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CLINICAL STUDY

Seasonal variation of C-reactive protein and atherosclerotic cardiovascular events in hemodialysis patients

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ABSTRACT

Background: Atherosclerotic cardiovascular diseases (ACVD) is the most common cause of mortality in hemodialysis (HD) patients and the annual mortality in this population is about 10%. Inflammation is one of the most important predictor of ACVD morbidity and mortality in these patients. Recent studies demonstrated that levels of inflammatory markers and ACVD mortality vary seasonally in healthy population and in high-cardiac-risk populations. In this retrospective analysis, we aimed to determine seasonal variation of inflammation and ACVD morbidity and mortality in HD patients. *Material and methods*: Data were retrieved retrospectively for 1 year. Patients with acute or chronic infections or inflammatory conditions were excluded from the analysis. Laboratory data and ACVD-related events were retrieved from patients' files and these data were classified into seasonal periods. *Results:* Sixty-two patients were included in the final analysis. During follow-up period, geometric means of serum hsCRP levels were similar in all of the seasonal periods (4.17, 4.17, 4.57, and 4.17 mg/L in winter, spring, summer, and autumn, respectively). Means of hsCRP values were significantly higher in patients with active-ACVD compared to patients with no-ACVD in winter (3.38 vs. 13.18 mg/L, $p < 0.05$) and in autumn (3.63 vs. 23.4 mg/L, $p < 0.05$). There were 5 mortality and 7 morbidity and 12 combined morbidity and mortality related to ACVD and the distribution of these events were similar in all of the seasonal periods. *Conclusions:* Our study demonstrates that hsCRP levels and ACVD events do not show seasonal variation in HD patients.

Keywords: inflammation; mortality; seasonal variation; hemodialysis

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INTRODUCTION

Atherosclerotic cardiovascular disease (ACVD) is the leading cause of morbidity and mortality in hemodialysis (HD) patients and rate of cardiovascular death is about 30 times higher in HD patients than general population.[1] Traditional as well as chronic kidney disease (CKD) related risk factors contribute to increased cardiovascular mortality in this population.[2] Among many CV risk factors, inflammation is the main predictor of mortality in this population.[3] Uremic patients, even in the absence of overt infection or inflammation, have chronic low-grade inflammation[4] and abnormally elevated C-reactive protein (CRP) levels is observed in 30–50% of HD patients.[5,6]

Systemic inflammatory status can fluctuate substantially over time in healthy controls and as well as in HD patients.[7–9] Several other studies have also shown a seasonal variation in inflammatory markers with the highest levels being in the winter months compared to spring and summer months.[10–14] However, some other studies did not confirm these findings.[15–17] The variation in inflammatory response is even greater in patients with established ACVD confirming the dynamic inflammatory status in these patients.[18]

Seasonal variations in the incidence of cardiovascular events have also been reported by several investigators with a peak in winter months.[19,20] Cold weather has been shown to alter physiologic hemodynamics (blood pressure, sympathetic tone) and the hematological factors that contribute to the development of arterial thrombosis.[10,21] But, to date, no study has concluded that seasonal variations in plasma CRP are related to reported seasonal variations in ACVD events.

To the best of our knowledge, the possible relation between seasonal variability of CRP levels and ACVD events has not been evaluated in a HD population as well. Therefore, in this study, we aimed to evaluate the seasonal variation in inflammation and as well as morbidity and mortality secondary to ACVD in HD patients.

MATERIAL AND METHODS

Subjects

The study protocol was approved by the Institutional Review Board at the Marmara University and written informed consent was obtained from all patients. A cohort of prevalent HD patients older than 18 years and undergoing HD treatment for at least 6 months was included in this study. All of the patients were from the same HD center. Baseline and follow-up data of the patients have been longitudinally collected from 1 January 2007 to 1 January 2008. Exclusion criteria were (1) signs or symptoms of clinical infection within the last 3 months before the enrollment into the study and any infectious or inflammatory conditions (e.g., diabetic foot, pneumonia) during the study period, (2) glucocorticoid or nonsteroidal anti-inflammatory medication use other than acetylsalicylic acid, (3) those with temporary vascular access, (4) central line insertion or any other invasive procedure during the study period, (5) HIV infection, (6) chronic hepatitis B or C infections, and (7) history of neoplastic, inflammatory, or immunological diseases.

