EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 6
07-12
Year: 2018

THE RELATIONSHIP BETWEEN CARDIAC RISK FACTORS AND TOTAL BILIRUBIN LEVELS IN PATIENTS WITH CHRONIC RENAL FAILURE

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Article Received on 22/03/2018 **Article Revised on 15/04/2018** **Article Accepted on 06/05/2018**

ABSTRACT
Chronic kidney disease (CKD) is a worldwide public health problem with increasing incidence and prevalence, poor outcomes and high cost. CKD is closely related to cardiac diseases and cardiovascular disease increases the risk of the negative consequences in patients with CKD. Cardiovascular disease is the main cause of morbidity and mortality in patients with CKD and end stage renal disease (ESRD). In our study, we aimed to determine the relationship between cardiac risk factors and serum total bilirubin in 99 patients with glomerular filtration rate (GFR) less than 60 ml/ min/ 1.73 m^2 who did not receive renal replacement therapies (RRT) and 94 patients undergoing hemodialysis (HD). The research is planned retrospectively and the demographic characteristics and labaratory values were evaluated. The relationship between these parameters and total bilirubin levels was investigated. In our study, all Framingham cardiovascular risk scores were observed to be lower in patients with high total bilirubin levels. However, these differences in mean scores were not statistically significant. Total bilirubin levels were not significantly different between hemodialysis patients and non-hemodialysis patients. The mean values of triglyceride, RDW, neutrophil / lymphocyte ratio, sCRP, parathormon and phosphorus parameters were higher in hemodialysis patients than in non-hemodialysis patients. The higher mean values of the cardiovascular risk parameters in hemodialysis patients are thought to be associated with a higher rate of cardiovascular events than in non-hemodialysis patients. Patients without hemodialysis treatment had lower total bilirubin levels when GFH was lowered. As a result, total bilirubin has been found to be protective effects against cardiovascular diseases and renal damage.

KEYWORDS: Chronic Kidney Disease, Cardiovascular Disease, Total Bilirubin Level.

INTRODUCTION
Chronic renal disease is a worldwide public health problem with poor outcomes and increasing incidence and prevalence.[1] Chronic kidney disease (CKD) is defined as reduced glomerular filtration rate (GFR) and affects 10-20% of adults worldwide.[2]

Diabetes and hypertension are the main causes of CKD in the majority of countries. The incidence, prevalence and progression of CKD are likely to vary by ethnicity, epigenetic effects and by the social determinants in health. Renal impairment in renal disease can be determined by the presence of albuminuria, defined as albumin / creatinine ratio> 30 mg/ day for two spot urine samples. GFH can be calculated from calibrated serum creatinine by prediction equations such as the Diet Modification in Renal Disease (MDRD) Study or the Cockcroft-Gault Formula.[3] The stages of CKD are defined by the estimated glomerular filtration rate. Term of Chronic renal failure usually corresponds to stages 3-5. End-stage renal failure (ESRF) represents the last stage of CKD, in which the accumulation of toxins, liquids, and electrolytes, normally excreted by the kidneys, leads to uremic syndrome.[4] ESRF is increasing all over the world and affecting millions of people. In our country, an average of 15,000 patients are diagnosed with ESRF every year.[5] Renal replacement therapies (RRT) in ESRF patients are; hemodialysis (HD), peritoneal dialysis, and renal transplantation.[6] In Turkey, according to center based data in 2013, a total of 66.711 patients were applied RRT. The most common type of RRT in our country is hemodialysis with 79% rate followed by renal transplantation with 14% and peritoneal dialysis with 7% rates.[7] There are over 400,000 patients with ESRF in the US, and over 300,000 of these patients are under dialysis program.[8] CKD is closely related to heart diseases and adverse outcomes are much more frequent in chronic kidney patients with cardiovascular disease (CVD).[2] Cardiovascular disease is the main cause of morbidity and mortality in patients

