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CLINICAL STUDY

Which Parameter Is More Influential on the Development of Arteriosclerosis in Hemodialysis Patients?

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ABSTRACT

Arteriosclerosis is characterized by stiffening of arteries. The incremental elastic modulus (Einc) measurement is a good marker of arterial wall stiffness. Metabolic, inflammatory and hemodynamic alterations cause structural changes and vascular complications in end stage renal disease. The aim of the present study was to evaluate the factors that may affect the development of arteriosclerosis by measurement of Einc in hemodialysis (HD) patients. Thirty-two patients (16 men; 16 female) on chronic HD with a mean age of 42.2 ± 19.3 (range: 15–80) were included in the study. The carotid Einc was measured to determine arteriosclerosis by high-resolution echo-tracking system (Acuson Aspen, Acuson Corp., Mountain View, California, USA). Einc measurement was calculated from transcutaneous measurements of common carotid arterial (CCA) internal diameter and wall thickness and carotid pulse pressure. Common carotid compliance and distensibility were determined from changes in carotid artery diameter during systole and simultaneously measured carotid pulse pressure. Common carotid artery stuffiness (Einc) was influenced by age, systolic

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blood pressure (SBP), pulse pressure (PP), calcium (Ca) and alkaline phosphatase (ALP). The distensibility of CCA was correlated with age, SBP, diastolic blood pressure (DBP), PP, Ca, ALP, and parathormone (PTH). The inflammatory parameter, hs-CRP, was increased with Einc. The mean Einc measurement was found significantly increased in patient receiving vitamin D. In conclusion, the stiffening of carotid artery in HD patients is related not only to hemodynamic changes (increased SBP, PP) but also to metabolic (increased Ca) and to inflammation (increased hs-CRP). Carotid Einc is accepted independent risk factor for cardiovascular mortality. Because of the positive correlation between Einc and serum Ca, vitamin D and Ca containing phosphorus (P) binders should be used carefully.

Key Words: Einc; Hemodialysis; Distensibility; Vitamin D; Calcium.

INTRODUCTION

The mortality of end stage renal disease (ESRD) is high despite advances in dialysis treatment. About half of the deaths are attributed to cardiovascular disease. Clinical and epidemiologic studies have shown that cardiovascular disease is related to alteration of function in large conduit arteries.[1] Vascular hypertrophy, an adaptive mechanism according to the Laplace law, is responsible for ischemic heart disease, sudden death, peripheral artery disease and congestive heart disease.[2] Arteriosclerosis is characterized by dilation/hypertrophy and stiffening of arteries. In literature, clinical studies have indicated that arterial stiffening is an independent predictor of overall and cardiac mortality either in ESRD patients or in general population.[3]

The incremental elastic modulus (Einc), which is the slope of the relationship between stress and strain of arterial vessel; is a marker of stiffening. The presence of increased stiffness of arterial wall is influenced by aging, renal dysfunction and combination of these two parameters. Nevertheless, the factors associated with large artery stiffness in ESRD have not yet been identified. The aim of the present study was to investigate whether there is an association among Einc (a marker of stiffening of arteries) blood pressure, metabolic and inflammatory parameters.

PATIENTS AND METHODS

Thirty-two patients (16 males and 16 females) on chronic HD treatment with a mean age of 42.2 ± 19.3 (range: 15–80) were included in the study. The causes of renal failure were chronic glomerulonephritis ($n = 10$), interstitial nephritis ($n = 11$), hypertension ($n = 5$), polycystic kidney disease ($n = 1$), and unknown ($n = 5$). The patients with diabetes mellitus, angina pectoris, peripheral vascular diseases and systemic diseases were excluded. The mean HD duration was 48.6 ± 38.5 months (range: 7–144 months). Twenty patients were dialyzed three times weekly and the rest twice weekly. Bicarbonate dialysate with 1.25 mmol/L of calcium and semisynthetic

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polysynthane membranes were used for dialysis therapy. The patients were on antihypertensive treatment, vitamin B, C, and D supplementation, calcium acetate and/or aluminium hydroxide, iron sucrose and erythropoietin according to serum calcium (Ca), phosphorus (P), parathyroid hormone (PTH) and hemoglobin levels. Twenty-one (66%) of the patients were on vitamin D therapy. Blood samples were obtained before the onset of HD session and prior to heparin. Alkaline phosphatase (ALP), Ca and P were also measured. The CaxP products were determined by multiplying these two values. Intact parathormone (iPTH) and ferritin were assessed by electrochemiluminence immunoassay (E 170, Roche). High sensitivity C-reactive protein (hs-CRP) was analyzed by a nephelometric immunoassay.