All patients were receiving conventional HD for 4 h three times weekly. All of the patients were dialyzed with bicarbonate dialysate by using polysulfone dialyzers (Fresenius Medical Care, Lexington, USA), which did not change during the whole study period. Water processing (central double reverse osmosis system with endotoxin membrane) and the type of concentrate were also common for the whole study patients and during the whole study period. Dialysate and blood flow rates were 500 and 350 mL/min, respectively.

Thirty-seven patients who had malignancy (n = 5), renal transplantation (n = 1), vaccination (n = 4), acute infections (n = 12), surgical procedures (n = 4), diabetic foot (n = 6), other inflammatory conditions (n = 5) were excluded from the analysis. Sixty-two patients (23 female) were included in the final analysis.

Laboratory methods

As a requirement by the social security system in Turkey, biochemical analysis for serum creatinine, calcium and phosphorus, serum albumin, hemoglobin and parameters of dialysis adequacy (Kt/V) are measured monthly. Serum iron and iron binding capacity, ferritin, plasma iPTH, and high-sensitive C-reactive protein (hsCRP) levels are determined every 3 months and triglyceride, HDL-cholesterol, LDL-cholesterol, and total cholesterol levels every 6 months. All of the measurements were performed in a central laboratory. Blood samples were collected before a midweek HD session from the vascular access. Serum samples were transported to the central laboratory immediately and processed on the same day. The hsCRP values were detected by using highly sensitive immunonephelometric assay (ABCO Diagnostic s.r.l, Sant' Angelo, Italy). The dialysis dose was calculated according to Daugirdas formula.[22]

Data collection and definitions

Information that was obtained from the database included age, gender, duration of dialysis, cause of end stage renal failure (ESRD), predialysis systolic blood pressure (SBP) and diastolic blood pressure (DBP), body mass index (BMI), serum albumin, hsCRP, serum calcium and phosphate, intact parathyroid hormone (iPTH) hemoglobin level (Hb), serum iron, transferrin saturation, ferritin levels, use and dose of erythropoietin and serum lipid levels.

Hypertension was defined as blood pressure greater than 140/90 mmHg at the clinic visit and/or the use of any antihypertensive medications (based on the Joint National Committee definition of hypertension). Blood pressure targets for treated patients with hypertension were based on published guidelines.[23]

Diabetes mellitus was defined as the current use of oral hypoglycemic agents or insulin and/or a history of diabetes mellitus. Patients were classified as smokers if they had a recent or current history of regular tobacco use. Atherosclerotic cardiovascular events were defined as myocardial infarction; the need for coronary angioplasty or coronary bypass surgery; transient ischemic attack or cerebrovascular accident; or the need for peripheral artery angioplasty, bypass surgery, or amputation due to peripheral arterial disease and ischemic colitis. Atherosclerotic CVD profiles in each patient were evaluated using the CVD portion of the index of co-existing diseases (ICED) (Table 1).[24] The score in each category of vascular disease [coronary artery disease (CAD), cerebral vascular events (CVE), and peripheral vascular disease (PVD)] was used to classify patients into three groups:

No-ACVD: ICED score 0 in each of the three categories and a negative cardiac catheterization within the past year.

Stable-ACVD: ICED score of 1 in at least one category and no ICED score of 2 in any category.

Active-ACVD: ICED score of 2 in at least one category.

Winter is considered to start on 1 January and ends on 31 March, spring from 1 April to 30 June, summer

TABLE 1. Scoring for atherosclerotic cardiovascular diseases by the modified index of co-existing diseases.

Score	Coronary artery disease	Cerebral vascular events	Peripheral vascular disease
0	Absence of disease in past or present by history and negative cardiac catheterization within the past year	Absence of disease in past or present by history	Absence of disease in past or present by history
1	Past diagnosis of CAD or myocardial infarction (MI); or evidence of past MI by electrocardiogram (ECG) or echocardiography; or angiographically defined CAD; or history of coronary neovascularization procedures **and** Past 3 months free of angina, acute MI, or ischemia by ECG or other diagnostic tests	Past diagnosis of cerebral vascular events (CVE), symptomatic carotid stenosis, or transient ischemic attacks, or history of carotid endarterectomy or incidental brain computer tomography findings compatible with CVE **and** Past 3 months free of stroke or TIA diagnosis or symptoms	Diagnosis of peripheral vascular disease (PVD) or aortic aneurysm; history of amputation of digits or extremities secondary to PVD, peripheral arterial bypass or aortic aneurysm repair **and** Past 3 months free of intermittent claudication, recurrent cellulitis, skin infections, toe gangrene, or pain at rest secondary to PVD
2	If any of the following in the past 3 months: Stable or exertional angina, angina during HD, acute MI, or ischemia by ECG or other diagnostic tests	If any of the following in the past 3 months: Stroke or TIA diagnosis or symptoms	If any of the following in the past 3 months: Intermittent claudication, recurrent cellulitis, skin infections, toe gangrene, or pain at rest secondary to PVD

