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Low Serum Fetuin A Levels and Cardiovascular Events in End-Stage Renal Disease (ESRD) Patients

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Abstract: The atherosclerotic Cardiovascular Disease (CVD) is frequently observed in End-Stage Renal Disease (ESRD) patients; according to the hypothesis of non-traditional risk factors for CVD, accelerated atherogenesis in these patients could be linked to both vascular calcification and inflammation. α2-Heremans-Schmid Glycoprotein (AHSG) also known as Fetuin-A, is considered a negative marker of inflammation and represents one of the *in vivo* circulating calcification modulators; these molecules are proteins working as endogenous inhibitors of $Ca \times PO_4$ precipitation and are probably involved in the pathogenesis vascular calcification. Aim of this study is to evaluate the differences in serum Fetuin-A levels between 2 Haemodialysis (HD) patient groups distinguished on the basis of history of cardio and/or cerebrovascular events. All patients took part in clinical data collection and 2 patient groups were identified as no cardiovascular and cardiovascular on the basis of history of cardio and/or cerebrovascular events. Serum Fetuin-A levels were determined using sandwich immunoenzymatic assay, ELISA (Epitope Diagnostics Inc., San Diego, CA, USA). Serum Fetuin-A levels were significantly lower in cardiovascular HD patients than in those without cardiovascular event. The role of Fetuin A in the context of the different pathogenetic moments of atherosclerosis remains unclearly assessed; it would be of some interest to investigate the hypothesis, almost unexplored, of a relationship between low Fetuin A levels and endothelial dysfunction.

Key words: Fetuin-A, ESRD, inflammation, vascular calcification, CVD

INTRODUCTION

The atherosclerotic Cardiovascular Disease (CVD) is frequently observed in End Stage Renal Disease (ESRD) patients (Foley and Parfrey, 1998) and represents a leading cause of morbidity and mortality in HD patients (Qureshi *et al*., 2002) according to the hypothesis of non-traditional risk factors for CVD, accelerated atherogenesis in these patients is linked to both vascular calcification and inflammation (Stenvikel *et al*., 2005). Furthermore, recent data (Jono *et al*., 2006) suggested the role of inflammation in the pathogenesis of vascular calcification, which is probably multifactorial and certainly involves to bone and mineral homeostasis disorders. However, is known the role of some *in vivo* circulating calcification modulators (Moe and Chen, 2004), working as endogenous inhibitor of $Ca \times PO_4$ precipitation which are proteins including the α2-Heremans-Schmid glycoprotein (AHSG), also named Fetuin-A; this molecule also represents a negative marker of inflammation (Schlieper *et al*., 2007). It led the interest in the role of Fetuin-A as possible marker of both vascular calcification *in vivo* and inflammation, that are considered non-traditional risk factors for CVD (Stenvikel *et al*., 2005). In aim to better define the relationship between Fetuin-A and cardiovascular disease in ESRD patients, in this study we measure serum Fetuin-A levels in 72 Haemodialysis (HD) patients and evaluate the differences in the molecule serum concentrations between 2 dialysis patient groups, distinguished on the basis of history of cardio and/or cerebrovascular events.

MATERIALS AND METHODS

We enrolled 72 patients undergoing HD treatment at the dialysis unit of the University of Palermo. The enrolment started in March 2007 and finished in June 2007; all patients who were eligible and gave consent were included in the study. All subjects were consecutive patients admitted to the Department of Nephrology and Dialytic Techniques, undergoing standard bicarbonate HD treatment for more than 36 months, using synthetic membranes (Polyflux B, Gambro Dialysatoren GmbH, Hechingen, Germany, or Arylane Series L, Gambro

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Table 1: Baseline characteristics and serum Fetuin-A levels of the patient groups

