中文題目：動脈硬化和總膽固醇在血液透析患者中的關聯性

英文題目：The Association Between Arterial Stiffness and Total Cholesterol in Patients with hemodialysis

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Background:

There are approximately 2 million people suffering from end-stage renal disease (ESRD) globally, with an increasing rate of 5-7% per year. As we known, ESRD patients have lower quality of life, higher hospitalization rates, and higher annual mortality rates comparing to healthy population. The leading cause of mortality in ESRD patients is cardiovascular (CV) events and following complications. Although the relation between CV disease and high mortality have been demonstrated, the main contributors to CV disease have not been identified in the ESRD population. In fact, traditional CV risk factors, such as hypercholesterolemia have not been found to be reliable predictors of mortality risk in hemodialysis patients, as previous studies have shown these factors are paradoxically associated with better survival in the hemodialysis population.

In recent years, many studies emphasized the role of arterial rigidity in the development of CV diseases, and it was shown that stiffening of arteries is associated with increased CV mortality and morbidity. The relation between arterial stiffness and dyslipidemia have been mentioned in general and HTN population; however, we had no idea about the association of arterial stiffness and dyslipidemia in patients with ESRD.

The purpose of this study was to find out the correlation between arterial stiffness and total cholesterol in patients with hemodialysis.

Method and Materials:

We performed an observational, cross-sectional cohort study. The study cohort was comprised of all patients with ESRD who were under regular hemodialysis in National Taiwan University Hospital Hsin-Chu Branch between January of 2018 and June of 2018.

We recorded the clinical parameters of each enrolled patient when enrollment, including age, gender, history of diabetes mellitus (DM), and duration of hemodialysis, serum total cholesterol, pre-dialysis blood urea nitrogen, pre-dialysis creatinine, albumin, alkaline phosphatase (ALK-P), ferritin, intact parathyroid hormone, total calcium, phosphate, calcium-phosphorus (Ca x P) product

and Kt/V. We also collected cardiothoracic ratio (CT ratio) for heart condition evaluation. The severity of arterial stiffness was estimated by brachial-ankle pulse wave velocity (baPWV). The primary outcome was severe arterial stiffness which was defined as baPWV level more than 1800 cm/sec. Because of high association between age and baPWV, we divided the patients into younger group (age < 65 years) and elder group (age $\geq$ 65 years) to decrease the effect of age in the analysis.

For baseline characteristics, continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as frequency and percentage. For continuous variables, the differences among groups were compared using the Mann-Whitney U test. For categorical variables, the chi-squared or Fisher exact test was used. Logistic regression analysis was performed to identify determinants of severe arterial stiffness. To determine the variables of significance, we put the variables, including age, gender, DM, albumin > 3.5 gm/dl, ferritin > 500 ng/ml, kt/v>1.2, iPTH > 600 pg/ml, Ca x P > 55 mg^2/dl^2, hemodialysis vintage, ALK-P, total cholesterol and Uric acid, which were known predictors found by previous studies into multivariate regression analysis. We used IBM SPSS statistics version 24 (Armonk, NY: IBM Corp) software. A two-sided p-value < 0.05 was considered statistically significant.

Results:

We enrolled 217 patients who were under regular hemodialysis in National Taiwan University Hospital Hsin-Chu Branch between January of 2018 and June of 2018.

The mean age of all participants was 66.54 years and the proportion of male was 52.07%. In our cohort (Table 1), 117 (53.9%) patients presented with severe arterial stiffness (baPWV more than 1800 cm/sec). Comparing to the no severe arterial stiffness group, the severe arterial stiffness group were older (71.91 ± 12.14 years vs 60.25 ± 12.05 years, p<0.001), higher serum ferritin level (513.94 ± 301.36 ng/ml vs 488.93 ± 628.60 ng/ml, p=0.048), lower pre-dialysis creatinine level (10.81 ± 2.37 mg/dl vs 11.94 ± 2.63 mg/dl), higher CT ratio (0.53 ± 0.06% vs 0.49 ± 0.06%, p<0.001), and with higher prevalence of DM (65.8% vs 41.0%, p<0.001). In addition, total cholesterol level had no statistically significant difference between severe arterial stiffness group and no severe arterial stiffness group.

In multivariate logistic regression analysis (Table 2), elder age [odds ratio (OR), 1.10; 95% confidence interval (C.I.), 1.07-1.14; p<0.001) and DM (OR, 4.07; 95% C.I., 2.05-8.00; p<0.001) were able to predict severe arterial stiffness in our cohort. However, serum total cholesterol level (OR, 1.01; 95% C.I., 1.00-1.02; p=0.074) could not predict the severity of arterial stiffness in patients with hemodialysis. In the subgroup analysis, serum total cholesterol had no association with severe arterial stiffness in younger (age < 65 years) and elder groups (age≧65 years). In the younger

group, patients with Ca x P product more than 55 mg^2/dl^2 (OR, 4.37; 95% C.I., 1.28-14.92; p=0.019) had higher probability of severe arterial stiffness. In the elder group (age $\geq$ 65 years), patients with serum albumin level more than 3.5 gm/dl (OR, 3.25; 95% C.I., 1.08-9.71; p=0.035) appeared to have higher association with severe arterial stiffness.

