

ORIGINAL**Serum YKL-40 Level is Associated with Geriatric Nutritional Risk Index (GNRI) and γ -GTP in Hemodialysis Patients**Kohsuke Yamada^{1,3}, Toru Hyodo², Syunichiro Urabe², Satomi Haga², and Toshio Hosaka³¹Department of Nutrition and Dietetics, Kamakura Women's University, Kamakura City, Japan, ²Dialysis Center, Eijin Clinic, Hiratsuka City, Japan, ³Graduate School of Integrated Pharmaceutical and Nutritional Sciences, University of Shizuoka, Shizuoka City, Japan

Abstract : Chitinase-3-like protein 1 (YKL-40) is a glycoprotein associated with inflammation and tissue remodeling that has recently been used as a marker of inflammation in hemodialysis (HD) patients. In this study, we aimed to determine whether YKL-40 has potential to serve as a nutritional parameter in Japanese HD patients. The serum YKL-40 concentration, hematological parameters, inflammatory marker levels, anthropometric measurements, and laboratory values were measured in 88 patients receiving HD. The geriatric nutritional risk index (GNRI) was used as a nutritional assessment tool. 45.4% of patients were malnourished. YKL-40 correlated positively with age, alkaline phosphatase, alanine transaminase and γ -glutamyl transpeptidase (γ -GTP) levels, but not with nutritional status, and correlated inversely with ankle brachial index score, a predictor of atherosclerosis. Furthermore, multiple regression analysis confirmed that γ -GTP, GNRI and age correlated with YKL-40. YKL-40 elevation was associated with γ -GTP, GNRI and age in HD patients. *J. Med. Invest.* 69:101-106, February, 2022

Keywords : YKL-40, γ -GTP, hemodialysis, malnutrition, inflammation

INTRODUCTION

Chitinase-3-like protein 1 (YKL-40) derives its name from a structure which consists of three N-terminal amino acids, tyrosine (Y), lysine (K) and leucine (L). The molecular mass of YKL-40 is 40 kDa. YKL-40 is secreted by cancer cells, macrophages and neutrophils, and is known to be involved in cell proliferation and differentiation, as well as angiogenesis and inflammation (1-5). Moreover, serum YKL-40 level increases in association with hepatopathy and fibrosis of hepatocytes (6-16). Elevated YKL-40 is associated with liver fibrosis and also with endothelial damage (14).

Hemodialysis (HD) patients are typically undernourished, and it is widely believed that prolonged malnutrition and chronic inflammation increase the risk of arteriosclerosis. Therefore, evaluation of the associations among malnutrition and inflammation is important for improving the survival of HD patients (17).

Recently, urinary YKL-40 level was reported to increase in response to tubular cell damage in acute kidney injury (18-21). In diabetic patients, plasma and urinary YKL-40 levels are associated with the progression of diabetic nephropathy (22-25). YKL-40 is also reportedly useful as an inflammation marker in HD patients (26-29). However, little is known about the association between YKL-40 and nutritional status in HD patients. Herein, we evaluated the association of YKL-40 with nutritional-related parameters in Japanese HD patients.

MATERIALS AND METHODS*Subjects*

The subjects were recruited from among HD patients at Eijin Clinic (Kanagawa, Japan), which is an outpatient facility. The study inclusion criteria were ongoing HD therapy for at least 6 months prior to enrollment and being in stable condition without co-morbidities such as heart failure, infection, cirrhosis, respiratory disease, nephrotic syndrome, malignancy, liver injury, or severe inflammation. None of the patients were perioperative or had suffered recent severe injuries. Because of the high incidence of kidney cancer in HD patients, computed tomography (CT) is routinely performed for screening. Cases suspected to have low-density fatty liver based on CT images suggesting liver injuries and disorders, including hepatitis, were excluded. In total, 88 patients (65 men, 23 women) were enrolled in the study (Figure 1). The mean age, presented as the mean \pm standard deviation (SD), was 68.5 \pm 13.5 years, and the mean HD duration was 6.2 \pm 5.8 years. The prevalence of diabetes among our subjects was 52.3%. The patients had been provided dietary

