ORIGINAL ARTICLE

Aldosterone levels in patients on haemodialysis: Relationship with body fat mass and adipocytokines

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ABSTRACT

Background: It has been recently shown that serum aldosterone (SA) levels are correlated with insulin resistance, excess body fat and levels of adipocytokines. **Aim**: To establish SA levels in patients on haemodialysis (HD) and the possible association with excess body fat and/or serum adipocytokine levels. **Methods**: 28 stable patients on HD. Mean age: 73.7±13.3 years; 53.6% men. Mean time on HD: 40.2± 40.8 months. None were diabetics nor treated with drugs that interfere with the renin-angiotensin-aldosterone-system. 18 patients were anuric. All measurements were performed prior to the midweek HD session. **Results**: SA levels (median: 28.1; 25th percentile (p25):10.4; 75th percentile (p75):98.6 ng/dl) were above the normal range in 53.6% of patients. Plasma renin activity (PRA) (median: 1.05; p25: 0.16; p75: 3.1 ng/mL/hour) was above the normal range in 21.4% of patients. There were no statistically significant differences in SA levels between anuric and non-anuric, male and female, presence and absence of myocardiopathy. There were no statistically significant correlations of SA levels or PRA with urine volume, residual renal function, dose or time on dialysis. age, or comorbidity. SA levels were positively correlated with PRA (r=000.70; p< 0.0001); body fat mass (r=0.40; p=0.03); leptin (r=0.45; p =0.01); leptin/adiponectin ratio (r=0.52 p=0.005) and negatively with serum adiponectin levels (r=- 0.37; p=0.05). In stepwise multiple regression analysis, the best model to explain SA levels included PRA and LAR (r=0.78; r^2=0.60). **Conclusions:** SA levels were elevated in a high percentage of HD patients. SA levels were correlated with PRA, body fat mass and adipocytokines.

Key-words: Aldosterone, haemodialysis, adiponectin, leptin, boy mass fat.

INTRODUCTION

Cardiovascular (CV) disease is the major cause of morbidity and mortality in patients with chronic kidney disease (CKD) Stage 5, and its prevalence is markedly greater than in the age-matched general population. Such increased risk is due to the high prevalence of traditional and kidney-related risk factors[1]. The role of adipose tissue and adipocytokines in CV risk in this population is not sufficiently defined. In contrast to the general population, a higher body mass index (BMI) is associated with better survival among haemodialysis (HD) patients[2], although an excess of body fat mass is associated with insulin resistance in non-diabetic chronic HD patients[3]. Altered secretory patterns of adipose tissue may play a crucial role in the metabolic disturbances observed in advanced kidney disease and have been hypothesised to play a role in insulin resistance. Leptin and adiponectin play important and opposite roles in the regulation of cardiovascular and metabolic

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homeostasis. Leptin/adiponectin ratio (LAR) has recently been proposed as a new atherogenic index[4].

Furthermore, human adipocytes produce an as yet unidentified mineralocorticoid-releasing factor that stimulates adrenal aldosterone production[5] and this hormone in turn promotes the release of pro-inflammatory adipocytokines that cause systemic inflammation, oxidative stress and insulin resistance[6]. In fact, obesity is associated with an increase in aldosterone production and high levels of this hormone promote the development of insulin resistance[7].

Plasma aldosterone levels have emerged as an indicator of adverse prognosis in several cardiac and non-cardiac conditions, including heart failure[8] and acute myocardial infarction[9]. There are few studies measuring aldosterone levels in haemodialysis (HD) patients. Drechsler and colleagues determined aldosterone levels in 1,255 diabetic patients on dialysis and showed that high aldosterone levels were associated with an increased risk of all-cause mortality as well as sudden cardiac death[10]. Hung and colleagues in a prospective cohort study in 328 HD patients showed that SA levels were inversely associated with adverse outcomes; volume overload underlies this paradox. In the absence of volume overload, SA was an independent risk factor for all-cause mortality and CV events in this population[11]

We hypothesised that adipose tissue could promote the release of aldosterone by mechanisms independent of the RAAS, and that aldosterone might contribute to the pathogenesis of CV disease in dialysis patients by altering the pattern of secretion of fatty tissue adipocytokines, and consequently promoting insulin resistance.

The aim of this study was to measure plasma aldosterone levels in patients on HD and the possible association with excess body fat (bioimpedance) and/or serum adipocytokine levels.

■ PATIENTS AND METHODS

This is a cross-sectional study performed in April 2015. Subjects were recruited among chronic HD patients at the Hospital General (Segovia, Spain) and its affiliated centre: Los Olmos (FRIAT). Selection criteria included: age >18 years; patient on HD for at least six months; not to have: a) diabetes mellitus b) any intercurrent acute illnesses in the last three months; c) data from dialysis treatment; d) inability to perform

bioimpedance owing to metallic prostheses or amputations; e) treatment with drugs that interfere with RAAS (including angiotensin receptor blockers (ARB), angiotensin converting enzyme (ACE) inhibitor and aldosterone receptor blockers).

