ORIGINAL ARTICLE

EVALUATION OF SMOKING AS AN ADDITIONAL RISK FACTOR FOR CARDIOVASCULAR DISEASES AMONG HEMODIALYSIS PATIENTS BY INCREASED LEVELS OF IL-6, TNF-ALPHA, hsCRP AND ENDOTHELIN-1

EVALUACIÓN DEL TABAQUISMO COMO FACTOR DE RIESGO ADICIONAL DE ENFERMEDADES CARDIOVASCULARES EN PACIENTES EN HEMODIÁLISIS SEGÚN NIVELES ELEVADOS DE IL-6, TNFα, hsCRP y ENDOTELINA-1

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ABSTRACT

Introduction: Cardiovascular diseases (CVD) are one of the most common causes of mortality in chronic kidney disease. Smoking is a well defined risk factor for atherosclerotic cardiovascular disease. Interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), high sensitive C-reactive protein (hsCRP) and endothelin-1 (ET-1) have found elevated in chronic inflammatory process. We aimed to evaluate if IL-6, TNF-alpha, hsCRP and ET-1 are increased in smoker hemodialysis (HD) patient compared to non-smoker HD individuals to potentially refer us cardiovascular diseases noninvasively. **Material and methods:** 80 smoker and 50 non-smoker maintenance hemodialysis male patients with similar demographic characters, dialysis and support treatment and metabolic profile. In addition to routine tests, we took samples for evaluating IL-6, TNF-alpha, hsCRP and endothelin-1. P values were measured. **Results:** In smoker HD patients, IL-6, TNF-alpha, hsCRP and endothelin-1 levels were found increased compared to non-smoker individuals. The difference was statistically significant. **Conclusion:** This study may refer to us that smoking is an additional risk factor among HD individuals by increased levels of IL-6, TNF-alpha, hsCRP and ET-1.

KEYWORDS: interleukin-6; tumor necrosis factor-alpha; high sensitive C-reactive protein; endothelin-1; hemodialysis; renal dialysis; smoking

RESUMEN

Introducción: Las enfermedades cardiovasculares (EC) constituyen una de las causas más frecuentes de mortalidad en los casos de enfermedad renal crónica. El tabaquismo es un factor de riesgo bien definido para la enfermedad cardiovascular aterosclerótica. Se encontraron valores elevados de Interleucina-6 (IL-6), factor de necrosis tumoral

alfa (TNFα), proteína C-reactiva de alta sensibilidad (hsCRP) y Endotelina-1 (Et-1) en el proceso inflamatorio crónico. El objetivo fue analizar si los valores de IL-6, TNFα, hsCRP y Et-1 son más elevados en los pacientes fumadores en hemodiálisis que en los no fumadores para predecir una posible enfermedad cardiovascular de forma no invasiva. **Material y métodos:** Se incluyeron pacientes masculinos en hemodiálisis de mantenimiento, 80 fumadores y 50 no fumadores, similares en cuanto a sus características demográficas, tratamiento de diálisis y de mantenimiento, y perfil metabólico. Además de los análisis de rutina, se tomaron muestras para evaluar los valores de IL-6, TNFα, hsCRP y Endotelina-1. Se midieron los valores de p. **Resultados:** Se halló una diferencia estadísticamente significativa en los niveles de IL-6, TNFα, hsCRP y Endotelina-1: fueron más elevados en los pacientes sometidos a hemodiálisis que eran fumadores en comparación con los no fumadores. **Conclusión:** Este estudio podría demostrar que el tabaquismo es un factor de riesgo adicional para los pacientes que se tratan con hemodiálisis según muestran los valores elevados de IL-6, TNFα, hsCRP y Et-1.