from 1 July to 30 September, and autumn from 1 October to 31 December.

Statistical analysis

Statistical analysis was performed with SPSS for windows version 11.0 (SPSS, Chicago, IL, USA). Because hsCRP values are distributed in a skewed manner, logarithmic transformation was applied to this data for statistical interference and proper means (i.e., geometric means) were used to describe results. The other data are expressed as mean ± SD, unless otherwise mentioned. Repeated measures within the subjects were compared by using either paired *t*-test or repeated measures ANOVA followed by Turkey's multiple comparison test. The variables between the subjects were analyzed by one-way ANOVA followed by Turkey's multiple comparison tests. The Fischer exact test was used to compare the categorical variables. The hsCRP values were also categorized as <10 and ≥10 mg/L to use in categorical and one-way ANOVA analysis. A two-tailed *p*-value less than 0.05 was considered statistically significant.

RESULTS

Between January 2007 and January 2008, a total of 62 patients (23 female) were included in the final analysis. Patients' demographic characteristics are summarized in Table 2. Patients were on HD for 69 ± 53 (range 6–255) months. Mean of the age and body mass index were 58 ± 14 years and 26.8 ± 4.9 kg/m^2, respectively. Causes of ESRD were diabetic nephropathy in 19.3%, hypertensive nephrosclerosis in 28%, chronic glomerulonephritis in 26.2%, autosomal dominant polycystic disease in 6.6%, chronic interstitial nephritis in 6.2%, and unknown cause in 13.1%. Fifty-seven (92%) of the patients had an arteriovenous fistula and five (8%)

TABLE 2. Demographic characteristics of study population at baseline.

Female gender (%)	37.1
Age (year)	58 ± 14
Duration of dialysis (months)	69 ± 53
BMI (kg/m^2)	26.8 ± 4.9
SBP (mmHg)	130 ± 30
DBP (mmHg)	79 ± 13
Diabetes mellitus (%)	19.3
Hypertension (%)	62
Smokers (%)	21
Regular exercise (%)	7
Patients on acetylsalicylic acid (%)	14.6
Patients on statin treatment (%)	14
Erythropoietin users (%)	84
ICED Score	
0 point (%)	69.4
1 point (%)	19.4
2 point (%)	11.3

Notes: Data are presented as mean ± SD. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

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had a permanent catheter. Fifty-two patients (84%) were on treatment with erythropoietin, 55 (88%) on intravenous iron (maintenance treatment, 100 mg/month, for the whole study period), 11 (17%) on acetylsalicylic acid, 13 on ACEI or ARBs (21%), and 5 (8%) on statins. Eighteen (29%) patients were active smokers (Table 2).

During follow-up, *Kt/V*, URR, hemoglobin, serum calcium and phosphorus, and PTH levels were similar in all of the seasonal periods. Serum albumin levels were significantly higher in autumn compared to winter and spring. Total cholesterol and LDL-cholesterol levels were significantly lower in summer compared to winter (Table 3). Geometric means of the serum hsCRP levels were also similar in all of the seasonal periods (Table 3). When the hsCRP values were categorized as <10 and ≥10 mg/L, the number of patients with hsCRP levels ≥10 mg/L, were similar in all of the seasons [16 (25%), 14 (22%), 18 (29%), and 17 (27%) patients in winter, spring, summer, and autumn, respectively, $p = 0.887$]. The hsCRP values were not related to gender, smoking status, regular exercise, morbidity, and mortality in all of the seasons. However, geometric means of hsCRP values were significantly higher in ICED-2 scored patients compared to ICED-0 scored patients in winter (3.38 vs. 13.18 mg/L, $p < 0.05$) and in autumn (3.63 vs. 23.4 mg/L, $p < 0.05$). The hsCRP values were also not related to age, duration of HD, hemoglobin, *Kt/V* values in all of the seasons.