with CKD and ESRF.[4] Cardiovascular mortality is 10 to 30 times higher in dialysis patients than in the general population. Patients were found to have a 16 to 40 fold higher risk of mortality from cardiovascular causes before they reached to ESRF phase. Traditional and non-traditional factors are influential in the development of CVD in CKD.[9] The presence of traditional risk factors stated in the Framingham study such as age, blood pressure elevation, diabetes mellitus (DM), hyperlipidemia, obesity, and atherosclerosis were found to be associated with increased atherogenicity in CKD and high morbidity and mortality rates due to atherogenic diseases.[10] In ESRF, mortality is significantly increased due to cardiovascular diseases. In patients with less severe renal impairment, these effects are not better defined.[11] Recent studies have shown that serum bilirubin is associated with CVD risk factors such as diabetes, metabolic syndrome and body mass index (BMI). Serum bilirubin has a protective effect on CVD. Serum bilirubin has been shown to be protective against CVD-related events by its antioxidant effects.[12] We also planned to evaluate the relationship between cardiac risk factors and total bilirubin levels in patients with CKD in this study. Demographic characteristics such as age, height and weight and; serum creatinine, proteinuria, lipid profile, albumin, hemoglobin $A1_C$, neutrophil/ lymphocyte ratio, RDW, calcium, phosphorus, PTH, high sensitive CRP (hs CRP), fasting insulin, blood glucose levels and total bilirubin levels were evaluated. The relationship between cardiovascular risk parameters and total bilirubin levels in CKD was investigated. With this feature, our research was done as a quantitative retrospective research.

MATERIALS AND METHODS

This study was carried out by evaluating the results of routine anamnesis and examinations during routine clinical check-ups of 99 patients who did not receive RRT with GFR under 60 ml/ min/ 1.73 m^2 and 94 patients who received HD. Our study is a cross-sectional, retrospective study.

Patients' age, weight and height measurements, BMI values, arterial blood pressure, medical history, drug and smoking history, premature CVD history were recorded. Serum glucose, uric acid, calcium, phosphorus, spot urine proteinuria, HbA1c, total cholesterol, HDL cholesterol and plasma triglysythide (TG) concentrations, insulin, parathormone, hemogram, RDW, neutrophil/ lymphocyte ratio and hs CRP were studied. GFR of patients was calculated with Cockcroft-Gault formula from calibrated serum creatinine.

While examining the relationship between cardiovascular risk factors and total bilirubin levels; Joint British Societies (JBS) and Edinburgh University cardiovascular risk factors calculators were used.[13]

In the analysis of the data, IBM SPSS 19 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0, Armonk, NY: IBM Corp.) package program was used. Continuous variables in the presentation of data were expressed as mean ± standard deviation, median (min-max); categorical variables were expressed as "n" and percentages. Chi-square test was used to analyze categorical variables. When statistically significant differences were tested between groups in terms of continuous variables, the fit of the variables to the normality hypothesis was tested. The t-test was used for independent groups in the independent group comparisons for the hypothesized variables. Mann-Whitney U test was used in cases where the assumption of normal distribution was not provided. $p < 0,05$ were considered statistically significant.

RESULTS

Patients who did not receive HD treatment were divided into two groups as GFH <30 ml/ min/ 1.73 m^2 and 30-60 ml/ min/ 1.73 m^2. In non- HD group; 53 (53.5 %) were women and 46 (46.5 %) were male. The mean age of the HD patients was 60.4 ± 13.7, while in non- HD group was 71.0 ± 13.2 and was statistically different ($p < 0.001$). In HD group; 58 (61.7 %) of the patients were diabetic and 36 (38.3%) were non- diabetic. In non- HD group 65 (65.7 %) were non- diabetic and 34 (34.3 %) were diabetic. 37 of the HD patients (39.4 %) were non-smokers, and 57 (60.6 %) had smoking history. In non-HD group; 60 (60.6 %) were non- smokers and 39 (39.4%) were smokers. Smoking rates between study groups were statistically different ($p = 0.003$). The mean BMI of hemodialysis patients was 26.0 ± 5.1, and was 27.9 ± 4.0 in non- HD patients with statistical significance ($p = 0.004$). The mean systolic blood pressure of patients with HD was 123.7 ± 19.3 mmHg, and was 143.9 ± 15.4 in non- HD group with statistically significant difference ($p < 0.001$). The diastolic blood pressure averages of the HD patients were 75.0 ± 9.7 while were 83.7 ± 8.7 in non- HD group with statistical difference ($p < 0.001$).

The mean duration of CKD in HD patients was 12.5 ± 5.4 and was found to be 7.2 ± 4.9 in non- HD group with statistical difference ($p < 0.001$).

Triglyceride, cholesterol, HDL, LDL, RDW, neutrophil/ lymphocyte ratio, hs CRP, calcium, parathormone, phosphorus, uric acid and $HbA1_C$ levels between groups were statistically significantly different as shown in Table 1.

There was no statistically significant difference in the mean values of total bilirubin and glucose levels in HD patients and non- HD group (Table 1).

