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Original Article

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Effects of Interdialytic Weight Gain and Salt Intake on Serum Vascular Endothelial Growth Factor-C (VEGF-C) Levels in Hemodialysis Patients

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ABSTRACT

Objective: Sodium may accumulate in subcutaneous tissue without any osmotic (non-osmotic) effect. There are insufficient data on non-osmotic sodium mechanisms in hemodialysis patients. We aimed to investigate the relationship between serum vascular endothelial growth factor-C levels, interdialytic weight gain, and salt intake in hemodialysis patients.
Methods: The study included 20 anuric hemodialysis patients (11/9; female/male) with stable interdialytic weight gain in the last 3 months. Pre- and post-dialysis sodium and vascular endothelial growth factor-C levels were studied in 2 consecutive hemodialysis sessions. Fluid body components were determined by body composition monitor. The formulas derived from serum sodium and body fluids were used to calculate the interdialytic salt intake. The determinants of serum vascular endothelial growth factor-C levels were analyzed.
Results: Salt intake in the interdialytic period was 10.36 ± 5.16 g/day and interdialytic weight gain 3.4% (0.53-6.98). While no correlation was found between salt intake and vascular endothelial growth factor-C levels in the correlation analysis, a moderate correlation was found between interdialytic weight gain and pre-and post-dialysis vascular endothelial growth factor-C levels (r: 0.453; P = .045 and r: 0.454; P = .044, respectively). In the partial correlation analysis performed by controlling the salt intake effect, an increase in this correlation was detected (r: 0.489; P = .34 and r: .525; P = .018, respectively). There was no relationship between age, gender, hemodialysis vintage, and vascular endothelial growth factor-C levels.
Conclusion: A moderate correlation was detected between interdialytic weight gain and serum vascular endothelial growth factor-C levels and it may be a clinical reflection of long-term volume and salt loading. However, more extensive studies are needed to clarify this relationship and determine the factors affecting serum vascular endothelial growth factor-C levels in hemodialysis patients.
Keywords: Hemodialysis, interdialytic weight gain, non-osmotic sodium, salt, VEGF-C

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INTRODUCTION

Sodium (Na) is the most crucial cation of extracellular fluid. The osmotic activity created by sodium and accompanying anions plays a vital role in maintaining the extracellular fluid. Previous studies have shown that sodium can accumulate in subcutaneous tissue without any osmotic (non-osmotic) effect.[1,2] Sodium accumulation in the interstitial space, with increased polymerization and sulfation of glycosaminoglycans, causes hypertonicity and osmotic stress. Mononuclear phagocyte system (MPS) cells activate tonicity responsive enhancer-binding protein (TonEBP) and induce local regulatory cascades to maintain interstitium integrity in response to osmotic stress. Tonicity responsive enhancer-binding protein binds to the promoter region of the gene coding vascular endothelial growth factor-C (VEGF-C) and induces VEGF-C secretion from MPS cells. Vascular endothelial growth factor-C protects the interstitial space from osmotic stress by inducing endothelial nitric oxide synthase expression

and lymphangiogenesis.[3,4] Any step of this cascade blockage leads to sodium storage in interstitial space and salt-sensitive hypertension.[5]

Salt and fluid intakes are the most important determinants of interdialytic weight gain (IDWG) in hemodialysis patients. The association between interdialytic salt intake, chronic volume load, increased blood pressure, and cardiovascular morbidity and mortality are well recognized in dialysis patients.[6-9] It has also been shown that sodium accumulates in tissue, especially in the subcutaneous tissue, in hemodialysis patients.[10-12] However, information on the relationship between salt intake or IDWG and non-osmotic sodium accumulation in hemodialysis patients is limited. This study aimed to investigate the relationship between serum VEGF-C levels, IDWG, and salt intake in hemodialysis patients.

METHODS

Patients

The Ethics Committee of Hacettepe University approved the study protocol (GO 13/510-19), and all persons included in the study signed the informed consent form. Twenty adult patients (11 females and 9 males) under regular hemodialysis treatment (3 times/week) for at least 6 months at Hacettepe University Hospital hemodialysis unit were included in the study. The dialysis duration was 4 hours, and the same high flux dialysis membranes were used in all patients. Interdialytic time was similar and 44 hours in all patients. Anuric patients (urine output <100 mL/day) were enrolled to ensure that no sodium was excreted via urine. Exclusion criteria were significant volume overload and increased cardiothoracic ratio on physical examination, and the presence of active or chronic infection. Since patients were under regular hemodialysis for at least 6 months, they were considered to reach their dry body weight before enrollment. Interdialytic weight gain is expressed as a percentage based on the patient's dry weight. Patients with stable IDWG in the last 3 months were included in the study, and patients with severe IDWG (≥10% of dry weight) were also excluded from the study. Demographic characteristics, co-morbid conditions, and current medications of patients were obtained from medical records.