The common carotid artery (CCA) diameter (D) and wall motion were measured by high resolution echotracking system (Acuson Aspes, Acuson Corp., Mountain view, California, USA). Common carotid compliance and distensibility were calculated from changes in D during systole (Ds) and diastole (Dd) and simultaneously measured common carotid pulse pressure (ΔP) according to formula:

$$\text{Compliance} : [\pi Dd\ (Ds - Dd)/2]/\Delta P(\text{m}^2.\text{kPa} \times 10^{-7})$$

$$\text{Distensibility} : 2[(Ds - Dd)/Dd]/\Delta P(\text{kPa}^{-1} \times 10^{-3})$$

The common carotid artery measurements were taken in the right carotid artery. The common carotid lumen cross-sectional area (LCSA) was calculated as $\pi(D^2/4)$. The common carotid intima-media thickness (IMT) was measured at the same level of the diameter measurements. The intima-media cross-sectional area was calculated as $\pi(D/2 + \text{IMT})^2 - \pi(D/2)^2$. The incremental elastic modulus, which is the slope of the stress–strain relationship of arterial vessels, was calculated following formulae:

$$\text{Einc} = 3(1 + \text{LCSA}/\text{IMCSA}) \times 1/\text{Distensibility}$$

Blood pressure (BP) measurements were obtained prior to HD session with conventional sphygmomanometer. The predialysis systolic blood pressure (SBP) and diastolic blood pressure (DBP) were the means of 4 separate measurements. Pulse pressure (PP) calculated as SBP minus DBP.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS software (version 9.05; SPSS Inc., Chicago, IL, USA). Results are given as means $\pm$ SD, $p < 0.05$ was considered significant.

RESULTS

The clinical characteristics of the patients are shown in Table 1 and the CCA measurements are shown in Table 2.

Carotid Einc measurements were significantly correlated with mean age ($r = 0.543$; $p = 0.001$), SBP ($r = 0.399$, $p = 0.02$), PP ($r = 0.402$, $p = 0.02$). Moreover, there was a significant positive correlation with serum Ca ($r = 0.463$, $p = 0.008$),

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Table 1. Clinical and laboratory variables of subjects.

	Mean ± SD
Age (years)	42.2 ± 19.3
Males:Females (ratio)	16/16
On vitamin D replacement	% 66
HD duration (months)	48.6 ± 38.5
SBP (mmHg)	139.2 ± 19.5
DBP (mmHg)	85.1 ± 11.9
PP (mmHg)	53.4 ± 13.5
Serum Ca (mg/dL)	8.8 ± 0.8
Serum P (mg/dL)	6.4 ± 1.7
Serum ALP (IU/L)	413.4 ± 187.4
iPTH (pg/mL)	5.24 ± 468.8
CaX P (mg^2/dL^2)	57.1 ± 15.6
Ferritin (ng/mL)	1172.6 ± 973.4
hs-CRP (mg/L)	8.0 ± 8.4

Table 2. Common carotid artery measurements of the patients.

	Mean ± SD
IMT (μm)	707.1 ± 249.3
IMCSA (mm^2)	22.1 ± 9.3
Compliance (m^2, kPa × 10^{-7})	9.15 ± 3.6
Distensibility ($kPa^{-1} \times 10^{-3}$)	15.56 ± 5.12
Einc (kPa × 10^3)	0.85 ± 0.28

a negative correlation with serum ALP ($r = -0.369$, $p = 0.038$). On the other hand nonsignificant negative correlation was found with P ($r = -0.192$) and PTH ($r = -0.266$) (Table 3).

