92 subjects who were suspected to have coronary artery diseases. Serum levels of fetuin-A, MGP, OPG, and OPN were measured using ELISA.
Results: Fetuin-A level was significantly correlated with MGP level ($p = 0.242$, $p = 0.021$). On the other hand, the fetuin-A level was not correlated with OPG ($p = 0.048$, $p = 0.649$) and OPN ($p = 0.007$, $p = 0.948$) levels.
Conclusions: We found the positive correlation between fetuin-A and MGP levels in human serum. Fetuin-A may collaborate with MGP to inhibit vascular calcification.

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Background

Vascular calcification has been considered to be a passive, degenerative and end-stage vascular disease. However, recent studies suggest that vascular calcification is a process actively regulated by bone-associated proteins. Vascular calcification is frequently found in hemodialysis patients; this condition may be attributed to the deficiency of calcification inhibitors in their serum. Fetuin-A, a circulating glycoprotein secreted by the liver, is a potential candidate.[1] Recent reports have shown that low fetuin-A levels are associated with all-cause and cardiovascular mortality in hemodialysis patients, possibly through the regulation of vascular calcification. We recently demonstrated that fetuin-A levels were inversely associated with coronary artery calcification[2] and atherosclerotic calcified plaque[3] in patients without renal dysfunction; this suggested that fetuin-A can function as a calcification inhibitor regardless of renal function. Several other bone-associated proteins, such as the matrix Gla protein (MGP), osteoprotegerin (OPG), and osteopontin (OPN), are also presumed to inhibit vascular calcification.[4]

Aims

Considering that all these factors occur in bloodstream, it is possible that fetuin-A can coordinate with these inhibitors to regulate vascular calcification. However, little is known about the relationship between fetuin-A and other calcification inhibitors. In this study, we examined the association of fetuin-A with MGP, OPG, and OPN.

Methods

The study participants have previously described.[2] In brief, we consecutively enrolled 92 patients (74 men and 18 women) who were suspected to have coronary artery diseases. Patients with acute coronary syndrome, diabetes (a fasting glucose level $\geq$126 mg/dl (7.0 mmol/l) or treatment with insulin or oral agents) and overt renal dysfunction (a creatinine level $>$1.2 mg/dl (106 μmol/l)) were excluded. Fasting serum samples were collected and stored at $-80\ ^{\circ}C$ until use. Serum levels of fetuin-A were measured using enzyme-linked immunosorbent assay (ELISA) kits (BioVender Laboratory Medicine, Modrice, Czech Republic)[2,3]. The serum level of MGP was determined using a competitive ELISA kits (VitaK Inc., Maastricht, The Netherlands) as previously reported.[5] The serum levels of OPG and OPN were measured using ELISA kits from Cosmo Bio (Tokyo, Japan) and Immuno-Biological Laboratories (Shizuoka, Japan), respectively. We used a Spearman's rank correlation test to study the association of fetuin-A with MGP, OPG, and OPN.

Results

Fetuin-A level was 271.9 [226.1—299.7] (median [interqurtile]) ranged from 139.5 to 504.9 μg/ml. As previously reported, the fetuin-A levels were significantly lower in the presence of coronary artery calcification.[2] The MGP, OPG, and OPN levels were 112.3 [94.2—124.0] (ranged from 57.8 to 170.2) U/L, 1.02 [0.78—1.27] (ranged from 0.29 to 2.24) ng/ml, and 26.8 [20.3—33.9] (ranged from 1.1 to 93.7) ng/ml, respectively. Fetuin-A level was significantly correlated with MGP level ($\rho = 0.242$, $p = 0.021$)(Fig. 1). On the other hand, the fetuin-A level was not correlated with OPG ($\rho = 0.048$, $p = 0.649$) and OPN ($\rho = 0.007$, $p = 0.948$) levels.

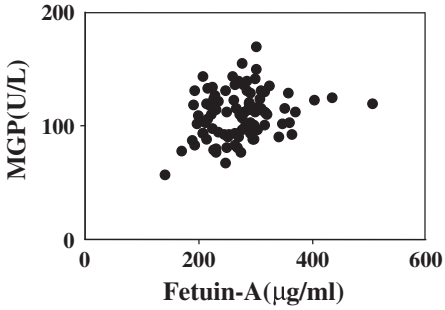

Figure 1 Correlation between serum levels of fetuin-A and matrix Gla protein (MGP).

Conclusion

In this study, we first demonstrated the positive correlation between fetuin-A and MGP levels in human serum. Because MGP is known to be a calcification inhibitor, it is possible that fetuin-A collaborates with MGP to inhibit vascular calcification. A study by Price et al. has discussed this collaboration in great detail. They discovered a novel protein—mineral complex, called the fetuin—mineral complex (FMC), in rat serum.[6] Interestingly, the FMC contains calcium, phosphate, fetuin-A, and MGP.[6] The FMC is also called the calciprotein particles (CPPs).[4] Although a recent study by Matsui et al. confirmed the existence of the FMC or CPPs, precise analysis of structure of FMC including MGP is necessary.[7] However, these studies observed the formation of FMC under limited conditions such as high-dose treatment with etidronate that inhibits normal bone mineralization[6] or renal failure.[7] Further, FMC has not yet been reported in human serum. Therefore, further studies must be performed to confirm the existence of FMC and to examine the association of such a complex with the extent of vascular calcification. Analyzing the constituents of the FMC may result in the detection of a stronger correlation between fetuin-A and MGP. In addition to issues described above, there are important limitations in this study. First, the number of subjects was small. Farther, very recent report has suggested the difference between two widely-used commercial fetuin-A ELISA kits (BioVender Laboratory Medicine, Modrice, Czech Republic; Epitope Diagnostics Inc., San Diego, US).[8] It seems to depend on fetuin-A glycosylation level.[8] The standardization of fetuin-A measurement is urgent need. In conclusion, we found the positive association between fetuin-A and MGP. However, further studies are needed to confirm our observations in larger cohort, considering the significance of FMC and the different assay systems for fetuin-A.

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