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Relationship Between Serum Fetuin-A Levels and Carotid Intima-media Thickness in Turkish Patients with Mild to Moderate Psoriasis. A Case-control Study

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ABSTRACT Previous studies have associated severe psoriasis and psoriatic arthritis with an increased risk of atherosclerosis. However, the association between patients with mild-to-moderate plaque-type psoriasis and atherosclerosis has yet to be studied in depth. This study investigates a) possible correlations between carotid intima-media thickness (CIMT) and serum fetuin-A levels in patients with mild-to-moderate psoriasis and b) correlations between psoriasis severity index (PASI) and fetuin-A levels. The latter correlation was recently reported to be important for wound healing and vascular calcification. In this prospective study, a total of 70 patients with mild-to-moderate psoriasis and 66 control participants were included. PASI, CIMT, and serum fetuin-A levels were examined in all patients. Although the difference in fetuin-A values was not statistically significant between patients with mild-to-moderate plaque-type psoriasis and control groups (P=0.401), the CIMT levels in the psoriasis group were significantly higher than the control group (P=0.002). There were no correlations among fetuin-A levels, CIMT, and PASI. This study establishes an association between mild to moderate psoriasis and atherosclerosis. This study also concludes that, similarly to patients with severe psoriasis, CIMT levels are a better indicator of cardiovascular risk than serum fetuin-A levels in patients diagnosed with mild-to-moderate plaque-type psoriasis.

KEY WORDS: cardiovascular disease, fetuin-A, psoriasis, carotid intima-media thickness, psoriasis area and severity index

INTRODUCTION

Psoriasis is a chronic recurrent inflammatory skin disease affecting 2-3% of the world's population (1). This condition is a systemic immunological disease that is mainly driven by activated T-helper 1 (Th1) and Th17 lymphocytes. Atherosclerosis is also characterized by Th1-related inflammation, both systemically and locally in arterial walls and atherosclerotic plaques (2). It appears that the inflammatory mechanisms resulting in psoriasis and atherosclerosis overlap significantly.

When assessing coronary artery disease and generalized atherosclerosis, carotid artery intima-media thickness (CIMT) detected by high-resolution B-mode ultrasound is a good indicator of an increased risk of subclinical atherosclerosis (3-7). CIMT is determined by the distances between the vascular intima and media composed of endothelium, smooth muscle, and connective tissue (7). The area between the endothelial and smooth muscle layers is also the area of lipid deposition and plaque formation in patients with atherosclerosis (8).

Fetuin-A is a serum glycoprotein that is synthesized mainly by hepatocytes. A consensus has not been reached regarding how fetuin-A affects the cardiovascular system, including any possible contributions to atherosclerosis. Mori *et al*. hypothesize that fetuin-A contributes to vascular disease in two distinct ways: by increasing insulin resistance and dyslipidemia and by reducing ectopic calcification (9). These authors also report that varied results were obtained from different patients depending on the severity of disease (9). To our knowledge, there is only one report on the status of fetuin-A in patients with psoriasis (10).

Furthermore, there are reports on fetuin-A interacting with transforming growth factor (TGF)-β and epidermal growth factor (EGF), which play an important role in the pathogenesis of psoriasis (9). In this study we explored a) possible associations between fetuin-A and the severity of psoriasis skin lesions and b) correlations between fetuin-A and subclinical atherosclerosis in mild to moderate psoriasis patients (11).

PATIENTS AND METHODS

Patients and controls

This was a prospective cross-sectional case-controlled study of 70 patients who attended our dermatology clinic and who were diagnosed with mild-to-moderate plaque-type psoriasis between April 2012 and March 2014. A control group of 66 healthy volunteers, matched for age, gender, and body mass index were recruited.

Age, sex, body mass index, blood pressure, and CIMT were measured and recorded for all of the patients and volunteers. Psoriasis area and severity index (PASI) was calculated in patients with psoriasis. The following parameters were assessed in all patients and healthy volunteers at the time of clinical evaluation: complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (Rf), serum urea, creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum glucose, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (after an overnight fast).