The CCA distensibility was significantly correlated with age ($r = -0.729$, $p = 0.000$), SBP ($r = -0.527$, $p = 0.004$), DBP ($r = -0.423$, $p = 0.003$), PP ($r = -0.414$, $p = 0.03$), Ca ($r = -0.546$, $p = 0.03$), ALP ($r = 0.385$, $p = 0.04$) and PTH ($r = 0.404$, $p = 0.03$). When inflammatory parameters were analyzed, hs-CRP ($r = 0.388$, $p = 0.02$) was significantly correlated with Einc, but ferritin levels did not. Einc was not influenced by HD duration and DBP. There was nonsignificant correlation between HD, hs-CRP and ferritin with distensibility (Table 3).

The mean Einc measurements in patients receiving vitamin D and those who do not were $0.936 \pm 0.300\,\text{kPa} \times 10^3$ and $0.686 \pm 0.129\,\text{kPa} \times 10^3$ respectively, and this difference was statistically significant ($p = 0.003$) as seen in Fig. 1. Figure 2 shows a positive relationship between serum Ca and Einc ($r = 0.463$, $p = 0.008$). The use of vitamin D was associated with high Einc measurements. The correlation between serum Ca levels and Einc was more prominent in our patients.

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Table 3. The correlation between the common carotid artery Einc and distensibility with hemodynamic, metabolic, and inflammatory parameters in patients.

	Einc		Distensibility	
Correlation coefficient (r)	Correlation coefficient (r)	P value	Correlation coefficient (r)	P value
Age (years)	0.543	0.001	−0.729	0.000
HD (months)	−0.151	NS	0.143	NS
SBP (mmHg)	0.399	0.02	−0.527	0.004
DBP (mmHg)	0.244	NS	−0.423	0.003
PP (mmHg)	0.402	0.02	−0.414	0.03
Ca (mg/dL)	0.463	0.008	−0.546	0.03
P (mg/dL)	−0.192	NS	0.311	NS
Ca x P (mg^2/dL^2)	−0.061	NS	0.133	NS
ALP (IU/L)	−0.369	0.038	0.385	0.04
PTH (pg/mL)	−0.266	NS	0.404	0.03
Ferritin (ng/mL)	0.301	NS	−0.245	NS
CRP (mg/L)	0.388	0.02	−0.200	NS

NS = not significant.

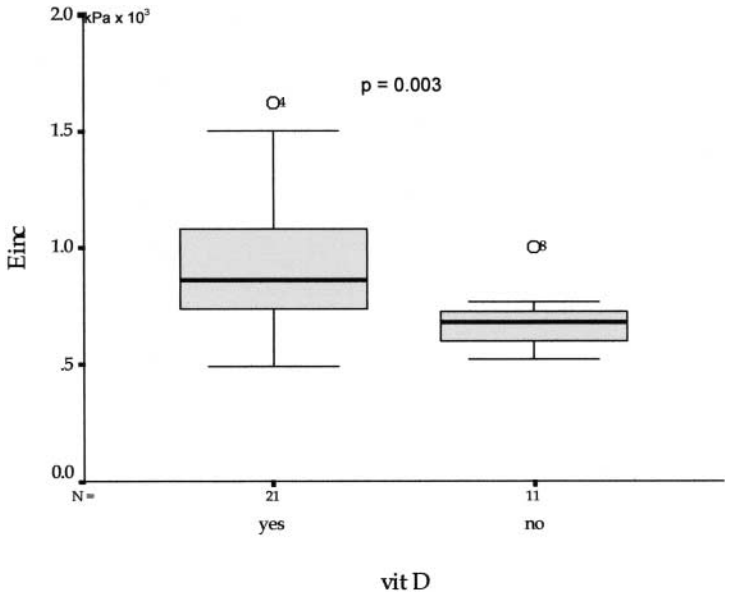


Figure 1. The box plots showing the difference of Einc measurements according to vitamin D therapy.