The mean values of triglyceride, RDW, neutrophil/ lymphocyte ratio, hs CRP, parathormone and phosphorus parameters were found higher in HD patients than non-HD patients (Table 1). The mean values of cholesterol, HDL, LDL, calcium, uric acid, $HbA1_C$ were found to be lower in HD group than non- HD group (Table 1).

Table 1. Laboratory Parameters of Groups

	HD (+)	HD (-) CRF (+)	P
Total bilirubin	0,6±0,3 0,6(0,1-1,6)	0,6±0,3 0,6(0,2-1,6)	0,507
Glucose	129,8±61,8 112,5(59,0-360,0)	116,2±41,8 104,0(64,0-330,0)	0,074
Triglyceride	201,7±103,4 187,5(44,0-581,0)	160,7±84,3 148,0(43,0-595,0)	**0,003**
Total cholesterol	175,0±49,1 167,0(63,0-375,0)	212,6±50,9 209,0(115,5-397,0)	**<0,001**
HDL	43,1±33,9 37,5(4,3-309,0)	46,4±10,8 45,0(25,0-90,0)	**<0,001**
LDL	90,4±35,2 93,4(12,4-183,0)	132,5±42,1 131,0(53,8-251,0)	**<0,001**
RDW	14,8±1,6 14,6(12,3-20,1)	13,9±1,7 13,4(11,9-20,7)	**<0,001**
Neutrophil / lymphocyte	4,2±8,5 3,0(1,2-83,0)	2,5±1,2 2,2(0,8-7,2)	**0,046**
Sensitive CRP	12,6±15,5 6,0(3,0-92,4)	8,2±9,5 5,2(0,2-80,5)	**0,018**
Calcium	8,9±0,6 8,8(6,5-10,3)	9,5±0,7 9,5(6,6-10,7)	**<0,001**
Parathormon	469,3±393,9 367,8(33,2-1882,0)	160,9±163,1 111,1(14,2-928,7)	**<0,001**
Phosphorus	4,9±1,2 5,0(2,0-7,5)	3,7±0,7 3,7(1,8-5,9)	**<0,001**
Uric acid	6,3±1,1 6,2(3,1-9,7)	6,9±1,6 7,0(3,5-11,2)	**0,005**
$HbA1_C$ level	5,9±1,4 5,5(4,2-10,9)	6,4±1,3 5,9(4,2-12,9)	**0,012**

The relationship between total bilirubin level and cardiovascular risk factors was examined and all Framingham cardiovascular risk scores were observed to be lower in patients with high total bilirubin levels. However, these differences in mean scores were not statistically significant (Table 2).

Table. 2. Framingham Risk Scores According to Total Bilirubin Level.

	Total bilirubin		p
	=<1	>1	
*Coronary Heart Disease	24,8±18,0 21(0-71,7)	20,9±13,6 22,0(0,0-47,4)	0,400
*Myocardial Infarction	13,2±11,9 9,1(0,0-47,3)	12,1±10,9 10,1(0,0-36,5)	0,722
*Stroke	9,7±10,4 5,6(0,0-49,6)	7,3±5,6 6,6(0,0-21,0)	0,363
*Cardiovascular Disease	35,0±21,5 33,1(0,0-82,4)	32,4±17,2 36,8(0,0-58,8)	0,634
*Death from Coronary Heart Disease	8,9±8,7 6,6(0,0-37,8)	7,1±5,9 7,3(0,0-18,5)	0,413
*Death from Cardiovascular Disease	16,7±16,4 10,4(0,0-65,9)	13,7±10,1 13,8(0,1-29,4)	0,479
** Calculation of BNF / JBS2 cardiovascular disease. FD equals the sum of CHC and STROKE	34,5±27,3 27,3(0,0-118,9)	28,2±16,4 31,4(0,1-53,5)	0,364

*Calculated using Framingham equation (FD)
**Joint British Societies

DISCUSSION

In modern living conditions, people in the normal population are exposed to many cardiovascular risk factors. These factors are thought to be associated with changes in biochemical parameters and also with treatment modalities.

