Interleukin 6 concentration elevation as a risk of carotid intima-media thickness in chronic kidney disease patients with dialysis

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ABSTRACT

Aim To investigate the relationship between IL-6 concentration and the risk of carotid artery calcification in chronic kidney disease patients with dialysis (CKD-5D).

Methods This analytic observational cross-sectional study includes 95 clinically stable patients who underwent regular haemodialysis for at least three months at Rasyida Renal Hospital Medan, Indonesia. Serum IL-6 level was measured using the enzyme-linked immunosorbent assay (ELISA). Carotid artery calcification was determined by measuring Carotid Intima-Media Thickness (CIMT) using Real-Time B-mode ultrasound.

Results There were 53 males (55.8%) of the total samples with the mean duration of haemodialysis of 81.28±67.40 months. Ultrasound examination showed that 28 samples (29.5%) had carotid artery calcification. Statistical test significantly showed that patients with IL-6 ≥81.1 pg/mL were more likely to have carotid artery calcification with an increased risk of 12.92 times (95% CI: 5.54-30.12) compared to the group of patients who had IL-6 level <81.1 pg/mL (p <0.001).

Conclusion This study proves that a high level of IL-6 can increase the risk of carotid artery calcification in CKD-5D patients.

Key words: chronic kidney disease, interleukin-6, carotid intima-media thickness

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INTRODUCTION

Cardiovascular disease is a primary cause of morbidity and mortality in patients with chronic kidney diseases (CKD), and it accounts for approximately 39% of deaths among those on dialysis (1). One of the causes is vascular calcification that can occur both in tunica intima and media, which later contributes to the occurrence of myocardial ischemia, arrhythmia, and stroke (2,3). This vascular calcification has become a strong independent predictor of mortality in the general population (4) and dialysis population (5-7).

Chronic kidney disease is associated with a chronic inflammatory state characterized by increased levels of proinflammatory cytokines (8). As one of the proinflammatory cytokines, IL-6 is known as a central regulator of the inflammatory process and plays a crucial role in the induction of immune effectors and acute phase responses. IL-6 is also strongly associated with morbidity and a strong predictor of cardiovascular mortality in patients undergoing haemodialysis (9,10).

The aim of this study is to investigate the relationship between IL-6 concentration and carotid artery calcification in CKD-5D patients.

PATIENTS AND METHODS

 Patients and study design

This study was an analytic observational with a cross-sectional design. Ninety-five clinically stable patients who underwent regular haemodialysis for at least three months at Rasyida Renal Hospital (Medan, Indonesia) and were willing to conduct laboratory and ultrasonography examination, which was proven by signing an informed consent, were included in this study. The patients with incomplete medical record data were excluded from the study.

The investigation was approved by the Health Research Ethical Committee of the Medical School of Universitas Sumatera Utara/H. Adam Malik General Hospital

Methods

The patients were interviewed to determine history of previous illness and how long they had been undergoing haemodialysis.

Standard laboratory methods examined serum phosphate and calcium level. The IL-6 analysis was performed by measuring serum level based on the ELISA technique. Ultrasonography (USG) examination was performed by a radiologist who did not know the patient’s clinical condition. The presence of carotid artery calcification was defined if the thickness or distance between the intima-media tunica as measured by real-time B-mode ultrasound was >1 mm. Levels of calcium and phosphate were measured using the multiplication of serum level of phosphate and calcium (Ca x P).

Statistical analysis

The characteristic of regular haemodialysis patient data was expressed as a percentage for categorical data. Numerical data were expressed as mean ± standard deviation (SD) if normally distributed and expressed as median (min-max) if the data distribution were not normally distributed. The normality test was done using Kolmogorov Smirnov. The χ2 or Fisher’s Exact test was used to compare proportions between the two groups with variable data categories. The logistic regression test was used to explain the association between risk factors and carotid calcification. The p <0.05 was considered significant. To determine the cut-off value of the IL-6 level as a predictor of the calcification carotid artery, the receiver operating characteristics (ROC) curve was used to obtain the area under the curve (AUC) value.

RESULTS

There were 53 (55.8%) males of the total samples, the mean duration of haemodialysis (HD) was 81.28±67.40 months. The median level of calcium, phosphate and calcium phosphate was 9.80 mg/dL, 5.50 mg/dL and 53.76 mg²/dL². Through the ELISA method, the mean IL-6 level was 97.95±117.93 pg/mL.

The results of the USG examination showed that most patients did not experience carotid artery calcification, 67 (70.5%) (Table 1).

The total area under the curve was 95.9% with p<0.001 (95% CI: 91.2% - 100.0%), meaning that the IL-6 level had an excellent diagnostic value (> 90%) (Figure 1).

Based on the analysis with the ROC curve, the cut-off value of IL-6 level can also be determined, which has the highest combination of sensitivity and specificity. The curve showed that the IL-6 level with a value of 81.1 had the highest combinat-
The higher IL-6 level above the cut-off value, the higher the risk of calcification. The cut-off point value of IL-6 ≥81.1 had an excellent diagnostic value and accuracy (Table 2, Figure 2).