Patients with any of the following criteria that could affect their cardiovascular status were excluded from the study: history of smoking; hypertension (systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg); body mass index >30 kg/m^2, coronary artery disease, dyslipidemia (total cholesterol and triglyceride levels in fasting plasma >200 mg/dL), diabetes mellitus (fasting glucose levels >110 mg/dL), chronic renal failure, thyroid disease, rheumatic disease, previous systemic treatment of cardiovascular disease, pregnancy, and a PASI ≥12 (12).

The study was approved by the Ethics Committee of the University of Sifa and was conducted according to the ethical principles of the Declaration of Helsinki. All patients provided informed consent before participating.

Psoriasis areas and severity index score

The psoriasis areas and severity index (PASI) score was utilized as an objective method to score psoriasis severity, induration, erythema, and scaling on body surfaces of each patient (13). The PASI score was calculated in all patients as described by Fredriksson and Pettersson (14). A PASI score below 7 was defined as mild, between 7 and 12 as moderate, and above 12 as severe disease (12).

Carotid intima-media thicknesses

The intima-media thicknesses (IMT) of the common carotid artery (CCA) was obtained using a real-time ultrasound scanner (Siemens, Acuson Antares, Germany) with a 7.5 MHz, 50 mm linear transducer. CIMT measurements were obtained while the patient was lying in the supine position with their neck rotated in the opposite direction of the examining physician. CCA images were obtained to measure IMT using three different-angled views for each vessel. Initially, a transverse scan of the CCA was performed on the longest extension possible, from the base of the neck to the carotid bulb. At least three IMT points were measured in the near and far walls of the most thickened area of each vessel. Lateral wall measurements were also taken when both thickening was evident and accurate images were possible. Subsequently, two longitudinal view scans of the vessel were taken in the posterolateral (PL) position, with the transducer positioned parallel to the posterior border of the sternocleidomastoid muscle, and in the anterolateral (AL) position, with the transducer positioned parallel to the anterior border of the sternocleidomastoid muscle. At least three IMT measurements were obtained for each near and far wall of each position. Optimal B-mode settings of gain, depth, focal zone placement, and compression were individually adjusted for each vessel to enhance the arterial wall structures and image quality. IMT was measured manually using electronic calipers, as previously described by Sidhu and Desai (15). The maximum IMT value was selected for each angle. For further data analyses, the maximum

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value of either the right or left carotid artery was also measured. An IMT of greater than 1.0 mm was considered to be abnormal (16).

Biochemical parameters

For sample preparation, 8 mL of venous blood was collected in serum tubes (Vacuette-Z Serum Sep Clot Activator, Greiner bio-one GmbH, Kremsmünster, Austria) and centrifuged at 2000 g after clotting for 10 min at room temperature. Serum samples were stored at -80°C until time of the assay. Fetuin-A was measured with a human enzyme-linked immunosorbent assay (ELISA) kit (analytical sensitivity: 0.37 ng/mL) (Alfha-2-Heremans Schid Glycoprotein, Uscn Life Science Inc. Wuhan, China).

Statistical analyses

The normality of data was analyzed using the Kolmogorov-Smirnov Test. All numerical variables with a normal distribution were expressed as a mean ± standard deviation, while data that were not determined to be normally distributed were expressed as median with interquartile ranges (IR). Continuous variables were compared using Student's *t*-test or the Mann-Whitney U test. Correlations among CIMT, PASI, and fetuin-A were determined using Pearson's partial correlation calculation. *P* values of less than 0.05 were considered statistically significant. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20 (SPSS, Chicago, IL).

RESULTS

The demographics of patients and controls, including age, sex, and body mass index, were similar. Total cholesterol, LDL, HDL, triglyceride, ESR, CRP, serum glucose, AST, urea, creatinine, and uric acid levels were not statistically significant between psoriasis and control groups. Rf and ALT levels were found to be significantly higher in the psoriasis group (*P*=0.021, *P*=0.018, respectively).

Median CIMT levels were significantly higher in patients with mild-to-moderate psoriasis compared to controls (patients with psoriasis: 0.80 (0.36), controls: 0.55 (0.24); *P*=0.002) (Figure 1). The difference in mean serum concentration of fetuin-A was not statistically significantly between groups (patients with psoriasis: 4.599±3.429 ng/mL, controls: 3.677±2.616 ng/mL; *P*=0.401) (Figure 2). Demographic information, laboratory findings, CIMT levels, and PASI scores of patients with psoriasis and controls are presented in Table 1. There were no correlations found among the serum fetuin-A levels, CIMT levels, and PASI scores. Correlations of fetuin-A with CIMT, PASI, glucose, and LDL for all patients and controls are presented in Table 2.

