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THE RELATIONSHIP OF HIGH SENSITIVE C-REACTIVE PROTEIN AND PLASMA TRIIODOTIRONINE IN END STAGE RENAL DISEASE WITH NON THYROIDAL ILLNESS SYNDROME

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Abstract

Background: End stage renal disease (ESRD), with or without dialysis, is a condition with chronic inflammatory state. Chronic kidney disease (CKD) in its course causes alteration in thyroid hormone metabolism, without underlying intrinsic thyroid abnormalities, known as non-thyroid illness syndrome (NTIS). The aim of this study is to determine the relationship between HsCRP levels as a marker of inflammation with plasma T3 levels in ESRD patients, with or without hemodialysis.

Methods: This is a cross sectional study which assessed the relationship between HsCRP levels as a marker of inflammation with plasma T3 levels in ESRD patients, held in Haji Adam Malik General Hospital in Medan. The research sample was chosen consecutively. Patients were taken for venous blood for HsCRP, TSH, T3, fT4, albumin, RFT and for patients undergoing regular hemodialysis (HD), blood samples were taken just before the next HD session.

Results: There is no significant relationship between the etiology of ESRD, both DM and hypertension on HsCRP and T3 levels in both group of patients undergoing hemodialysis and those not undergoing hemodialysis ($p > 0.05$). Based on statistical analysis, there is no correlation between hemodialysis duration with T3 and HsCRP levels in the group of patients undergoing HD ($p>0.05$). There is a significant correlation between HsCRP levels and T3 levels in the ESRD group undergoing hemodialysis ($R = -0.667$; $p = 0.001$).

Conclusion: There is a strong negative correlation between HsCRP levels and plasma T3 levels in ESRD patients both HD and non HD groups.

Introduction

End stage renal disease (ESRD), with or without dialysis, is a condition with chronic inflammatory state. Uremic toxin represented by high level of ureum, deflation of GFR and the dialysis itself, along with other biological factors cause chronic inflammatory state in chronic kidney disease (CKD). Some underlying diseases such as diabetes mellitus and hypertension, which are also the most frequent etiologies of CKD, also contribute to the inflammatory status in a patient. The worsening of a patient's nutritional status, mostly marked by low albumin, contributes to the inflammatory state in CKD patients.[1] CKD in its course causes alteration in thyroid hormone metabolism, without underlying intrinsic thyroid abnormalities, known as non-thyroid illness syndrome (NTIS) and characterized by low triiodothyronine (T3) with normal TSH and free thyroxin (T4).[2-5]

Song et al. reported prevalence of NTIS in 60% of cases in stage 4 CKD and 79% in cases of stage 5 CKD, whereas in previous studies, NTIS in hemodialysis patients reported about 72%.[6] Decreased thyroid function which is characterized by a low active form of the thyroid hormone T3 at plasma concentrations, is associated with markers of inflammation and endothelial dysfunction in CKD patients.[7]Zocalli et al. in their study suggested that the risk of vascular calcification increased three times higher in patients with low T3 compared with normal T3 levels.[8] Research by Elnagar et al. found that serum levels of high sensitive C-Reactive Protein (HsCRP) increased significantly in the group of patients undergoing hemodialysis compared to those without hemodialysis. Serum T3 levels were also reported to be significantly decreased in hemodialysis patients compared to CKD patients who did not undergo hemodialysis.[9]

The aim of this study is to determine the relationship between HsCRP levels as a marker of inflammation with plasma T3 levels in ESRD patients, with or without hemodialysis.

Methods

This is a cross sectional study which assessed the relationship between HsCRP levels as a marker of inflammation with plasma T3 levels in ESRD patients. The study held in Haji Adam Malik General Hospital in Medan, with inclusion : male and female patients aged ≥ 18 years, patients with end-stage renal disease (LFG <15 mL / min) who have not undergone kidney replacement therapy, patients with end-stage renal disease (LFG <15 mL / min) who have undergone hemodialysis therapy ≥ 3 months and willing to be included in this research. With exclusion criteria: patients with a history of thyroid disease, patients with a history of thyroid treatment (PTU, methimazole, thionamides, lithium, amiodarone, interferon) in the last 3 months and patients with a history of liver disease, fever and infection.

Each patient who met the inclusion criteria and did not meet the exclusion criteria, was defined as subject of the study and the patient would fill out the consent letter after receiving an explanation. The research sample was chosen consecutively. Patients were taken for venous blood for HsCRP, TSH, T3, fT4, albumin, RFT and for patients undergoing regular hemodialysis, blood samples were taken just before the next hemodialysis session. Hemodialysis session that approved by the national health insurance in this hospital is twice a week, five hours each, regularly. Bivariate analysis is performed to determine the relationship between independent and dependent variables. The statistical test used was the Pearson correlative test with an alternative to the Spearman test for abnormal data distribution. Analysis using SPSS 23 (Statistical Product and Service Solution) computer program and 95% confidence interval. Significant value if $p < 0.05$.