PALABRAS CLAVE: interleucina-6; factor de necrosis tumoral alfa; proteína C-reactiva altamente sensible; endotelina-1; hemodiálisis; diálisis renal; tabaquismo

INTRODUCTION

End stage renal failure (ESRD) and cardiovascular morbidity, mortality, atherosclerosis

Cardiovasvular diseases (CVD) are the most common causes of morbidity and mortality in patients with chronic kidney disease.[1] Cardiovascular mortality was found 10-30 times increased in ESRD population compared to normal population. It is properly known that the major risk factor for cardiovascular diseases is atherosclerosis due to not only traditional risk factors such as diabetes mellitus, dyslipidemia, smoking, male sex, age, obesity but also nature of chronic kidney disease.[2] In recent studies CKD related pathopyhsiologic changes such as uremia, hyperphosphatemia, elevated CaxP level, hyperparathyroidism, oxidative stress, inflammation, protein-energy wasting, asymmetric dimethylarginine, P-cresol, fetuin-A, hsCRP may contribute as additional risk factors for CVD.[3-4]

Chronic inflammation, markers

Chronic inflammation among the patients with ESRD is a common process. The major pathophysiologic mechanisms include decreased clearance of proinflammatory cytokines, volume overload with endotoxinemia, oxidative and carbonyl stress, decreased levels of antioxidants, increased presence of comorbid conditions such as recurrent infections, cardiovasvular diseases, bone metabolism disorders.[1]

The chronically elevated hsCRP levels are associated with subsequent endothelial dysfunction and atherosclerotic cardiovascular disease.[4-6] Tibuakuu et al reported that hsCRP and IL-6 were promising for early detection of atherosclerosis caused by smoking.[7]

Endothelin-1 (ET-1) is a potent vasoconstrictor derived from the endothelium. Its concentration is mainly elevated during endothelial inflammation and atherosclerosis.[8-9] In patients with CKD, plasma ET-1 concentrations are elevated, due to both increased production and decreased renal clearance (10). Several studies with small numbers of individuals have showed that a high plasma ET-1levels in hypertension may play a role on early atherosclerosis and end-organ damage (11). On the other hand, role of ET-1 in smoker HD patients remains unclear.

TNF-alpha, which is known as a proinflammatory cytokine has been found increased in CKD.

Increased level of TNF-alpha also has several effects on multiple systems including cardiovascular damage.[12] Smoking cause pathological increase of inflammatory cytokines including TNF-alpha and IL-6.[12-15]

Aim

Chronic inflammation in ESRD patients

is potentially increased due to multiple factors related to hemodialysis. Also, cigarette has a major role on chronic inflammation and atherosclerosis. We aimed to evaluate if the smoker ESRD patients under HD have increased degree of atherosclerosis by evaluating levels of TNF-alpha, IL-6, hsCRP and ET-1 levels compared to non-smoker HD patients. This experiment may refer us to evaluate if smoking is an additional risk factor for cardiovascular diseases pathogenesis by measuring inflammatory biomarkers and endothelin-1 in maintenance HD patients.

MATERIAL & METHODS

Study Design

This study was designed as multicenter, observational, open labeled analytic and retrospective.

Ethics Statement

Our study protocol was approved by Izmir Katip Çelebi University, Health Research and Application Center (Izmir/ Turkey) (IRB no: 188, Date: 28/08/2014) Written informed consent was obtained from each patient.

Definition of the Individuals

80 smoker (at least 3 pack- year) and 50 non-smoker male ESRD individuals aged 20-55 years old ongoing routine HD programme without any interruption for at least 6 months in Izmir Tepecik Health and Application Center were included for our study during January 2008-December 2013.

Exclusion criteria were morbid obesity, nonregulated diabetes mellitus, history of collagen tissue disorders, malignancies and usage of antituberculous, antipsychotic drugs, etc., hemodialysis access with central venous hemodialysis catheter. For the better separation of groups, ex smokers were also excluded.

Evaluation of Patients

Smoker individuals' smoking histories were recorded. Amount of cigarette usage was briefly estimated by pack/ year. Pack-years were calculated by dividing the mean number of cigarettes smoked a day by 20 and multiplying with the number of smoking years.

Both smoker and non-smoker individuals were questioned how many years they were on HD programme. Their urine amount, age, etiology of ESRD were questioned. Their height, weight, systolic and diastolic blood pressure and body mass index (BMI) were measured. BMI was calculated as weight in kilograms divided by height in meters squared.

Blood pressure of individuals were taken 3 times a day in the morning, lunch, evening on a full stomach in the interdialysis day. Mean value of blood pressure 3 times taken were measured.