Detection of Interdialytic Weight Gain and the Total Amount of Body Fluid by Body Composition Monitor

Body weight of the patients was measured by the dialysis staff before and after every hemodialysis sessions. Body composition monitor (BCM) (Fresenius Medical Care, Bad Homburg, Germany) was used to evaluate fluid status of the patients. Body composition monitor is a reliable method for body fluid volumes determination and can be used safely in both hemodialysis and peritoneal dialysis patients.[13-15] All BCM measurements of the patients were carried out 5 minutes before and 15 minutes after the dialysis sessions and in the supine position. Electrodes were attached to the hand and foot contralateral to the dialysis fistula or graft, and the measurements were conducted as described in the manufacturer's manual.

The hydration status (HS) of the patients was determined according to their values of ΔHS and described in previous study.[16] ΔHS can be calculated from the difference between the normal extracellular water (ECW) expected and the measured ECW. Subjects with values of ΔHS between −1.1 L and +1.1 L were considered to be normohydrated. However, those with values of ΔHS lower than −1.1 L were considered underhydrated, and those with values of ΔHS greater than +1.1 L were considered overhydrated (fluid overload). Ultrafiltration amount was determined according to pre-determined dry weight without any other intervention.

Measurement of Serum Na and Vascular Endothelial Growth Factor-C Levels

Blood samples of patients were obtained 2 times: first, at the end of the first dialysis session of 2 consecutive dialysis sessions (post-dialysis-1) and second, before the beginning of the second dialysis session (predialysis-2). Serum sodium levels were also measured in the same samples to evaluate total body sodium. Blood samples were centrifuged and separated to detect serum VEGF-C levels, and then these samples were kept at −20°C until the analysis time. Serum VEGF-C levels were determined by using an enzyme-linked immunosorbent assay (ELISA) kit (Eastbiopharm, Zhejiang, China).

First of all, the change in total body sodium, and indirectly the amount of sodium taken in the interdialytic period, was calculated using the formula below. Salt intake was then calculated using the equation of 1 g salt = 17.1 mEq of sodium.

*TBF^2: total body fluid before the second dialysis, TBF^1: total body fluid after the first dialysis (adapted from reference[17]).

Amount of Na intake (mEq) = (TBF^2 × instant Na level^2) − (TBF^1 × instant Na level^1)

MAIN POINTS

- Sodium can accumulate in subcutaneous tissue without any osmotic (non-osmotic) effect. Sodium accumulation causes hypertonicity and osmotic stress and then induces vascular endothelial growth factor-C (VEGF) secretion from mononuclear phagocyte system cells.
- Information on the relationship between salt intake or interdialytic weight gain (IDWG) and non-osmotic sodium accumulation in hemodialysis patients is limited.
- Serum VEGF-C levels showed a significant variation among in hemodialysis patients and showed a moderate correlation with IDWG.
- High serum VEGF-C levels may be a reflection of chronic higher IDWG.

Table 1. Demographic and Clinical Features of the Study Patients	
Age (years)	54.65 ± 13.08
Gender (female), n (%)	11 (55)
BMI (kg/m^2)	26.44 ± 6.1
Hemodialysis vintage (month)	88.5 (6-301)
Chronic kidney disease etiology, n (%)	
Diabetes mellitus	3 (15)
Hypertension	2 (10)
Polycystic kidney disease	2 (10)
Amyloidosis	3 (15)
Urologic causes	5 (25)
Glomerulonephritis	1 (5)
Unknown	4 (20)
Coronary artery disease, n (%)	5 (25)
Congestive heart failure, n (%)	4 (20)
Antihypertensive drug use, n (%)	2 (10)

Statistical Analysis

All analyses were conducted using the SPSS for Windows, version 25 (IBM Corp., Armonk, NY, USA). Normality distribution was evaluated with the Shapiro–Wilk test. The data were expressed as mean ± standard deviation in the variables showing normal distribution and median (minimum-maximum) in those that did not show normal distribution. Paired-samples *t*-test was used to compare dependent non-parametric variables in those with normal distribution, and Wilcoxon test was used in those without normal distribution. Spearmans' correlation analysis and partial correlation analyses were performed in the correlation analysis between VEGF-C levels and IDWG and salt intake. *P* values <.05 were considered statistically significant.