Results and conclusion

The study was followed by 40 subjects who met the inclusion criteria, after previously excluding 5 subjects with abnormal TSH and fT4 findings. A total of 27 persons were men (67.5%) and the mean age was 51.72 ± 12.65 years. The majority of subjects were 17 Batakethnic (42.5%), followed by Java as many as 14 persons (35%), Karo 8 persons (20%) and Nias 1 person (2.5%). The majority of subjects had DM comorbid disease in 25 people (62.5%), followed by hypertension in 13 people (32.5%). The mean duration of patients undergoing HD was 24.45 ± 22.98 months. The mean hemoglobin, urea, creatinine were 8.18 ± 1.41; 146.53 ± 32.24 and 8.94 ± 3.87. The mean eGFR, Albumin and HsCRP were 7 ± 3.4; 3.17 ± 0.6 and 6.10 ± 4.8. While the mean of the thyroid hormones profil, TSH, fT4 and T3 were 1.68 ± 1.05; 0.85 ± 0.21 and 0.49 ± 0.19.

Table1.Baseline Subject Characteristic

Characteristic	**N = 40**
Gender, n (%)	
Male	27 (67.5%)
Female	13 (32.5%)
Age (years), mean±S.D	51,72 ± 12.65
Tribe, n (%)	
Batak	17 (42.5%)
Jawa	14 (35 %)
Karo	8 (20 %)
Nias	1 (2,5 %)
HD duration (months)	24,45 ± 22,98
Hypertension, n (%)	13 (32,5%)
Diabetes Mellitus, n (%)	25 (62,5%)
GN, n (%)	2 (5,0%)

Haemoglobin (g/dL)	8,18 ± 1.41
Ureum (mg/dL)	146.53 ± 32.24
Creatinin (mg/dL)	8.94 ± 3.87
eGFR (mL/min)	7 ± 3.4
Albumin (g/dL)	3.17 ± 0.6
HsCRP (mg/L)	6.10 ± 4.8
TSH	1.68 ± 1.05
fT4 (ng/dL)	0.85 ± 0.21
T3 (ng/mL)	0.49 ± 0.19

Based on statistical analysis, there's significant differences in T3 levels found in the group of patients who did not undergo hemodialysis based on albumin status. The patient group with hypoalbuminemia status had a lower T3 value of 0.413 ± 0.048 ng / mL (= 0.039). In this statistical analysis, there were also insignificant differences in HsCRP levels in the group of patients who did not undergo HD, with higher HsCRP levels in the group of patients with hypoalbuminemia status with a mean of 7.664 ± 5.797 mg/L (p = 0.394). While based on statistical analysis, there were no significant differences in T3 and HsCRP in the group of patients undergoing hemodialysis based on albumin status.

Table 2.Comparison of Study Groups by Age, Etiology of Chronic Kidney Disease and Laboratory Parameters

Variables	HD (n=20)	Non HD (n=20)	*p*.
Age (years) : $\bar{x} \pm SD$	50,30 ± 12,57	53,15 ± 12,89	0,483
Etiology of CKD			
- DM : n (%)	14 (56,0%)	11 (44,0%)	0,117
- Hypertension : n (%)	4 (30,8%)	9 (69,2%)	
Haemoglobin (g/dL) : $\bar{x} \pm SD$	8,06 ± 1,15	8,3 ± 1,65	0,606
Renal Function Test			
- Ureum(mg/dL)	147,1 ± 33,62	145,95 ± 31,66	0,912
- Creatinin (mg/dL)	10,17 ± 4,02	7,72 ± 3,37	0,044
- eGFR (ml/min)	5,95 ± 3,12	8,05 ± 3,54	0,054
Albumin (g/dL)	3,22 ± 0,65	3,12 ± 0,54	0,603
HsCRP(mg/L)	5,20 ± 4,17	6,98 ± 5,31	0,248
Thyroid Function Test			
- TSH	1,57 ± 0,93	1,79 ±1,16	0,498
- fT4 (ng/dL)	0,90 ± 0,24	0,80 ± 0,16	0,135
- T3 (ng/mL)	0,55 ± 0,24	0,43 ± 0,06	0,023

Based on statistical analysis, there is no significant relationship between the etiology of CKD, both DM and hypertension on HsCRP and T3 levels in both the group of patients undergoing hemodialysis and those not undergoing hemodialysis (> 0.05).