Laboratory tests included serum creatinine, fasting blood glucose, low density lipoprotein (LDL), triglyceride, hemogram, calcium, phosphorus, Kt/V, albumin, parathormone in a routine procedure, in the interdialysis day. As inflammatory biomarkers IL-6 TNF-α, hsCRP, ET-1 were measured by obtaining a blood sample in the interdialysis day. IL-6 and TNF-α were measured by commercially hsCRP was determined using an automated immunoturbidimetric assay with a Roche Diagnostics (Mannelheim, Germany) kit. ET-1 was determined by ELISA (Endothelin EIA kit, Cayman Chemical Company, Ann Arbor, MI 48101 respectively.)

Statistical Analysis

Paired sample test and p values of parameters were measured as statistical analysis. P values of less than 0.05 were regarded statistically significant. No subgroup analysis was performed for anthropometric, routine biochemical parameters. Multivariate analysis was used to obtain adjusted odds ratios comparing the higher tertiles of CRP, IL-6, ET-1 and TNF-α. All statistical analyses were performed using SPSS (SPSS, Chicago, IL, USA), version 13.0 for Windows (Microsoft Corp, Redmond, WA, USA). Mean value was used.

RESULTS

80 smoker and 50 non-smoker male patients

on hemodialysis programme completed the study.

Etiologies of CKD in smoker group were 41.25% (n=33) of diabetes mellitus, 27.5 %(n=22) of hypertensive nephrosclerosis, 12.5% (n=10) of glomerulonephritis, 6.25% (n=5) of obstructive uropathologies, 3.75% (n=3) of cystic renal diseases, 8.75% (N=7) of unknown etiology. Etiologies of CKD in non-smoker group were: 50% (n=25) of diabetes mellitus, 38% (n=19) of hypertensive nephrosclerosis, 4% (n=2) of glomerulonephritis, 4% (n=2) of obstructive uropathologies, 2% (n=1) of cystic renal diseases, 2% (n=1) of unknown etiology. Both groups' hemodialysis were performed with arterio- venous (A-V) fistule. Diabetes mellitus incidence, which is also positive risk factor for inflammation was similar in both groups without any significance. Thus, we found no statistically significant difference between two groups as a risk factor for inflammation.

Results were published extensively in **table 1**. Mean age was 46± 7.1 in smoker and 45.3± 6.4 in non-smoker group. Mean duration of HD was 40.3± 7.9 in smoker and 47.7± 16.09 in non-smoker group. Both smoker and non-smoker groups routinely measured blood pressure, ferritin, creatinine,calcium, phosphorus, hemoglobin levels, fasting blood glucose and lipid parameters, Kt/V, were similar with no statistically significance. In addition to conservational evaluation parameters, IL-6,TNF-alpha, hsCRP and ET-1 were measured.

Table 1: Conventional parameters and inflammatory parameters of smoker and non smoker individuals. TNF-alpha: Tumor necrosis factor- alpha, IL - 6 :interleukin – 6, hsCRP: high sensitive C-Reactive Protein, ET-1: endothelin-1, BMI: body mass index, LDL-cholesterol: low density lipoprotein- cholesterol, intactPTH: intact parathormone, (sd:Standard deviation)

	Smokers (n=80) Mean±sd	**Non smokers (n=50) Mean±sd**
IL-6 (pg/ml)	11.3± 12.6	5.06± 2.33
TNF-alpha (pg/ml)	30.6± 23.3	17.5± 5.03
hsCRP (µg/ml)	8.58± 1.36	6.21± 0.58
ET-1 (pg/ml)	10.8± 2.4	8.7± 1.6
Age	46± 7.1	45.3± 6.4
Dialysis period (month)	40.3± 7.9	47.7± 16.09
Diuresis (ml/day)	83.3±47.5	83.1± 45.9
BMI (kg/m²)	21.6± 1.4	21.1± 1.2
Hemoglobin (gr/dl)	11.08± 0.73	10.6± 1.2
Phosphorus (mg/dl)	4.8± 0.4	4.8± 0.3
Calcium (mg/dl)	10.1± 0.7	9.9± 0.5
LDL-cholesterol (mg/dl)	96.9± 31.3	98.4± 21.4
Triglyceride (mg/dl)	126.7± 17.4	130.1± 21.1
Albumin (gr/dl)	3.8± 0.2	3.8± 0.1
KT/V	1.7± 0.07	1.68± 0.15
intactPTH (pg/ml)	216.3± 49.4	241.9± 56.6
Ferritin (ng/ml)	617.5± 97.6	600± 108.6
Creatinine (mg/dl)	8.9± 1.9	9.3± 1.4
Systolic Blood Pressure (mm/Hg)	130.8± 19.7	129.8± 12.8
Diastolic Blood Pressure (mm/Hg)	77.8± 5.1	79± 6.7
Fasting Blood Glucose (mg/dl)	94.3± 8.2	97.2± 5,1