All measurements were taken fasting and with the patient prone, prior to the midweek HD session. The following studies were performed in every patient:

1. Multifrequency whole body bioimpedance assessment using the Body Composition Monitor (Fresenius Medical Care, Bad Homburg, Germany). We measured lean tissue index (LTI); fat tissue index (FTI); relative fat mass (kg/m²); total water (TW); extracellular water (ECW), intracellular water (ICW). We estimated relative overhydration (rel OH) calculating the difference between initial body weight (Kg) and dry body weight measured with BCM.

2. A comprehensive biochemical and haematological study that included serum levels of glucose; albumin; cholesterol; transferrin; haematocrit; creatinine; sodium and potassium; pH; bicarbonate; and ultrasensitive C reactive-protein (CRP_s), all measured by routine methodology in our laboratory.

3. Dialysis dose was estimated using Kt/V Daugirdas II formula; and protein ingestion using the protein catabolic rate normalised to actual body weight (nPCR).

4. The volume of diuresis and the residual renal function were calculated by collecting 24-hour urine the day prior to the midweek HD session.

5. Hormonal study. Blood samples were immediately centrifuged, separated and frozen at −80ºC. All hormones were determined simultaneously in a centralised laboratory using specific commercial methods. Serum aldosterone (SA) was determined in plasma EDTA by chemiluminescent competitive assay (LIAISON®, Dia Sorin); intra and inter assay coefficient of variation were 3.5% and 9.5% for an average value of 6.8 ng/dl and 1.8% and 5.6% for an average value of 28.8 ng/dl, respectively; SA normal range for our laboratory is 1.17-23.6 ng/dl. Plasma renin activity (PRA) was determined in plasma EDTA, by chemiluminescent assay (LIAISON®, Dia Sorin); intra and inter assay coefficient of variation were 2.1%-2.38% for an average value of 2.25 ng/ml/h and 6.8%-7.3% for an average

value of 8.25 ng/ml/h, respectively; PRA normal range for our laboratory is 0.23-3.32 ng/ml/h. Leptin was determined by ELISA (enzyme immunoassay) in the DSX Palex (DRG) ng/ml; the intra and inter assay coefficient of variation were 5.9%-6.9 and 8.6-11.5%, respectively; its normal range is 7.36±3.73 ng/ml in females and 3.84±1.79 ng/ml in males. Adiponectin was determined by ELISA (enzyme immunoassay) in DSX Palex (Millipore) ng/ml; variation coefficient intra and inter assay were 2.4-8.4 and 1.9-7.4%, respectively.

6. Comorbidity was assessed using the Charlson Index, as modified by Beddhu[12].

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), Version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Normal data distribution was explored by the Kolmogorov-Smirnov test. Data are given as means ± SD for continuous variables with normal distribution or as percentages for categorical variables. SA levels and ARP were normally distributed. The Chi-squared test and Fisher's exact test were used to compare proportions. Student's t or Mann-Whitney U test were used to compare means. Pearson`s test was used to establish linear correlation coefficients; if any variable was ordinal or didn't have a normal distribution we used Spearman´s rho. To analyse the factors related to SA levels we used a stepwise multiple regression analysis, including those variables that were significant in the univariate analysis as well as confounding factors (age, sex, comorbidity index, and history of cardiac disease). A p value of less than 0.05 was considered significant

A written informed consent was obtained from all study patients. The study is in accordance with the declaration of Helsinki about Ethical Principles for Medical Research Involving Human Subjects.

■ RESULTS

Socio-demographic, clinical and anthropometric characteristics of the 28 patients included in our study are shown in table 1. All HD patients were dialysed with synthetic membranes and high flow dialysis. 18 patients were anuric (residual volume of diuresis <100ml/24 hours).

Table 2 shows mean and median values of SA, PRA, leptin, adiponectin and LAR. All hormones values were

Table 1

Sociodemographic, clinical and anthropometric characteristics

Age (years)	73.7±13.3
Sex (% males)	53.6%
Heart failure history(%)	28.6%
Ischaemic cardiopathy(%)	25%
Charlson Index (median and range)	8 (4-12)
Time on dialysis (months)	40.2±40.8
24 hours urine volume (ml)	189±308 (0-1000)
Residual renal function (ml/min)	1.3± 3.1 (0-10)
Body weight (Kg)	64.1±12.9
Body mass index (BMI)*	26.2±4.6
Fat mass (kg/m2)	14.3±5.8
Overhydration (litres)**	1.2±1.2
Inter-dialysis weight gain (kg)	1.9±0.8
Systolic blood pressure (mmHg)**	136±27.8
Diastolic blood pressure (mmHg)**	68.6±12.3
KT/V	1.6±0.33