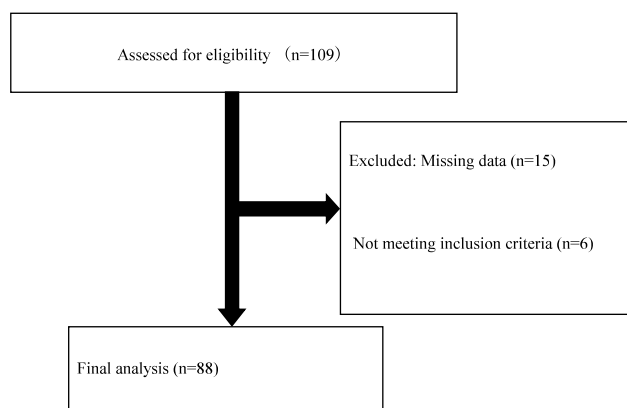


Figure 1. Flow diagram of inclusion and exclusion criteria

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Address correspondence and reprint requests to Toshio Hosaka MD, Ph.D, Graduate School of Integrated Pharmaceutical and Nutritional Sciences, University of Shizuoka, Shizuoka City, 422-8526, Japan and Fax : +81954-264-5567.

education by a dietitian.

Written informed consent was obtained from all subjects. The study protocol was approved by the institutional review board of Eijin Clinic (No.2018-01) and Kamakura Women's University (No.19014-1). The study was registered with the University Hospital Medical Information Network (UMIN) clinical trial registry (UMIN ID : UMIN000040897) and fully adhered to the guidelines of the Declaration of Helsinki.

Laboratory procedures

Blood samples were collected before the first dialysis session of the week. Serum albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine transaminase (ALT), γ -glutamyl transpeptidase (γ -GTP), urea nitrogen, uric acid, creatinine, total cholesterol, triacylglycerol levels, total ion binding capacity (TIBC), hematocrit, and lymphocyte count were determined employing standard laboratory techniques with the use of an automatic analyzer. Serum prealbumin and high-sensitivity C-reactive protein (hs-CRP) were quantified by laser nephelometry. YKL-40 and interleukin-6 (IL-6) were quantified by a double-sided sandwich-type enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems ; Minneapolis, MN, USA). We referred to the following reference value for healthy subjects : a serum YKL-40 level of 46.1 ± 19.4 ng/mL, an hs-CRP level of 0.08 - 0.17 mg/mL and an IL-6 level of 1.3 - 2.0 pg/mL (30-34). The HD dose was calculated using the following equation :

$$Kt/V_{\text{urea}} = -\ln(R - 0.008 \times t) + [4 - (3.5 \times R)] \times UF/W$$

where Kt/V is single-pool Kt/V , R is the ratio of post-dialysis to pre-dialysis serum urea nitrogen, t (in hours) is the duration of dialysis, UF is the ultrafiltrate volume (L) and W (kg) is the post-dialysis body weight (35).

Evaluation of protein intake

Dietary protein intake was measured to determine the normalized protein catabolic rate (nPCR), which was calculated using the equation published by the Kidney Disease Outcomes Quality Initiative (K/DOQI) Hemodialysis Adequacy Working Group :

$$\text{nPCR (g/kg/day)} = C_0 / [36.3 + 5.48 (Kt/V) + 53.5 / (Kt/V)] + 0.168$$

where C_0 (mg/dL) is the pre-dialysis concentration of serum urea nitrogen. The data collected during the first dialysis session of the week were used for these calculations (35).