Table 3. Relationship of CKD Aetiology with HsCRP and T3

Variables	DM (mean ± SD)	*p.*	Hypertension (mean±SD)	*p.*
HD				
T3	0,527 ± 0,212	0,411	0,52 ± 0,15	0,586
HsCRP	4,829 ± 3,45	0,552	6,62 ± 6,74	0,462
Non HD				
T3	0,41 ± 0,054	0,211	0,45 ± 0,08	0,283
HsCRP	8,3 ± 6,6068	0,229	5,36 ± 3,97	0,229

Based on statistical analysis, the correlation between hemodialysis duration with T3 and HsCRP levels in the group of patients undergoing HD was -0.160 and -0.238 with p = 0.499; p = 0.312. These results indicate that the duration of hemodialysis is not related to T3 and HsCRP levels in patients with end-stage renal disease undergoing hemodialysis.

Table 4. Correlation of HD Duration with Level of HsCRP and T3

Variables	HD duration (in months)	*p.*
HsCRP	-0,238	0,312
T3	-0,160	0,499

Based on statistical analysis, there is a significant correlation between HsCRP levels and T3 levels in the CKD group undergoing hemodialysis (R = -0.667; = 0.001). There is no correlation was found between the parameters of ureum, creatinine, eGFR, albumin and fT4 with T3 levels in the HD group (p> 0.05). These results indicate strong correlation between HsCRP levels and T3 levels in patients with end stage renal disease undergoing hemodialysis.

Table 5 .Correlation of T3 level and other parameters in HD group

Variables	T3	
	r	*p.*
Ureum	-0,017	0,945
Creatinin	0,256	0,277
eGFR	0,073	0,758
HsCRP	-0,676	0,001
Albumin	0,153	0,521
fT4	0,113	0,635

Table 6 Correlation of T3 level and other parameters in non HD group

Variables	T3	
	r	*p.*
Ureum	0,069	0,773
Creatinin	-0,238	0,313
eGFR	0,256	0,277
HsCRP	-0,567	0,009
Albumin	0,412	0,071
fT4	0,057	0,811

From 40 subjects, the majority of were male, as many as 27 people (67.5%) with an average age of 51 ± 12.65 years old. This study is consistent with research conducted by Zeerati in Iran where the average age of suffering

from ESRD is 45.6 ± 16.9.9.[5]This is also in line with the 2017 IRR report, the largest proportion of patients undergoing HD is age range of 45-64 year.[10]In this study, the most common comorbidity was Diabetes Mellitus followed by Hypertension. This is in line with data from 2014 USRDS where Diabetes Mellitus is a major cause of ESRD in the United States.[11]

In this study it was found that there was no relationship between the aetiology of CKD, both DM and hypertension, with HsCRP and T3 levels. This is in line with the results of the study of Abraham et al., who also concluded that there was no relationship between HsCRP levels and diabetes status and hypertension in his study.[12] This proves that whatever the etiology of CKD in a patient, does not directly influence the inflammation that occurs in the course of patients with ESRD so it also does not affect the changes in thyroid hormone in end-stage kidney disease. According to Ackhurin in his study on inflammation in CKD, inflammation that arises in the course of CKD caused by decreased elimination of cytokines, recurrent infections, oxidative stress, intestinal dysbiosis, periodontal disease, metabolic acidosis, vitamin D deficiency and factors related to dialysis, not directly caused by the underlying disease.[1]

In this study, it was found that decreased HsCRP and T3 levels were not related to the length of time a patient underwent HD. This data is in line with the research of Ali et al. in Palembang which also concluded that there was no significant correlation between dialysis duration and serum HsCRP concentration in CKD patients undergoing HD, so that with no association between HD duration and HsCRP levels, there was no effect on T3 level.[13] In contrast to Abd-Elhafeez's study which identify HD groups, it was found that decreased T3 levels were associated with dialysis duration.[14] These findings might be related to the theory that HsCRP was optimally concentrated after 24 hours. The length of time a patient undergone HD therapy is not directly related to inflammation in CKD and in the future, changes in T3 levels, related to inflammation caused by uremia toxin and hemodialysis exposure itself. Through the process of hemodialysis, the uremia toxin will be discharged through the machine, characterized by decreased ureum levels after HD, so that within 24 hours after HD uremia levels are relatively close to the normal range. After 24 hours until the next HD session, then the uremia toxin is collected again, which certainly increases inflammation in hemodialysis patients, and so on the process takes place.