* BMI=weight (Kg)/ height2; **Before dialysis

Table 2

Mean and median hormones values

	Mean ±SD	Median	Percentiles 25/75
SA* (ng/dl)	79.1±106.1	28.1	10.4/98.6
PRA** (ng/ml/h)	2.15±2.9	1.05	0.16/3.1
Leptin (ng/ml)	18.3±23.1	7.8	1.8/27.8
Adiponectin (ng/ml)	34.0±22.3	29.1	20.6/37.0
Leptin/adiponectin ratio	0.85±1.36	0.35	0.06/1.02

*SA= serum aldosterone; **PRA= Plasma renin activity

normally distributed. SA levels were above the normal range (1.17-23.6 ng/dl) in 53.6% of patients and none below it. PRA was above the normal range (0.23-3.32 ng/mL/hour) in 21.4% of patients and below it in 35.7%.

Table 3 shows the characteristics of patients with SA levels above or below the median. Patients with SA above the median had significantly higher RPA and LAR and lower levels of adiponectin. Patients with higher SA had higher body weight, body mass index, relative fat mass and leptin levels although the differences were not statistically significant.

There were no statistically significant differences in SA levels between anuric and non-anuric, male and female and presence and absence of myocardiopathy. There were no statistically significant correlations of SA levels or PRA with urine volume, RRF, systolic or diastolic blood pressure, relative overhydration, dose of HD or time on dialysis, age or comorbidity.

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Table 3

Characteristics of patients with SA levels above or below the median

	Aldosterone≤28.1 (n=14)	Aldosterone>28.1 (n=14)	Signification
Age (years)	71.9±16.0	75.4±10.2	NS
Sex (% males)	50%	57.1%	NS
Heart failure history (HF) (%)	21.4%	35.7%	NS
Ischaemic cardiopathy (IC) (%)	14.3%	35.7%	NS
Heart disease (HF and/or IC) (%)	21.4%	57.1%	NS
Charlson Index	8.1±1.8	8.6±1.9	NS
Time on dialysis (months)	47.9±44	35.0±39	NS
Anuric (%)	57.1%	71.4%	NS
24 hours urine volume (ml)	228±234	329±292	NS
RRF* (ml/min)	1.3±3.2	1.2±2.9	NS
Body weight (Kg)	61.6±12.1	66.3±13.7	NS
Body mass index (BMI)	25.3±5.2	27.1±4.0	NS
Overhydration (litres)	1.17±0.9	1.24±1.39	NS
SBP/DBP (mmHg)**	145.7±27 / 69.5±12.1	126.5±25.9/ 67.5±12.8	NS NS
PRA***	0.84±1.03	3.4±3.6	0.02
Fat mass (kg/m2)	13±5.7	15.4±5.9	NS
Leptin (ng/ml)	12.1±18	24.4±26.4	NS
Adiponectin (ng/ml)	42.8±27.8	25.2±9.5	0.04
Leptin/adiponectin ratio	0.6±1.13	1.09±1.56	0.04

* RRF: Residual renal function; ** SBP/DBP: Systolic/Diastolic blood pressure; ***PRA: Plasma renin activity

SA levels were positively correlated with PRA (r= 0.70; p< 0.0001); body fat mass in kg/m2 (r=0.40; p=0.03); leptin (r = 0.45; p = 0.01); leptin/adiponectin ratio (r=0.52 p=0.005) and negatively with serum adiponectin levels (r= − 0.37; p=0.05).

To analyse the factors related to SA levels we used a stepwise multivariate regression analysis, including variables that were significant in the univariate analysis as well as confounding factors (age, sex, comorbidity index and history of cardiac disease). The best model to explain SA levels included PRA and LAR (r=0.76; r2=0.57).

■ DISCUSSION

Our study shows that SA levels are elevated in a high percentage of patients on a chronic HD programme and that these levels are correlated with PRA but also with body fat mass and adipocytokines. These findings lead us to questions, such as:

1. Is aldosterone activity increased in HD patients?
2. What is the role of adipose tissue and adipocytokines in the development of hyperaldosteronism?

3. Is aldosterone involved in the cardiovascular and metabolic adverse effects attributed to fat tissue?

■ Activity of the renin-angiotensin-aldosterone system in HD patients

An important finding of this study is that almost 80% of our patients had normal or elevated PRA, although most of them were anuric or had very low RRF. Our results confirm that PRA is the main factor related to the levels of AS which were above the normal range in 53.6% of patients.