DISCUSSION

Although psoriasis was previously described as a disease that affects only the skin and joints, many recent publications have described it as a systemic disease that is characterized by chronic inflammation. Autoimmune chronic inflammatory conditions, such as rheumatoid arthritis, systemic lupus erythematosus (SLE), and psoriasis, are associated with increased cardiovascular risk (17). In previous studies, severe psoriasis or psoriatic arthritis have been reported to be associated with an increased risk of atherosclerosis (18,19). However, the association between pa-

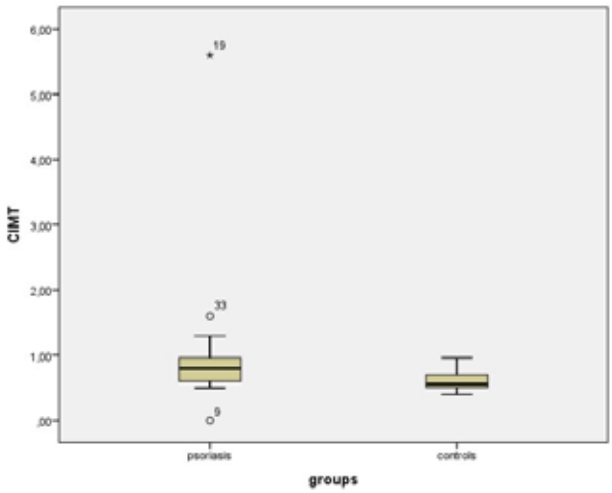

Figure 1. Box-plot graphics of carotid intima-media thickness (CIMT) levels in patients with psoriasis and controls.

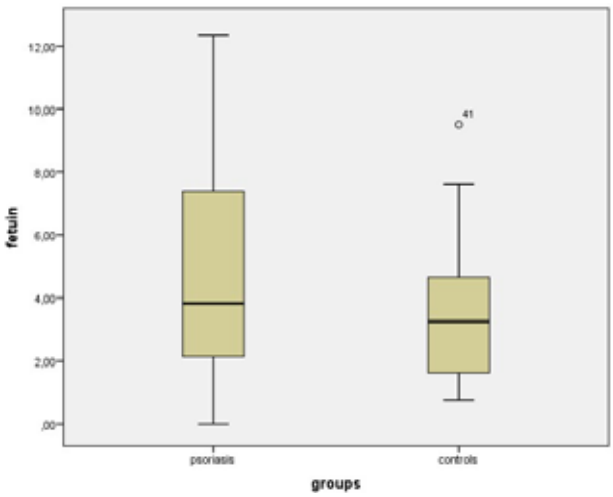

Figure 2. Box-plot graphics of fetuin-A levels in patients with psoriasis and controls.

Table 1. Demographics, laboratory findings, carotid intima-media thickness (CIMT) levels, and psoriasis severity index (PASI) scores of 70 patients with mild-to-moderate psoriasis and 66 matched controls*

Variable	Patients (n=70) Mean ± SD or median (IR)	Controls (n = 66) Mean ± SD or median (IR)	*P*
Age, years	34.03±10.29	32.33±9.25	0.617
Men/women	36/34	33/33	0.934
Body mass index, kg/m^2	25.45±4.53	25.94±4.89	0.753
Serum creatinine, mg/dL	0.81±0.30	0.65±0.10	0.077
Serum urea, mg/dL	27.57±10.36	23.41±5.053	0.191
Urıc acid, mg/dL	4.72±1.26	3.91±1.02	0.051
CRP level, mg/dL	0.15 (0.24)	0.13 (0.20)	0.874
ESR, mm/hour	7.00 (9.00)	10.50 (13.00)	0.309
RF, IU/dL	9.00 (2.00)	8.00 (0.68)	0.210
AST, U/L	18.97±4.34	17.00±2.89	0.087
ALT, U/L	22.74±11.67	15.9167±6.59	0.018
Total cholesterol, mg/dL	176.48±38.09	183.66±26.87	0.550
HDL cholesterol, mg/dL	51.97±16.15	55.03±13.17	0.557
LDL cholesterol, mg/dL	110.24±33.19	107.81±37.66	0.840
Triglycerides, mg/dL	128.57±102.33	112.91±75.65	0.579
Fasting serum glucose, mg/dL	91.00 (15.00)	90.50 (11.25)	0.660
Serum Fetuin A, ng/mL	4.59±3.42	3.67±2.61	0.401
CIMT, mm	0.80 (0.36)	0.55 (0.24)	0.002
PASI	8.32±5.43	-	-