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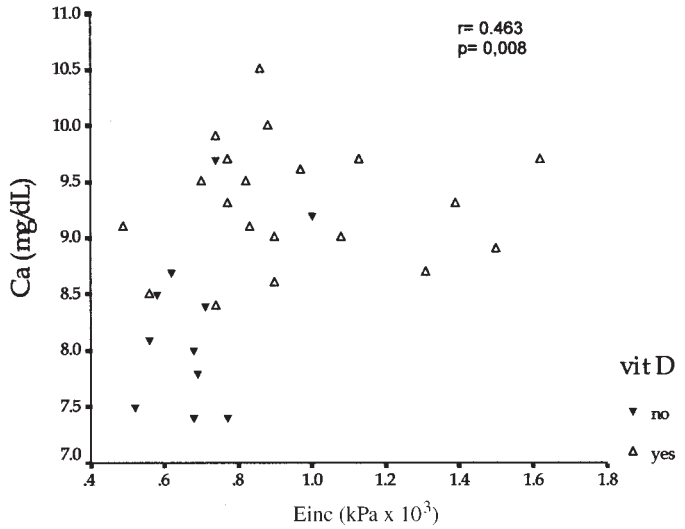


Figure 2. The correlation between Einc and serum Ca levels in patients with or without vitamin D treatment.

DISCUSSION

In uremic patients the arterial structural remodeling which is characterized by dilatation and hypertrophy of large arteries is associated with alterations in hemodynamic and nonhemodynamic factors.[4] This structural remodeling is with the stiffening of the aorta and the CCA.[5] Recently it has been shown that arterial stiffening is one of the major predictor of cardiovascular disease in ESRD.[3]

Arterial stiffening is known to be influenced by hypertension and age. Whereas in essential hypertensive patients decreased arterial distensibility is related to a higher distending blood pressure, decreased arterial distensibility is due to arterial wall thickening and structural changes in ESRD patients.[6] In literature, increased arterial stiffening was found independent of high blood pressure and age in uremic patients.[7] In our patients we found significant correlation between SBP and age with Einc, which is a marker of arterial stiffening as in literature. Distensibility was decreased with age and SBP as expected. Increased Einc in ESRD is related to altered intrinsic elastic material and architectural abnormalities as those seen in experimental uremia and in the arteries of uremic patients.[8,9] It is suggested that several factors such as endothelin, PTH, Ca, P, and chronic inflammatory changes may play an important role in alteration of the arterial structure in ESRD.

We found strong correlation between serum Ca levels and Einc measurement and this correlation was more prominent in patients receiving vitamin D therapy (Figs. 1 and 2). High levels of Ca and vitamin D treatment were associated with increased Einc in our patients (Fig. 2). But ALP was negatively correlated with Einc. The control of secondary hyperparathyroidism with vitamin D and Ca containing phosphate binders commonly causes calcification in tissue and vessels. We found that increased Einc was associated with high serum Ca level and Vit D therapy.

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But ALP showed a significantly negative correlation with Einc. In our patients while serum PTH levels decreased, Einc measurements increased as in serum P and Ca ×P products. According to these findings intensive therapy of secondary hyperparathyroidism can cause increased arterial stiffening and decreased distensibility in CCA in ESRD.

It is known that CRP is also an important factor in cardiovascular disease.[10] As in atherosclerosis we also observed that hs-CRP was high in patients with increased Einc.

The distensibility of CCA is closely related with age, SBP, DBP, PP, serum levels of Ca, P, ALP, and PTH . The alteration of the intrinsic elastic properties of arterial wall (increased Einc and decreased distensibility) can cause cardiovascular symptoms like in atherosclerotic heart disease. The relationship of positive Ca and P balance with vascular disease like calciphylaxis(calcific uremic arteriolopathy) has been observed.[11] The correlation of increased Einc and decreased distensibility with low PTH and ALP and high serum Ca may explain the high tendency for arteriosclerosis in adynamic bone disease these alterations with high serum levels of Ca and low serum levels of PTH, P, and ALP. Could deposition of Ca in other tissues and vessels instead of bone as in calciphylaxis be the cause of structural and functional abnormalities?

In conclusion, increased arterial stiffness and decreased distensibility are related to aging and high blood pressure in HD patients. Moreover, its relation to PTH, ALP, serum Ca, and P could suggest the role of secondary hyperparathyroidism, and even calciphylaxis. It is possible that presence of high inflammatory markers such as CRP along with the increased stiffening and distensibility of the CCA could be the cause or the outcome of arteriosclerosis.

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