The patients who had IL-6 level ≥81.1 pg/mL were experiencing more vascular calcification compared to those with IL-6 level ≤81.1 pg/mL (p<0.001) (Table 3). The risk of carotid artery calcification increased 12.92 times (95% CI: 5.54-30.12) if the patient had IL-6 level ≥81.1 pg/mL compared to the group of patients who had IL-6 level <81.1 pg/mL (p<0.001).

DISCUSSION

There are many risk factors that can cause kidney function to decline, such as genetic components, sex, age, diabetes, and hypertension (11). Sex has traditionally been seen as an essential factor influencing the development of kidney disease (12). Regardless of its etiology, females tend to progress more slowly to end-stage kidney disease (13). Our study shows that the prevalence of patients undergoing haemodialysis was commonly found in males (55.8%). These results are in line with the study of Lumturgul et al. in CKD patients. They found that most of the dialysis and non-dialysis patients in Thailand were male with the percentage of 55.4% and 53.5% respectively (14). The same results were obtained by Nakayama et al. (15) and Ok et al. (16).
Carotid artery calcification has been recognized as a risk factor for cardiovascular events in patients with end-stage renal disease (15). Traditional risk factors alone, such as hypertension and dyslipidaemia, do not sufficiently contribute to the high calcification burden in the dialysis patient (17,18). Hyperphosphataemia and increased level of calcium x phosphate products, which is caused by reduced renal phosphate excretion, were also identified as an essential cause of accelerated arterial calcification in this group of patients (4, 19-22). Our study and the study conducted by Barreto et al. (23) found the mean phosphate levels and calcium-phosphate multiplication still within the target range for dialysis patients determined by the Kidney Disease Outcomes Quality Initiative (KDOQI), which are 8.4-9.5 mg/L for calcium, 3.5-5.5 mg/dL for phosphate and <55 mg²/dL² for calcium-phosphate multiplication (24). Its target range was achieved probably because almost all patients have taken the phosphate binders drugs. A study conducted by Barreto et al. took 2.97 pg/mL as the cut-off IL-6 (23), while the study conducted by Kato et al. dividing the IL-6 cut-off into three groups consisting of ≤1.1 pg/mL, 1-1.2 pg/mL and >2 pg/mL (25). The IL-6 cut-off by Honda et al. was 8.1 pg/mL (sensitivity 63.3%, specificity 73.3%) (26). In this study, the IL-6 cut-off obtained was 81.1 pg/mL (sensitivity 96.4%, specificity 92.5%). This cut-off difference can be due to the characteristics of the sample and the cut-off method used. The prevalence of vascular calcification varies greatly from 60-100% depending on the location of the examination and the diagnostic method used and, in the area where the study was conducted (27). London et al. reported that 68% of 202 patients undergoing haemodialysis in France had arterial calcifications determined by radiography and echocardiography (28). A study conducted by Nakayama et al. in 135 patients undergoing routine haemodialysis at hospitals in Japan, the prevalence of carotid artery calcification was 71% (15). This study found that the prevalence of carotid artery calcification was 29.5%. This difference in prevalence can be due to sample characteristics such as genetic, demographic, lifestyle differences, as well as the distribution and number of samples. Systemic inflammation is commonly found in patients with chronic kidney disease undergoing routine haemodialysis (29). The exact cause is unknown. However, it is suspected that every time a patient undergoes haemodialysis, the formation of reactive oxygen species (ROS) occurs, which plays an essential role in endothelial dysfunction and atherogenesis, which is modulated by IL-6 (31). A study conducted by Beberashvili et al. showed chronic inflammation characterized by elevated levels of IL-6 correlated with all-cause mortality in stable chronic haemodialysis patients (32). A study conducted by Maddhumathi et al. showed that a median plasma IL-6 level in 206 patients undergoing haemodialysis was 7.9 pg/mL (ranging from 0.1 to 90.2 pg/mL), and was found to be higher in patients with vascular disease (9). In this study, from the 95 patients, we found that the proportion of patients with IL-6 >81.1 pg/mL was more likely to have carotid artery calcification with an increased risk of 12.92 times compared to the group of patients who had IL-6 levels <81.1 pg/mL. Similar results were also obtained by Kato et al. (25) and Krasniak et al. (33).

In this study, we found that the mean of the duration of haemodialysis was 81.28 ± 67.40 months and showed no significant relationship between the duration of haemodialysis and the occurrence of carotid artery calcification. It may be because the process of vascular calcification can occur at any time and started at a younger age (34). Even the study conducted by Nitta et al. with the mean duration of haemodialysis about 7.7 ± 5.8 years also showed no significant results between the duration of haemodialysis and the occurrence of vascular calcification (35).

In conclusion, this study proves that high level of IL-6 can increase the risk of carotid artery calcification in CKD-5D patients.

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TRANSPARENCY DECLARATION

Conflict of interest: None to declare.
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