*Values are the mean ± standard deviation (SD) or median (interquartile range-IR). CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; CIMT: carotid intima-media thickness; PASI: psoriasis areas and severity index; RF: rheumatoid factor; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

tients with mild-to-moderate plaque-type psoriasis and atherosclerosis had not been fully investigated.

In this study, CIMT levels were found to be significantly higher in patients with mild-to-moderate psoriasis compared to controls (patients with psoriasis: 0.80 (0.36), controls: 0.55 (0.24); *P*=0.002). However, we did not find any correlation between CIMT and PASI scores. These results seem to support previous reports that there is no correlation between disease activity and CIMT scores (18,20).

Psoriasis is characterized by excessive growth and aberrant differentiation of keratinocytes in skin lesions. Flisiak *et al*. previously reported that some inflammatory cytokines, including transforming growth factor (TGF) β1, are involved in the pathogenesis of psoriasis (21,22). Fetuin-A acts as an anti-inflammatory mediator and natural antagonist of TGF-β (9). In addition, TGF-β is important for negative regulation of keratinocyte proliferation. We hypothesized that reduced TGF-β in patients with psoriasis may be associated with increased levels of fetuin-A, and that fetuin-A is higher in patients with psoriasis when compared to healthy volunteers, which may be related to the observed PASI and/or correlation with CIMT.

Epidermal growth factor (EGF) appears to play a crucial role in the pathogenesis of psoriasis (23).

Wang *et al*. demonstrated that fetuin-A promotes HaCaT migration via signaling pathways that are similar to the pro-migratory pathways provoked by epidermal growth factor (EGF) and transforming growth factor-α stimulation (11). They demonstrated that a blockade of EGF receptor signaling has a limited effect on fetuin-A-promoted "wound closure" in primary human keratinocytes but significantly inhibits the effect of fetuin-A on HaCaT cells.

In this study, we aimed to investigate the possible associations between a) fetuin-A levels and the severity of plaque-type psoriasis and b) fetuin-A levels and atherosclerosis. However, no correlations between fetuin-A and PASI scores were observed.

Our analysis expands upon a study by Gerdes *et al*., in which it is hypothesized that the inflammatory status of patients with psoriasis resulted in a decrease in systemic fetuin-A levels. This decrease in fetuin-A may result in an increased risk of vascular calcification and could provide an explanation for how systemic inflammation during psoriasis contributes to the observed cardiovascular comorbidity (10).

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Table 2. Correlations of fetuin-A with carotid intima-media thickness (CIMT), psoriasis severity index (PASI), glucose, and LDH levels for all patients and controls

Correlation with fetuin A (all patients, n=70; controls, n=66)			
CIMT	r=-0.21	*P*=0.157	CI=-0.16 to 0.84
Fasting glucose	r=0.29	*P*=0.042	CI=-14.43 to 43.59
LDL	r=-0.43	*P*=0.002	CI=-20.71 to 25.56
PASI	r=0.04	*P*=0.807	-

r: Pearson's correlation; CI: confidence interval; statistically significant: *P*<0.05.

LDL: low-density lipoprotein; CIMT: carotid intima-media thickness; PASI; psoriasis area and severity index.

Gerdes *et al*. found low levels of fetuin-A in patients with chronic kidney disease, dialysis patients, and patients with end-stage renal disease with evidence of inflammation (24,25). In hemodialysis patients, low levels of fetuin-A were associated with increased cardiovascular and all-cause mortality (26). These findings are supported by the repeatedly described observation that fetuin-A is a negative acute phase protein that is down-regulated by acute inflammation. In the rat liver, it was shown that tumor necrosis factor alpha (TNF-a) can reduce fetuin-A gene expression, and in humans, this was shown for Interleukin (IL) 6 and IL-1b (27). Gerdes *et al*. found a significant reduction fetuin-A in patients with psoriasis with and without psoriatic arthritis (10).