In our study, no patient was being treated with ACE inhibitors or ARBs. In a previous study including 102 patients in dialysis, 28 patients treated with those drugs showed significantly lower levels of AS (data not shown). These data confirm that at least part of the hyperaldosteronism of dialysis patients is due to the activation of the RAAS and could help explain why the pharmacological blockade with ACE inhibitors / ARBs has a beneficial effect in preventing CV risk in many HD patients as shown by some authors[13-16].

■ The role of adipose tissue and adipocytokines in the development of hyperaldosteronism

Our results show that aldosterone levels correlated positively with body fat mass (kg/m2). Several studies have shown that adipose tissue, through unidentified factors, can stimulate the secretion of aldosterone from the adrenal gland[17,18]. In an interesting piece of research Kidambi and colleagues[19] compared the levels of SA and PRA in patients with and without metabolic syndrome (MS). Their results show no difference in PRA between both groups but patients with MS had significantly higher levels of SA, suggesting that in those patients a different mechanism to RAAS is responsible for the secretion of SA. The authors propose that adipose tissue is responsible for the secretion of aldosterone, independently of RAAS, and furthermore that aldosterone binding to MCR cause insulin resistance.

■ Is aldosterone involved in the cardiovascular and metabolic adverse effects attributed to fat tissue?

In our study we found a positive correlation between aldosterone levels and leptin and LAR, and a negative one with adiponectin. In addition, in the stepwise multiple regression analysis, LAR independently correlated with the levels of aldosterone. Adipose tissue is not only a store of excess energy but also a complex, essential and highly active metabolic and endocrine organ. The role of body fat mass in the development of uraemic insulin resistance can be attributed to adipocyte-derived hormones such as leptin and adiponectin, with opposing effects in regulating metabolism. Leptin, a protein that is secreted exclusively by adipocytes, plays an important role in insulin resistance[3,20] and adiponectin has anti-inflammatory, insulin-sensitizing, anti-atherogenic properties and as such a protective effect on CV disease[21]. An inverse correlation between adiponectin and insulin resistance, assessed by the HOMA-R index, has been reported in non-uraemic[22] and uraemic subjects[23].

In dialysis patients the levels of leptin and adiponectin are elevated, and the reduction in leptin renal clearance seems to be the main cause of this finding[24]. The prognostic significance of these adipocytokines levels in dialysis patients is controversial. Most authors have found a protective effect of adiponectin on CV mortality in dialysis patients[25] although some have found the opposite effect[26]. Recently Hung et al.[27] have shown that leptin/adiponectin ratio (LAR) has a good correlation with glucose-disposal rate measured by hyperinsulinemic-euglycemic glucose clamp in chronic HD

patients, and recently LAR has been proposed as a new atherogenic index since it has been associated with cardiovascular events in PD[4]

In this study we found an independent association between aldosterone levels and LAR index. Given that this LAR index has a good correlation with insulin resistance in patients with HD, we infer that aldosterone could play a pathogenic role in the development of insulin resistance but our data do not allow us to conclude a causal relationship. The association between hyperaldosteronism and insulin resistance was suggested 50 years ago when it was reported that patients with primary aldosteronism had an impaired glucose tolerance[28] and that tumour resection or pharmacological treatment reduced insulin levels (29, 30). The mechanisms by which aldosterone can lead to insulin resistance are not fully defined. There are MCR in skeletal muscle, pancreatic beta cells, liver and adipose tissue and their activation might lead to insulin resistance by decreasing insulin secretion, increased hepatic gluconeogenesis and release of adipocytokines. Emerging evidence supports a paradigm shift in our understanding of the RAAS and in aldosterone's ability to promote insulin resistance[31]. Research in animal models, with activated RAAS and insulin resistance, showed that blocking of MCR improved sensitivity to insulin and the uptake of glucose by skeletal muscle[32]. A recent study shows that the use of ACE inhibitors or ARBs on dialysis improves insulin sensitivity[33].

Our study is limited by its cross-sectional design and sample size, which does not allow us to make comparisons between obese and non-obese patients. It would be necessary to measure HOMA-IR or hyperinsulinemic-euglycemic clamp to establish the causal relationship between aldosterone and insulin resistance. A prospective study with higher numbers of patients is needed to see whether blocking MCR decreases insulin resistance in patients with excess body fat or elevated LAR.

■ CONCLUSIONS

SA levels were elevated in a high percentage of HD patients. In this study, almost 80% of the HD patients had normal or elevated PRA, although most of them were anuric or had a very low RRF. SA levels were correlated with PRA.

Our results confirm that PRA is the main factor related to SA levels of, although RAAS activation is paradoxical since it does not correlate with pre-dialysis

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hydration. SA levels were also associated to body mass fat and levels of adipocytokines. In the stepwise multiple regression analysis LAR was independently correlated with the levels of SA. In chronic HD patients LAR has a good correlation with insulin resistance parameters, so our results suggest but cannot prove a cause-effect relationship between SA and insulin resistance.

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