Characteristic	Group A (n = 40)	Group B (n = 32)
Age-years	65±14	64±16
Male sex-n (%)	24 (60)	21 (65)
Months of dialysis	>36	>36
Aetiology of ESRD-n (%)		
Hypertensive nephropathy	9 (22)	7 (22)
Diabetic nephropathy	5 (12)	6 (18)
Polycystic kidney nephropathy	7 (18)	3 (11)
Undetermined	19 (48)	16 (49)
BMI, kgm^{-2}	27±5.8	29±6.2
Fetuin-A, g L	0.51±0.06*	0.36±0.04*
CV risk factors-n (%)		
Diabetes	9 (22)	10 (32)
Hypertension	20 (52)	16 (51)
Smoking habit	10 (25)	11 (34)
Hyperlipaemia	6 (15)	1 (3)
CV events-n (%)		
Coronary heart disease	/	24 (75)
Cerebrovascular disease	/	8 (25)
-Peripheral vascular disease	/	8 (25)
Treatment **-n (%)		
Antihypertensive drugs	20 (52)	21 (65)
Antiplatelet	12 (30)	13 (41)
Antidiabetic drugs	9 (22)	9 (27)
Statines	6 (15)	22 (68)
Phosphate binder	16 (40)	16 (52)

*$p<0.05$; **Treatments started at least 2 months before sampling

Industries, Meyzieu Cedex, France) for 4 h, 3 times a week. Patients with liver failure, liver cirrhosis, hepatitis B or C, endocrine diseases, such as hypo/hyperthyroidism, hypo/ hypercortisolism, severe malnutrition (BMI< 20 kg m^{-2}), infectious and immunoinflammatory diseases were excluded from the study. At study baseline, all patients took part in clinical data collection (Table 1); it included the underlying cause of ESRD, smoking habit, drug therapy, history of weight loss and BMI as indicator of nutritional state, presence of physician-diagnosed hypertension, diabetes and/or hyperlipaemia along with respective drug therapy. All patients were distinguished on the basis of history of cardio and/or cerebrovascular events and divided in 2 groups (group A and group B); among group B, 8 patients presented history of atherosclerotic peripheral vascular disease. Serum Fetuin-A levels were assessed by a sandwich immunoenzymatic assay (ELISA) according to the manufacturer's specifications (Epitope Diagnostics Inc., San Diego, CA, USA); intra-and interassay coefficients of variation were 5.1 and 6.2%, respectively. To compare the differences between means, a paired sample t-test was performed using SPSS statistical software (Chicago, IL, USA).

RESULTS

Serum Fetuin-A levels were lower in patients with group B compared with group A (Table 1) and a statistical significance in the difference in Fetuin-A levels between 2 groups was observed ($p<0.05$) (Table 1).

DISCUSSION

The finding of low serum Fetuin-A levels in ESRD patients has been reported by previous Authors (Floege and Ketteler, 2004) and related to accelerated atherogenesis and CVD in these patients; it is largely accepted the role of Fetuin-A as possible marker of both vascular calcification *in vivo* and inflammation in HD patients (Ketteler *et al*., 2003). Our results are consistent with the hypothesis of an association between Fetuin-A and atherosclerosis, which has been investigated in the studies performed by Cozzolino *et al*. (2006), suggesting an association between low serum Fetuin-A levels and CVD in ESRD patients; nevertheless, is clearly assessed that ESRD patients are exposed to a chronic inflammation state due to dyalitic treatment (Wang *et al*., 2005). On the other hand, CVD pathogenesis recognize the intervention of immunoinflammatory pattern for enhancing endothelial dysfunction and is clear that inflammation, vascular calcification and endothelial injury are all envolved in the development of CVD (Willerson and Ridker, 2004).

CONCLUSION

In this perspective, our finding of lower Fetuin-A levels in dialysis patients with previous cardiovascular events could probably be explained by the coexistence, in atherosclerotic vessels, of low fetuin concentrations and activated flogistic markers and cellular species, along with HD-induced chronic inflammation. It would be interesting to investigate the role of Fetuin-A in atherogenesis to better define in which pathogenetic moment Fetuin-A is primarly envolved andto verify the hypothesis, almost unexplored, of a relationship between low Fetuin-A levels and endothelial dysfunction. Moreover, it would be of some interest to investigate the relationship between Fetuin-A and cardiovascular risk in those patients who underwent to cardiovascular events and presenting a generally preserved renal function.

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