RESULTS

Nine (55%) patients were women, and the mean age was 54.65 ± 13.08 years. The median dialysis vintage was 88.5 (6-301) months, and only 2 (10%) of the patients received antihypertensive agents (1 patient took amlodipine and the other took carvedilol). Demographic and clinical features of the patients are shown in Table 1.

Only 1 patient was hypervolemic (fluid overloaded) (ΔHS >1.1 L) according to the ECW status in the evaluation with BCM. The mean ΔHS of the patients was −0.83 ± 1.61 L and the median was −0.71 [(−4.51) − (1.69)] L.

When patients' pre- and post-dialysis clinical, hemodynamic, and laboratory parameters were compared, there were statistically significant increases in systolic and diastolic blood pressure, body weight, and extracellular volume at predialysis-2 compared to the post-dialysis-1. Although there was a numeric decrease in predialysis-2 VEGF-C levels compared to post-dialysis-1 VEGF-C levels, the difference was not statistically significant [1614.5 (897-5400) vs. 1795 (635-4362), respectively; *P* = .765] (Table 2).

The amount of salt intake in the interdialytic period was 10.36 ± 5.16 g/day and IDWG was 3.4 (0.53-6.98)%. There was no correlation between salt intake and pre-and post-dialysis VEGF-C levels, while a moderate correlation was found between IDWG and pre-and post-dialysis VEGF-C levels (*r*: 0.453; *P* = .045 and *r*: 0.454; *P* = .044, respectively). In the partial correlation analysis performed by controlling the salt intake effect, it was observed that this effect continued (*r*: 0.489; *P* = .34 and *r*: 0.525; *P* = .018, respectively) (Table 3).

There was no correlation between age and both post-dialysis and pre-dialysis VEGF-C levels (*r*: −0.128; *P* = .59 and *r*: −0.224; *P* = .342, respectively). Similarly, no correlation was found between the duration of hemodialysis and VEGF-C levels. There was no difference between post-dialysis (2321.82 ± 1098.96 vs. 1836.89 ± 1285.95; *P* = .375) and pre-dialysis [1875 (916-5400) vs. 1091 (897-4065); *P* = .102] serum VEGF-C values between women and men.

DISCUSSION

In our study, serum VEGF-C levels showed a significant variation among in hemodialysis patients and serum VEGF-C levels showed a moderate correlation with IDWG.

Table 2. Changes in Clinical and Laboratory Parameters of the Patients in the Interdialytic Period				
	Post-dialysis (1)	**Pre-dialysis (2)**	**Test Statistics**	***P***
Body weight (kg)	68.83 ± 20.92	71.19 ± 21.36	−11.079	<.001
Extracellular fluid (L)	14.52 ± 3.69	16.64 ± 4.2	−12.212	<.001
Systolic blood pressure (mm Hg)	99.6 ± 24.65	120.75 ± 24.67	−4.855	<.001
Diastolic blood pressure (mm Hg)	61.55 ± 13.12	72.95 ± 13.8	−4.52	<.001
Serum sodium (mEq/L)	135 (132-138)	135 (130-143)	−0.716	.474
VEGF-C (ng/mL)	1795 (635-4362)	1614.5 (897-5400)	−0.299	.765

VEGF-C, vascular endothelial growth factor-C.

Table 3. Relationship Between VEGF-C Levels and Interdialytic Weight Gain and Salt Intake

	Serum VEGF-C levels							
	Post-dialysis				Pre-dialysis			
	r^1	*P*	r^2	*P*	r^1	*P*	r^2	*P*
IDWG	0.453	.045	0.489	.034	0.454	.044	0.525	.018
Salt intake	−0.038	.875	−0.224	.356	0.077	.748	−0.206	.397

VEGF-C, vascular endothelial growth factor-C; IDWG, interdiyalitic weight gain; r^1, bivariate (Spearman's) correlation analysis; r^2, partial correlation analysis.