Anthropometric measurements

Patients were weighed before and after each dialysis session and the post-dialysis body weight served as the dry weight. The body mass index (BMI) was calculated from the dry weight. Midarm circumference (MAC) was measured using an Inset-Tape (Abbott Japan Co., Ltd., Tokyo, Japan) and triceps skinfold thickness (TSF) was measured using MK-60 skinfold calipers (Yagami Co., Ltd., Aichi, Japan) on the limb not being used for vascular access. The mid-upper arm muscular area (MAMA) was calculated using the following equation :

$$\text{MAMA} = (\text{MAC} - 31.4 \times \text{TSF})^2 / 12.56$$

MAMA, MAC, and TSF were measured in cm.

The ankle brachial index (ABI) score, an index used to evaluate peripheral arterial disease, was measured using a BP-203RPEIII network arteriosclerosis detection device (Omron Healthcare, Kyoto, Japan).

Geriatric Nutritional Risk Index

The Geriatric Nutritional Risk Index (GNRI), a nutritional assessment tool for HD patients, was calculated from serum albumin concentrations and body weight using the following equation :

$$\text{GNRI} = [14.89 \times \text{serum albumin (g/dL)}] + [41.7 \times \text{body weight} / \text{ideal body weight (kg)}]$$

Body weight / ideal body weight was set to 1 when the subject's body weight exceeded the ideal body weight. Ideal body weight in this study was defined as the value calculated from the subject's height and a body mass index (BMI) of 22 (kg/m^2). Malnutrition risk was defined as a GNRI under 91.2 (36). GNRI reportedly predicts mortality in HD patients (37-39). It is thus widely used in clinical settings at present (40).

Statistical analysis

All variables are presented as the mean \pm SD. Univariate analysis was performed to examine the relationships between YKL-40 and other parameters employing Spearman's rank correlation coefficient. Multivariate analysis was performed for parameters showing significant differences. Potential confounding factors for increased YKL-40 were assessed using a multiple regression analysis model based on general variables, atherosclerosis markers and correlations with PEW ($p < 0.10$). Two-sided P values of < 0.05 were considered to be statistically significant in all analyses. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (41).

RESULTS

The basic characteristics of the study participants, some of which are analyzed by gender such as anthropometric factor, are presented in Tables 1 and 2. The serum YKL-40 level of these subjects was 157.9 ± 85.5 ng/mL. This level was more than three times that in for healthy subjects and similar to the value obtained in a prior study of HD patients. (27, 30). Protein intake was 0.83 ± 0.16 g/kg/day. The recommended protein intake is 0.9 to 1.2 g/kg/day according to the guidelines of the Japanese Society for Dialysis Therapy. The patients tended to have lower protein intake overall. In fact, 45.4% of patients were undernourished according to the GNRI. The prevalence of diabetes was 52.3% in patients (Table 3), including two patients diagnosed with diabetes after starting HD therapy. Serum YKL-40 levels did not differ significantly between the diabetic and non-diabetic groups (142.05 ± 83.75 vs 175.59 ± 86.01 , $p = 0.077$). Univariate analysis showed YKL-40 to correlate positively with age, AST, ALP and γ -GTP, but inversely with ABI (Table 4). There was a tendency toward inverse relationships between YKL-40 and MAC, TSF and GNRI, three measures that are generally found to be low in a malnourished state, although these relationships were not significant (Table 4). Prior to the multiple regression analysis, independent variables were selected by eliminating multicollinearity with a variance inflation factor over 10 (data not shown). Age, γ -GTP and GNRI were found to be independently associated with YKL-40, allowing selection of a higher coefficient of determination for the adjusted r-square (R^2) (Table 5).

DISCUSSION

A prior study detected no correlation between the serum concentration of YKL-40 and creatinine in healthy subjects (42). A hemodynamic evaluation, however, revealed decreased plasma YKL-40 concentrations in the renal vein (43). Dialysis reportedly reduced serum YKL-40 concentrations by approximately one-sixth (44). We can reasonably speculate that renal clearance of YKL-40 was reduced, resulting in systemic accumulation which in turn resulted in a YKL-40 value three times that in