The distribution of ACVD events are presented on Table 4. In winter, one patient died as a result of cerebrovascular event. In spring, one patient died as a result of coronary artery disease. In summer, one patient died as a result of congestive heart failure, one patient as a result of acute myocardial infarction. One patient had acute myocardial infarction, two patients underwent coronary artery stenting, and one patient had CABGS in spring. In autumn, one patient died as a result of coronary artery disease, one patient underwent CABGS, one patient had coronary artery stenting, and one patient had carotis artery endarterectomy. There were no seasonal difference in the occurrence either of ACVD morbidity or ACVD mortality or

TABLE 3. Seasonal demographic and laboratory data.

	Winter	Spring	Summer	Autumn
BMI (kg/m^2)	26.8 ± 4.9	26.8 ± 4.9	26.6 ± 4.9	26.7 ± 4.8
SBP (mmHg)	130 ± 30	132 ± 31	128 ± 30	129 ± 30
DBP (mmHg)	79 ± 13	81 ± 13	78 ± 13	78 ± 13
ICED Score				
0 point (%)	73	73	69.8	69.8
1 point (%)	17.5	20.6	22.2	20.6
2 point (%)	7.9	4.8	6.3	8.1
Kt/V	1.4 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	1.4 ± 0.3
URR (%)	66 ± 8$^{\#}$	64 ± 9	67 ± 6	65 ± 10
hsCRP (mg/L)*	4.17	4.17	4.57	4.17
Hb (g/dL)	11.5 ± 1.5	11.6 ± 1.4	11.4 ± 1.3	11.5 ± 1.4
Serum albumin (g/dL)	4.0 ± 0.5	4.1 ± 0.4	4.1 ± 0.3	4.3 ± 0.3*
Total cholesterol (mg/dL)	194 ± 60		181 ± 54†	
Triglyceride (mg/dL)	199 ± 110		208 ± 157	
HDL-cholesterol (mg/dL)	41 ± 11		39 ± 12	
LDL-cholesterol (mg/dL)	110 ± 38		96 ± 29†	
Calcium (mg/dL)	9.1 ± 0.9	9.0 ± 1.0	9.3 ± 0.8	9.2 ± 0.8
Phosphorus (mg/dL)	5.0 ± 1.5	5.5 ± 2.0	5.2 ± 1.9	5.2 ± 1.7
PTH (ng/mL)	599 ± 557		556 ± 576	

Notes: Data are presented as mean ± SD unless otherwise mentioned. *Data are presented as geometric mean. hsCRP, high-sensitive C-reactive protein; URR, urea reduction ratio; PTH, parathormone.
$^{\#}p < 0.05$ versus spring,
$^{\star}p < 0.001$ versus winter and spring,
$^{\dagger}p < 0.01$ versus winter.

TABLE 4. Seasonal distribution of atherosclerotic cardiovascular events.

	ACVD mortality	ACVD morbidity	ACVD events combined
Winter (n = 62)	1 (1.6%)	0	1 (1.6%)
Spiring (n = 61)	1 (1.6%)	0	1 (1.6%)
Summer (n = 60)	2 (3.3%)	4 (6.6%)	10 (10%)
Autumn (n = 54)	1 (1.8%)	3 (5.4%)	4 (7.1%)

Notes: Data are presented as number and percentage. ACVD, atherosclerotic cardiovascular disease.

combined ACVD morbidity and mortality (p-values are 0.89, 0.34, and 0.08, respectively).

DISCUSSION

C-reactive protein (CRP) is a well-known marker for future myocardial infarction and stroke, and several studies have reported higher incidences of cardiovascular events during the winter months. Here, we retrospectively investigated the seasonal CRP variations in a HD cohort using a high-sensitivity immunoradiometric assay. We could not find any seasonal differences in hsCRP levels and ACVD morbidity and mortality in our HD population.