ESRD is an irreversible change in kidney function, which then causes impaired excretion, metabolic and endocrine function in its development in the clinical syndrome of uremia. Uremia is associated with endocrine disorders caused by hormonal degradation disorders. Uremia patients show complex thyroid dysfunction characterized by decreased T3 levels and lower fT4 levels (but still within the normal range) known as NTIS.[15]

In this study, there was a decrease in levels of thyroid hormone T3 in both groups, both in the group of patients who underwent HD and who did not undergo HD. In line with Elnagar's study, T3 levels were found to be lower in the group of patients undergoing hemodialysis compared to the control group.[15] This was also in line with the Haria and Lunia study which evaluated the status of thyroid hormone in CKD patients and obtained a decrease in T3 levels by 74% with TSH and fT4 levels were the same as controls.[16]This is in line with the SPNT characteristics in CKD, namely by decreasing T3 levels with normal TSH and fT4 levels.

In this study, a decrease in T3 levels was greater in the group of patients who did not undergo HD compared to the group of patients who underwent HD. But this is different from the Abd-Elhafeez study in which lower serum T3 levels were found in the group of patients undergoing hemodialysis compared to those not undergoing hemodialysis.[14]This was made possible by differences in the sample population in the non-HD CKD group in the Abd-Elhafeez study in Egypt i.e the average eGFR is 63.7 ± 17 ml / min, which means that the population of CKD in the study not only consisted of ESRD but there were also samples other than late stage of CKD, while in this study samples were taken from GKD G5 only. Another factor that has previously been revealed to influence changes in plasma T3 levels in CKD patients in addition to creatinine clearance is HsCRP levels, which reflects the inflammatory status in patients. Inflammation itself is influenced by many factors which will later contribute to the progression of CKD.

The malnutrition-inflammatory complex is a major problem in patients with ESRD. In this study no statistically significant relationship was found between albumin levels and T3 levels in both the group of patients undergoing HD and the group of patients not undergoing HD. In contrast to the Abd-Elhafeezet al. study which found that serum albumin levels were lower in the hemodialysis group compared to the CKD group who underwent conservative therapy.[14] In this study, we found higher albumin levels in the group who underwent HD than those who did not undergo HD, which might be caused by good care and support related to regular hemodialysis sessions, education about good nutrition and proper medication consumption. So, maybe higher albumin levels in the HD group with a mean of 3.22 ± 0.65 g / dL did not affect the degree of inflammation marked by HsCRP levels of 5.20 ± 4.17 mg / L. However, when albumin levels are grouped based on normal or low serum albumin levels of a patient with a cut-off of 3.5 g / dL, a significant difference in T3 levels is found in patients who do not undergo hemodialysis with hypoalbuminemia status, where T3 levels are lower at 0.413 ± 0.048 ng / mL compared to normal albumin status, and is associated with an increase in HsCRP levels, where levels are increased to 7.664 ± 5.797 mg / L.

In this study, we found a strong negative correlation between HsCRP levels and T3 levels. This is in line with Abd-Elhafeez's study which showed a strong negative correlation between T3 levels and HsCRP levels in both the hemodialysis group and those who did not undergo hemodialysis.[14]In this study, in the HD patient group, lower levels of HsCRP were obtained compared to the non HD patient group. In the HD patient group, higher T3 levels were obtained compared to the non HD patient group. This is different from the Elnagar study which found that HsCRP levels were higher in the HD patient group compared to non HD, and certainly affected lower T3 levels in the HD group compared to non HD.[15] By considering several factors such as age, hemoglobin level, urea level which are relatively similar between the two groups, it does not seem to be the reason why there are differences between the two studies. Albumin levels might play a major role on these differences. In this study, albumin levels were found to be higher in the HD patient group, thus explaining why HsCRP levels were lower and ultimately the T3 levels obtained were higher, when compared to the non HD group. Further, this study confirms that changes in thyroid hormone profile, especially decreases in T3 levels, are influenced by inflammation and nutrition in end-stage renal disease in term of NTIS.

It can be concluded that there is a strong negative correlation between HsCRP levels and plasma T3 levels in ESRD patients both those undergoing hemodialysis and those not undergoing hemodialysis. Further researches need to be done on thyroid hormones, especially plasma T3, which is carried out multicenter so that the data obtained can represent CKD patients in Indonesia. The next researcher can continue the research by observing the patient's mortality to see the effect of T3 levels on the mortality of patients with ESRD. In addition, if the results of similar studies are consistent, it is necessary to do research on the supplementation of thyroid hormones or other medications for decreasing T3 levels to reduce morbidity and mortality in patients with ESRD.

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