In our study, the mean serum concentration of fetuin-A was found to be higher in patients with psoriasis (4.59±3.42) as compared with controls (3.67±2.61), however, this difference was not statistically significant (*P*=0.401).

Ix *et al*. reported that among 1,375 community-living individuals without prevalent clinical cardiovascular disease, lower fetuin-A levels are independently associated with greater coronary artery calcification severity but not peripheral arterial disease or CIMT. They report that fetuin-A might initiate calcium deposition with in the vasculature but not atherosclerosis directly. Low fetuin-A levels also may cause patients to be predisposed to greater calcium deposition but not necessarily the initiation or progression of atherosclerosis (28). Our study and several others support this hypothesis (29,30). In our study, serum fetuin-A levels of patients with psoriasis were not significantly reduced as compared with controls. This could be because the CIMT levels of patients were found to be higher than that of controls. We also found that mild-to-moderate plaque-type psoriasis patients did not exhibit as much calcification as patients with severe psoriasis.

Fetuin A has also been reported to impair insulin signaling and adipocyte function. Fetuin A is associated with insulin resistance, diabetes mellitus, and obesity, all of which have been previously associated with psoriasis (9).

In this study, we observed a correlation between serum fetuin-A levels and fasting glucose, as well as between fetuin-A and LDL cholesterol.

A limitation of our study was that only a small number of patients were enrolled. Cross-sectional data from this small cohort does not allow for causality to be established. Future directions may include expanding our study to include more patients. Another limitation is that we did not analyze men and women separately.

CONCLUSION

Most importantly, this study describes an association between mild-to-moderate psoriasis and atherosclerosis, similarly to severe psoriasis. Interestingly, this association was seen in patients without taking other cardiovascular risk factors into consideration.

We recommend that when assessing the cardiovascular disease risk of patients with psoriasis, physicians should measure CIMT rather than the less appropriate serum fetuin-A values, as many other metabolic events influence fetuin-A levels.

Future studies should evaluate the effect of fetuin-A on excessive growth and aberrant differentiation of keratinocytes. In conclusion, the measurement of fetuin-A levels in psoriasis plaques is more appropriate than the measurement of levels of serum fetuin-A.

References:

1. Christophers E. Psoriasis – epidemiology and clinical spectrum. Clin Exp Dermatol 2001;26:314-20.
2. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005;352:1685-95.
3. Bots ML, Hofman A, De Jong PT, Grobbee DE. Common carotid intima-media thickness as an indicator of atherosclerosis at other sites of the carotid artery: the Rotterdam Study. Ann Epidemiol 1996;6:147-53.