Conclusions:

Our study showed that arterial stiffness in hemodialysis patients was significantly associated with age and DM; however, contrary to the general and HTN populations, serum total cholesterol level was not associated with the severity of arterial stiffness in our cohort. In addition, we found that C x P product which was related to the soft tissue calcification in renal insufficiency group could be the predictor of severe arterial stiffness in younger group and nutrition status had association with the severity of arterial stiffness in elder group.

Our findings may provide the information about the risk factors of arterial stiffness in patients with hemodialysis is distinct from other patient populations. Hence, it is vital that future studies focus on identifying risk factors unique to patients on hemodialysis patients and decipher the underlying mechanisms responsible for poor outcomes in patients with hemodialysis.

Table 1. Basic characteristics of hemodialysis patients with severe arterial stiffness and no severe arterial stiffness.

	All patients	Severe arterial stiffness group (PWV > 1800 cm/sec)	No severe arterial stiffness group (PWV < 1800 cm/sec)	p value
Patient number (%)	217 (100)	117 (53.9)	100 (46.1)	
Age (years)	66.54±13.40	71.91±12.14	60.25±12.05	<0.001
Male, number (%)	113 (52.1)	59 (50.4)	54 (54.0)	0.6
Diabetes, number (%)	118 (54.4)	77 (65.8)	40 (41.0)	<0.001
Dialysis Vintage (years)	7.26±5.03	6.74±4.50	7.85±5.55	0.209
Albumin (gm/dl)	3.75±0.37	3.73±0.35	3.78±0.38	0.1
ALK-P (IU/L)	103.82±92.53	108.81±100.12	97.99±87.68	0.344
Cholesterol (mg/dl)	148.10±35.59	147.31±38.70	149.03±31.74	0.282
Ferritin (ng/ml)	502.41±479.62	513.94±301.36	488.93±628.60	0.048
Pre-dialysis BUN (mg/dl)	79.11±21.77	77.56±20.63	80.92±22.99	0.289
Pre-dialysis Creatinine (mg/dl)	11.33±2.55	10.81±2.37	11.94±2.63	0.002

Total Ca (mg/dl)	9.02±0.72	9.07±0.70	8.96±0.74	0.426
P (mg/dl)	4.94±1.28	4.81±1.19	5.09±1.37	0.176
Ca x P Product (mg^2/dl^2)	44.50±12.02	43.56±11.17	45.59±12.91	0.393
Kt/V	1.43±0.20	1.43±0.19	1.43±0.21	0.783
iPTH (pg/ml)	525.70±512.61	515.81±522.54	537.41±503.03	0.793
CT ratio (%)	0.51±0.07	0.53±0.06	0.49±0.06	<0.001

All quantitative and normally distributed variables are reported as mean ± standard.

Abbreviations: ALK-P: Alkaline Phosphatase; BUN: blood urea nitrogen; Ca: calcium; CT ratio: cardiothoracic ratio; iPTH: intact parathyroid hormone; P:phosphate; PWV: pulse wave velocity.

Table 2. Baseline correlates between the risks factors of severe arterial stiffness in hemodialysis patients. Subgroups divided by age. Analysis by multivariate logistic regression.

	All patients		Age < 65 years		Age ≧ 65 years	
	Odds ratio* **(95% C.I.)**	**p value**	**Odds ratio*** **(95% C.I.)**	**p value**	**Odds ratio*** **(95% C.I.)**	**p value**
Age, per year	1.10 (1.07 - 1.14)	<0.001	1.13 (1.04 - 1.23)	0.004	1.10 (1.03 - 1.17)	0.003
Diabetes	4.07 (2.05 - 8.00)	<0.001	6.8 (2.14 - 21.28)	0.001	2.99 (1.23 - 7.30)	0.016
Cholesterol (mg/dl)	1.01 (1.00 - 1.02)	0.074	1.02 (1.00 - 1.03)	0.07		
Ca x P Product > 55 (mg^2/dl^2)			4.37 (1.28 - 14.92)	0.019		
Albumin > 3.5 (gm/dl)					3.25 (1.08 - 9.71)	0.035

* The variables which were put into in this multivariate logistic regression analysis: age, gender, DM, albumin > 3.5 gm/dl, ferritin > 500 ng/ml, kt/v>1.2, iPTH > 600 pg/ml, Ca x P > 55 mg2/dl2, HD vintage, ALP, total cholesterol and Uric acid.

Abbreviations: Ca: calcium; C.I.: confidence interval; P: phosphate.