To our knowledge, this is the first study evaluating the seasonal variation in inflammation and cardiovascular morbidity and mortality in a HD cohort. Woodhouse et al. studied 96 men and women with the ages between 65 and 74 years. The hsCRP levels increased from 2.4 to 5.7 mg/L in late winter compared to late-summer periods.[10] Crawford et al. also sampled 24 elderly subjects monthly to determine whether CRP had any seasonal variation. They reported that CRP had a summer low point and reached a peak in late February. The mean summer–winter increase in the studied group was 3.71 mg/L.[12] Sung et al. also reported a highly significant seasonal variation in CRP levels, with higher values during winter and spring than in summer in healthy Koreans.[14] However, in contrast to these studies, Frohlich et al. analyzed data from 16 healthy participants (8 women and 8 men, ages 20–41 years) each month for 1 year. While a seasonal difference of 58% was observed, it was not statistically significant and the authors concluded there was no strong, consistent evidence for an intraindividual or interindividual seasonal variation of CRP.[25] In another study, Horan et al. investigated two populations: elderly subjects (mean age 79 years) and young healthy adults (mean age 37 years). While the researchers observed a significant winter increase in CRP, especially in the elderly participants, this was largely explained by winter acute respiratory tract infections. After multivariate analysis, season was not associated with increases in CRP.[26] In our study, although hsCRP levels were similar in all of the seasons, it was about 10% higher in summer. This was in contrast to above-mentioned reports performed mainly in healthy or elderly populations.[10,12,14,26] Similar to our study, Rogowski et al. examined CRP levels for 1 year and found no seasonal variation in a group of 1677 apparently healthy patients in whom the presence of infection or inflammation was excluded.[27] In previous studies that are performed in HD patients, variation in CRP levels was also reported.[9,28,29] But these studies did not consider seasonal variation of inflammation and were limited to 4 months of follow-up at most.[9] In the study by Tsirpanlis et al., the intraindividual variation of CRP was more than 30%. The elderly patients had a more labile inflammatory status probably due to medical conditions such as degenerative diseases, advanced glycation end products.[9] Boenisch et al., followed up CRP and other inflammatory parameters weekly for 12 weeks and reported a 51% intraindividual variation even though they did not include patients with clinically apparent infections.[28] On the other hand, in the HEMO study, the intraindividual coefficient of variation for CRP was 88%.[29] This group reasoned that intercurrent illnesses during the study period could explain this large variability. In our study, the reasons we could not find variation in hsCRP levels was probably due to the fact we also excluded any patients with acute infections, vaccinations, malignancies, surgical procedures during the study period.

In the study by Rudnicka et al., the seasonal change in CRP was borderline and 23% of the variation was explained by cardiac CVD risk factors including smoking status, blood pressure, total cholesterol, high-density lipoprotein cholesterol, body mass index, self-reported diagnosis or treatment for heart problems, hypertension, and diabetes.[30] In our study, CVD risk profile of our patients was almost constant during the study period as determined by ICED scores. The other confounding factors that could potentially affect CRP values such as age,[31] body weight,[32] diet,[33] level of physical activity,[34] and medications used[35,36] were constant in all of the patients throughout the study period. Furthermore, membranes were also the same type dialyzers in all of the patients and the dialysate was ultrapure therefore excluding the possibility of lipopolysaccharide-induced inflammatory response.[37]

In this study, we could not demonstrate a relation between season and cardiovascular mortality and morbidity. Previously, it was reported that cardiovascular morbidity and mortality are elevated especially in the elderly during winter months in parallel to a hypercoagulable and inflammatory state in colder

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months.[11] Recently Moschos et al. reported a seasonal distribution in the incidence of acute myocardial infarction, which peaked during the winter.[20] Similarly, Spencer et al., reported 53% more cases of acute myocardial infarction in winter than during the summer in the second National Registry of Myocardial Infarction.[19] Sympathetic tone, blood pressure, myocardial oxygen consumption, red blood cell and platelet count, plasma beta-thromboglobulin, platelet factor 4, and plasma fibrinogen have been shown to increase, and antithrombin III to decrease, with colder weather.[21,38]

Limitations of the present study are the relatively small number of the cases and retrospective nature of the study. In addition, hsCRP determinations were performed on single occasions, whereas the Center for Disease Control and the American Heart Association recommends hsCRP determination twice that are performed 2 or more weeks apart.[18] However, the use of two such independent measurements taken 90 days apart was found to result in the classification of 90% of participants into the same or an immediately adjacent biomarker tertile, a percentage comparable to that observed for cholesterol.[7]

In conclusion, the results of the present study demonstrated no significant seasonal hsCRP variation and cardiovascular morbidity and mortality in HD exist when patients with acute inflammation or infection were excluded from the analysis.

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