4. Heiss G, Sharrett AR, Barnes R, Chambless LE, Szklo M, Alzola C. Carotid atherosclerosis measured by B-mode ultrasound in populations: associations with cardiovascular risk factors in the ARIC study. Am J Epidemiol 1991;134:250-6.
5. Simons PC, Algra A, Bots ML, Grobbee DE, van der Graaf Y. For the SMART Study (Second Manifestations of Arterial disease). Common carotid intima-media thickness and arterial stiffness: indicators of cardiovascular risk in high-risk patients. Circulation 1999;100:951-7.
6. Li R, Cai J, Tegeler C, Sorlie P, Metcalf PA, Heiss G. Reproducibility of extracranial carotid atherosclerotic lesions assessed by B-mode ultrasound: the atherosclerosis risk in communities study. Ultrasound Med Biol 1996;22:791-9.
7. Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. Circulation 1986;74:1399-406.
8. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb 1991;11:1245-9.
9. Mori K, Emoto M, Inaba M. Fetuin-A and the cardiovascular system. Adv Clin Chem 2012;56:175-95.
10. Gerdes S, Osadtschy S, Buhles N, Baurecht H, Mrowietz U. Cardiovascular biomarkers in patients with psoriasis. Exp Dermatol 2014;23:322-5
11. Wang XQ, Hung BS, Kempf M, Liu PY, Dalley AJ, Saunders NA, *et al*. Fetuin-A promotes primary keratinocyte migration: independent of epidermal growth factor receptor signaling. Exp Dermatol 2010;19:289-92.
12. Schmitt J, Wozel G. The psoriasis area and severity index is the adequate criterion to define severity in chronic plaque-type psoriasis. Dermatology 2005; 210:194-9.
13. VandeKerkhof PC, Schalkwijk J. Psoriasis. In: Bolognia JL, Jorizzo JL Rapini RP, editors. Dermatology. 2nd ed. Spain:Mosby; 2008. pp. 115-48.
14. Fredriksson T, Pettersson U. Severe psoriasis – oral therapy with a new retinoid. Dermatologica 1978;157:238-44.
15. Sidhu PS, Desai SR. A simple and reproducible method for assessing intimal-medial thickness of the common carotid artery. Br J Radiol 1997;70:85-9.
16. Kanters SD, Algra A, van Leeuwen MS, Banga JD. Reproducibility of *in vivo* carotid intima-media thickness measurements: a review. Stroke 1997;28:665-71.
17. Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, *et al*. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 2011;32:1769-818.
18. Gonzalez-Juanatey C, Llorca J, Miranda-Filloy JA, Amigo-Diaz E, Testa A, Garcia-Porrua C, *et al*. Endothelial dysfunction in psoriatic arthritis patients without clinically evident cardiovascular disease or classic atherosclerosis risk factors. Arthritis Rheum 2007;57:287-93.
19. Di Minno MN, Iervolino S, Peluso R, Scarpa R, Di Minno G. CaRRDs study group. Carotid intima-media thickness in psoriatic arthritis: differences between tumor necrosis factor-α blockers and traditional disease-modifying antirheumatic drugs. Arterioscler Thromb Vasc Biol 2011;31:705-12.
20. Altekin ER, Koç S, Karakaş MS, Yanıkoğlu A, Başarıcı I, Demir I, *et al*. Determination of subclinical atherosclerosis in plaque type psoriasis patients without traditional risk factors for atherosclerosis. Turk Kardiyol Dern Ars 2012;40: 574-80.
21. Flisiak I, Zaniewski P, Rogalska M, Myśliwiec H, Jaroszewicz J, Chodynicka B. Effect of psoriasis activity on VEGF and its soluble receptors concentrations in serum and plaque scales. Cytokine 2010;52: 225-9.
22. Flisiak I, Zaniewski P, Rogalska-Taranta M, Chodynicka B. Effect of psoriasis therapy on VEGF and its soluble receptors serum concentrations. J Eur Acad Dermatol Venereol 2012;26:302-7.
23. Wieduwilt MJ, Moasser MM. The epidermal growth factor receptor family: biology driving targeted therapeutics. Cell Mol Life Sci 2008;65:1566-84.
24. Rezg R, Barreto FC, Barreto DV, Liabeuf S, Drüeke TB, Massy ZA. Inhibitors of vascular calcification as potential therapeutic targets. J Nephrol 2011;24:416-27.
25. Hermans MM, Brandenburg V, Ketteler M, Kooman JP, van der Sande FM, Boeschoten EW, *et al*. Association of serum fetuin-A levels with mortality in dialysis patients. Kidney Int 2007;72:202-7.
26. Ketteler M, Bongartz P, Westenfeld R, Wildberger JE, Mahnken AH, Böhm R, *et al*. Association of low fetuin-A (AHSG) concentrations in serum with cardiovascular mortality in patients on dialysis: a cross-sectional study. Lancet 2003;361:827-33.

27. Mori K, Emoto M, Inaba M. Fetuin-A: a multifunctional protein. Recent Pat Endocr Metab Immune Drug Discov 2011;5:124-46.
28. Ix JH, Barrett-Connor E, Wassel CL, Cummins K, Bergstrom J, Daniels LB, *et al*. The associations of fetuin-A with subclinical cardiovascular disease in community-dwelling persons: the Rancho Bernardo Study. J Am Coll Cardiol 2011;58:2372-9.
29. Rittig K, Thamer C, Haupt A, Machann J, Peter A, Balletshofer B, *et al*. High plasma fetuin-A is associated with increased carotid intima-media thickness in a middle-aged population. Atherosclerosis 2009;207:341-2.
30. Mori K, Emoto M, Araki T, Yokoyama H, Teramura M, Lee E, *et al*. Association of serum fetuin-A with carotid arterial stiffness. Clin Endocrinol (Oxf) 2007;66:246-50.