Because we planned 2 similar groups with characteristics of hemodialysis programme, age, sex, BMI; we did not perform a subgroup analysis with those parameters. Conventional parameters were normalized by Kolmogorov-smirnov test (p> 0.05). That's because paired T test was performed. No relationship was found between smoker and non-smoker group. **(Table 2)**

Table 2. Paired T test was performed for Conventional parameters

	P value
Age	0.06
Dialysis period (month)	0.846
Diuresis (ml/day)	0.385
BMI (kg/m²)	0.333
Hemoglobin (gr/dl)	0.692
Phosphorus (mg/dl)	0.615
Calcium (mg/dl)	0.061
LDL-cholesterol (mg/dl)	0.736
Triglyceride (mg/dl)	0.293
Albumin (gr/dl)	0.353
KT/V	0.659
intactPTH (pg/ml)	0.168
Ferritin (ng/ml)	0.877
Creatinine (mg/dl)	0.509
Systolic Blood Pressure (mm/Hg)	0.661
Diastolic Blood Pressure (mm/Hg)	0.329
Fasting Blood Glucose (mg/dl)	0.431

Inflammation data were assessed with the KOLMOGROV-SMIRNOV TEST (STUDY VARIABLES). Only the hsCRP value was not normalized (p <0.005). Subsequently, both groups were tested for all of the inflammatory markers (IL-6, hsCRP, Endothelin-1, TNF-alpha) and Test of Homogeneity of Variances. The hsCRP and TNF-alpha values were found to be p <0.005. For this reason, the inflammation markers were compared with the nonparametric Mann-Whitney U Test. Plasma levels of inflammatory cytokines were statistically higher level in smoker individuals compared to non-smoker individuals. [IL-6: 11.3± 12.6 against 5.06± 2.33 (p<0.05), TNF-alpha: 30.6± 23.3 against 17.5± 5.03 (p<0.05), hsCRP: 8.58± 1.36 against 6.21± 0.58 (p<0.05); ET-1: 10.8± 2.4 against 8.7± 1.6 (p<0.05)] (**Table 3**). Those 4 parameters were evaluated with the Multivariate logistic regression analysis. Incresed levels of hsCRP and Endothelin-1 were found as an independent predictive risk factor for atherosclerosis (p<0.001).

Table 3. Mann-Whitney U Test was performed for inflammation markers

	P value
IL-6 (pg/ml)	0.012
TNF-alpha (pg/ml)	0.005
hsCRP (µg/ml)	<0.001
ET-1 (pg/ml)	<0.001

DISCUSSION

Majority of CKD individuals in all stage is estimated to die of cardiovascular disease although most subjects with CKD never reach dialysis.[16] It has been approved that all severity stages of CKD from mild disease to the dialysis-dependent end-stage renal disease (ESRD) are associated with an increase in cardiovascular risk and mortality.[17-20] Chronic inflammation might be one of the major causes of atherosclerosis due to uremic toxins, decreased clearance of toxic metabolytes, accompanying risk factors such as diabetes mellitus, hypertension, etc. most studies have revealed CKD as a predisposing factor for atherosclerosis with no clinical features of CVD.[17]