In our study, the relationship between total bilirubin level and cardiovascular risk factors was examined in patients with HD and CKD who did not undergo dialysis treatment, and all of the Framingham cardiovascular risk scores were lower in patients with high total bilirubin levels. Jin-Ping Lin et al. in 2006 determined that patients with higher serum bilirubin concentrations had a strong association with cardiovascular disease development at lower rates.[14] Another study by Jin-Ping Lin et al. in 2010 showed that serum bilirubin levels were associated with CVD risk factors such as diabetes, metabolic syndrome and BMI; in addition, there is less information about the role of genes controlling bilirubin concentrations and their association with the cardiovascular system.[12] In another study of the same group in 2003, they emphasized that bilirubin is an effective antioxidant that cleans the peroxide radicals. This effect is shown by reducing the oxidation of lipids and lipoproteins, especially low density lipoprotein. Thus, it has been shown to be effective against plaque formation and inhibition of atherosclerosis. In addition, they also revealed that UGT1A1 (a member UDP1 glucosyl transferase family) catalyzes the conjugation of glucuronic acid with bilirubin and consequently increases bilirubin elimination. The same study revealed that a gene with important effect on bilirubin levels belongs to chromosome 2q telomere and emphasized the link between the UGT 1A1 gene and serum bilirubin levels.[15]

In previous studies, serum bilirubin concentration was reported to be positively correlated with renal function. In a study conducted by Muhei Tanaka et al., serum total bilirubin concentration has been shown to be a new marker for CKD progression.[16]

Solak Y. et al. reported that the RDW value was an independent factor causing endothelial dysfunction in CKD.[17] A study by Allawi AAD found that high levels of sensitive CRP, an indicator of inflammation in hemodialysis patients, were atherosclerosis-promoting factor.[18] Hyperphosphatemia, calcitriol deficiency and secondary hyperparathyroidism are common complications of chronic kidney disease. Fibroblast growth factor-23 (FGF-23) is a new phosphaturic hormone that inhibits renal 1 alpha -hydroxylase activity and thus plays a role in the pathogenesis of secondary hyperparathyroidism. FGF-23 and PTH are inversely proportional to the estimated GFR, while calcitriol levels are linearly related to GFR.[19] High levels of FGF-23 have been identified to be influential in the development of cardiovascular events in a large number of studies.[20,21] Morsy MS et al. have argued that high levels of plasma parathyroid hormone results in adverse systemic consequences such as excessive intracellular calcium accumulation in myocytes and oxidative stress induction in vascular smooth muscle, and ultimately it contributes to the development of heart failure in CKD.[22] Control of phosphorus accumulation in CKD is crucial for the prevention of secondary hyperparathyroidism and metastatic calcification.[23]

In our study, mean values of triglyceride, RDW, neutrophil/ lymphocyte ratio, hs CRP, parathormone and phosphorus parameters were found higher in HD patients than in non- HD patients. The high mean values of the above mentioned cardiovascular risk parameters in HD patients suggests that a higher proportion of cardiovascular events may occur in this group in comparison with non-HD group. In our study, we could not examine the FGF-23 levels because it could not be studied in our hospital.

Better glycemic control, as reflected by low HbA1c levels, can prevent or slow the progression of diabetic nephropathy. HbA1c levels higher than 9 % are common in non-hemodialyzed CKD patients and are associated with significantly worse clinical outcomes.[24] In our study the rates of diabetes in early and advanced stages were different from each other and the rate of diabetes in the advanced stage was higher.

Iddo Z. Ben-Doov et al. have argued that serum uric acid value predicts the incidence of renal failure and all-cause mortality independent of demographic and clinical variables.[25] George Thomas et al. found that components of metabolic syndrome leads to decreased GFR, microalbuminuria, and increased proteinuria in CKD in their meta-anlysis.[26] In our study; glucose, triglyceride, cholesterol, HDL, LDL, CRP, uric acid, $HbA1_C$, insulin resistance were not statistically significant between early and advanced stages of CKD. This result may be related to the inadequate number of patients in our study.

Serum bilirubin has been shown to be a potent antioxidant and cytoprotective factor in a variety of studies. Seung Seok Han et al. have shown that high serum bilirubin levels protect the kidneys.[27] In our study, the mean total bilirubin level was higher in the early stage than in the advanced stage CKD.

CONCLUSION

In our study, all of the Framingham cardiovascular risk scores were observed to be lower in patients with high total bilirubin levels. The mean cardiovascular risk parameters were found higher in HD patients than in non- HD patients. The high values of the above cardiovascular risk parameters in HD patients suggest that cardiovascular events may occur at a higher rate in these patients.

In the early stage CKD patients, the total bilirubin levels were found to be than in the advanced stage. According to these findings, it can be considered that high serum bilirubin has protective effects on the kidney. There is a need for large-scale further investigations to evaluate the whole population despite the presence of relationship between serum bilirubin and CVD.

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