There are limited data regarding the effects of salt intake on serum VEGF-C levels in chronic kidney disease patients. In patients with non-dialysis chronic kidney disease, Slagmann et al[18] demonstrated that serum VEGF-C levels change by salt intake. Salt-rich diet was associated with increased blood pressure, extracellular fluid volume, and serum VEGF-C levels in patients with chronic kidney diseases (mean creatinine clearance of the patients was >80 mL/min).[18] On the other hand, data on non-osmotic sodium accumulation in dialysis patients are scarce. Dahlmann et al[10] found that VEGF-C levels were significantly lower in dialysis patients than in the healthy control group. They also showed that age was associated with increased tissue Na content both in dialysis patients and controls. The same study showed that VEGF levels decrease with age in healthy individuals but there was no relationship between age and VEGF levels in hemodialysis patients. Based on these findings, they argued that chronic inflammatory processes such as aging and dialysis could decrease VEGF-C levels and cause accumulation of sodium in the tissues.[10] Similarly, we did not find any relationship between VEGF-C levels and age in dialysis patients. We also did not find an association between VEGF-C levels and gender in dialysis patients.

In our study, we found a moderate correlation between IDWG and VEGF-C levels. There is no data in the literature regarding the relationship between salt and IDWG and VEGF-C levels in dialysis patients. However, Sahutoglu et al[19] found that serum VEGF-C levels in hypervolemic non-dialysis kidney disease patients were significantly higher than VEGF-C levels in normovolemics (healthy controls and normovolemic dialysis patients). Also, serum VEGF-C levels were significantly correlated with bioimpedance spectroscopy measurements.[19] It is well known that chronic hypervolemia is associated with mortality.[7,20] In our study, bioimpedance measurements showed that most of our patients (95%) were normovolemic or hypovolemic. Therefore, it is not possible to say that there is a correlation between serum VEGF-C values and volume status in our patients. However, it should be kept in mind that dry weight and IDWG in dialysis patients are different concepts, and many studies have shown the relationship between IDWG and mortality in dialysis patients.[21-24] As known, there is also a correlation between IDWG and left ventricular mass index, and IDWG is a risk factor for left ventricular hypertrophy.[25,26] On the other hand, a recent experimental study demonstrated the role of VEGF-C-related mechanisms in the accelerated progression of left ventricular remodeling in hypertensive rats.[27] In addition, in a study in which magnetic resonance imaging determined subcutaneous sodium content in patients with chronic kidney disease, it was shown that there was a significant correlation between skin sodium content and left ventricular mass.[28] These data may help to explain the correlation between IDWG and VEGF-C levels in our study, albeit indirectly. Also, Dahlmann et al[10] showed that patients with higher serum VEGF-C levels tended to improve Na excretion from their skin with hemodialysis.[10] This high level of VEGF-C can also be an adaptive protector against chronic volume overload. Considering together with the available information, this correlation between IDWG and serum VEGF-C levels in these stable patients in our study may be a reflection of long-term interdialytic fluid loads.

In our study, serum VEGF-C levels showed a significant variation among patients and serum VEGF-C levels showed a moderate correlation with IDWG. But, this finding is not sufficient to explain the considerable variation in these levels. Dahlman et al[10] argued that age and pro-inflammatory processes such as hemodialysis may affect serum VEGF-C levels. Although they showed that serum VEGF levels in hemodialysis patients were lower than in healthy controls, they did not show a correlation between age and VEGF levels.[10] Similarly, we did not find a correlation between age, gender, and serum VEGF-C levels in our study. Other factors may affect serum VEGF levels. Kopp et al[11] showed that ^{23}Na magnetic resonance imaging indicated increased sodium content in muscle and skin tissue of hemodialysis patients with type 2 diabetes and suggested that impaired glucose metabolism may be related to sodium and water content disorders.[11]

Our study had certain limitations. It has a cross-sectional design that was insufficient to answer the cause-effect relationship. It included a small number of patients and the period selected for the study was limited to the interdialytic period. Another limitation was the calculation of the amount of salt intake by indirect methods. Despite this fact, the amount of salt intake calculated in our study was similar to that found in the SALTURK2 study (14.8 ± 5.4 g/day) conducted by the Turkish Hypertension and Renal Diseases Association[29] and was relatively high. In addition, the evaluation of volume with only BCM is another limitation of our study.

CONCLUSION

As a result, a moderate correlation was determined between IDWG and serum VEGF-C levels. These results suggest that high serum VEGF-C levels may be a reflection of chronic higher IDWG. However, clinical studies with more patients and more extended follow-up periods are needed to support these results.

Ethics Committee Approval: Ethics committee approval was received from the Hacettepe University Non-Invasive Clinical Research Ethics Committee (Approval Date: December 11, 2013; Approval Number: GO 13/510-19).

Informed Consent: Written informed consent was obtained from all the patients who participated in this study.

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