Smoking plays a major role on CVD via lung mediated inflammation, endothelial dysfunction and reactive oxydative stress.[21] Tobacco smoking has been associated in various systemic immune and inflammatory biomarkers especially in elder and chronic smokers.[22] Wannamethee et al. evaluated specific inflammatory cytokines and biomarkers including hsCRP, IL-6, fibrinogen resulted that there is a positive correlation between tobacco use and increased levels of hsCRP, IL-6 and fibrinogen.[9] Multiple Risk Factors Intervention Trial (MRFIT) trial demonstrated that there is a positive association

between CVD mortality and increased level of hsCRP in those smoker men followed over a 17-year period (RR = 2.8; 95% CI, 1.4–5.4).[23] Kianoush et al. demonstrated that hsCRP, serial measurement of ankle brachial index, carotid intima thickness were significantly increased in smoker individuals compared to non-smokers. This data might indirectly refer us to subclinical atherosclerosis increase and a positive correlation with hsCRP.[24] Our study supports that increased level of hsCRP may be an independent risk factor as a prediction for atherosclerosis.

TNF- alpha and IL-6 have a major role on chronical inflammation with different mechanisms.[25]

Gene expressions of IL-6 and TNF-alpha were significantly increased in the *in vivo* mouse model with acute myocardial infarction after acute exposure of smoking, compared to cigarette naive group.[13]

Kastelein et al. demonstrated that acute smoking in younger and middle aged population caused an increased level of IL-6 in situ.[26] Sun Jia et al. proved that IL-6 may help us to classify clinical CVD and TNF-alpha level has a strong evidence for all cause mortality in ESRD individuals.[27]

Kuschner et al. reported that TNF-alpha levels in bronchoalveolar lavage was found significantly increased compared to non-smokers.[15] Feng et al. reported that, there was a negative correlation between glomerular filtration rate and soluble TNF- alpha.[14]

ET-1 plays a role on hypertension and end organ damage in ESRD individuals. Those findings may support that ET-1 may play a role on CVD in ESRD individuals.[28] ET-1 has major effects on cell proliferation, inflammation and fibrosis in renal tubular cells.[29-30] Our results are similar to be supportive as ET-1 has a predictive value for atherosclerosis as an independent risk factor. On the other hand, evidences about the potential effects of smoking in HD individuals are still unclear.

Most recent studies have proved that IL-6, TNF-alpha, ET-1 and hsCRP play a role on chronic inflammation with different mechanisms.[2-3,12] Chronic inflammation is also accelerated in CKD with different pathogenetic mechanisms. Most studies resulted that comparing to individuals with normal renal funcion, CKD individuals have higher levels of inflammatory biomarkers, chemokines, chronic inflammation has a major role on atherosclerotic CVD.[2-4,26]

CONCLUSION

We found hsCRP, IL-6, ET-1 and TNF-alpha significantly increased in smoker HD patients compared to non-smoker ESRD individuals with similar risk factors. IL-6, TNF-alpha, hsCRP and endothelin-1 are already increased in ESRD individuals. We consider that statistically significant increase of these markers are related to smoking, the only separator of two groups. This may refer to us that mortality in smoker HD patients due to CVD is increased compared to nonsmoker individuals. We consider that quitting smoking may reduce CVD mortality in HD individuals.

Limitations of our study could be stated that we were unable to evaluate atherosclerotic CVD with invasive tests such as coronary angiography to show atherosclerotic plaque or noninvasive tests such as echocardiography, holter ECG, measuring arterial stiffness or ankle-brachial index. Another limitation of the study is that the smoking dose determinations may be imprecise as we were unable to measure remnants' of tobacco, or we did not define relevant factors of smoking such as brand of cigarette, type of smoking, smoking technique etc. Also diabetic individuals could be excluded to decrease confusing risk factors. On the other hand, our hemodialysis individuals, diabetes is one of the most common causes of ESRD. Due to lack of individuals, we were unable to evaluate diabetic individuals specifically. Further studies to explore the relationship, pathogenesis of inflammatory biomarkers on atherosclerotic CVD and effect of smoking in maintenance HD patients are needed with larger populations and additional measurements to optimize the strength of our evidence.

Conflicto de intereses: Los autores declaran no poseer ningún interés comercial o asociativo que presente un conflicto de intereses con el trabajo presentado.

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