Table 1. Characteristics of patients on HD

	All patients (n=88)	Male (n=65)	Female (n=23)	<i>p</i> '
Age (y)	68.5 ± 13.5	68.5 ± 12.5	68.6 ± 15.9	NS
Duration of dialysis (y)	6.2 ± 5.8	6.3 ± 6.0	5.9 ± 5.1	NS
Diabetes (%)	52.3	55.4	43.5	NS
Smoking (%)	69.5	83.3	33.3	3.420E-5
BMI (kg/m ²)	22.5 ± 3.8	22.8 ± 3.6	21.5 ± 4.3	NS
MAC (cm)	24.6 ± 3.0	25.0 ± 3.0	23.3 ± 2.5	0.020
TSF (mm)	10.6 ± 5.4	10.3 ± 5.3	11.5 ± 5.5	NS
MAMC (cm)	21.2 ± 2.9	21.7 ± 2.9	19.7 ± 2.1	0.002
ABI	1.16 ± 0.14	1.17 ± 0.15	1.13 ± 0.12	NS
GNRI	91.4 ± 5.1	92.0 ± 5.0	89.9 ± 4.8	NS
Prevalence of malnutrition by GNRI	45.4	41.3	56.5	NS
nPCR (g/kg/day)	0.83 ± 0.16	0.83 ± 0.16	0.86 ± 0.18	NS

¹Mann-Whitney U test

Table 2. Blood analysis of HD patients

	All patients (n=88)
Albumin (g/dL)	3.49 ± 0.24
Prealbumin (mg/dL)	27.0 ± 6.2
ALP (IU/L)	219.1 ± 88.6
AST (IU/L)	10.9 ± 6.9
ALT (IU/L)	11.0 ± 8.0
γ-GTP (IU/L)	24.3 ± 17.5
Urea nitrogen (mg/dL)	58.8 ± 13.6
Uric acid (mg/dL)	7.5 ± 1.6
Creatinine (mg/dL)	10.0 ± 2.6
Total cholesterol (mg/dL)	147.9 ± 28.9
Triacylglycerol (mg/dL)	107.3 ± 67.2
TIBC (mg/dL)	230.8 ± 54.2
hs-CRP (mg/dL)	0.24 ± 0.31
YKL-40 (ng/mL)	157.9 ± 85.5
IL-6 (pg/mL)	26.1 ± 17.6
Hematocrit (%)	31.1 ± 3.3

Table 3. Primary diseases leading to HD

Disease	Number of patients
Diabetic nephropathy (excluding cases of diabetes diagnosed after HD therapy)	44
Chronic glomerulonephritis	18
Renal sclerosis	16
Polycystic kidney disease	1
Cause unknown	4
Others	5

Table 4. Correlation of YKL-40 with hematological, inflammatory, nutritional and anthropometric markers

Marker	YKL-40	
	<i>p</i>	<i>r</i>
Age (y)	2.820E-5	0.431
Duration of dialysis (y)	NS	0.061
BMI (kg/m ²)	NS	-0.163
MAC (cm)	0.080	-0.198
TSF (mm)	0.056	-0.216
MAMC (cm)	NS	-0.040
ABI	1.740E-3	-0.345
GNRI	0.073	-0.194
nPCR (g/kg/day)	NS	-0.120
Albumin (g/dL)	NS	-0.092
Prealbumin (mg/dL)	NS	-0.152
ALP (IU/L)	0.045	0.214
AST (IU/L)	0.014	0.262
ALT (IU/L)	NS	-0.078
γ-GTP (IU/L)	0.021	0.246
Blood urea nitrogen (mg/dL)	NS	-0.131
Urea acid (mg/dL)	0.081	-0.187
Creatinine (mg/dL)	NS	-0.131
Total cholesterol (mg/dL)	NS	0.013
Triacylglycerol (mg/dL)	NS	-0.050
TIBC (mg/dL)	NS	-0.012
hs-CRP (mg/dL)	NS	0.114
IL-6 (pg/mL)	NS	-0.069
Hematocrit (%)	NS	0.080

Spearman's rank correlation coefficients were used

Table 5. Association between parameters and YKL-40 by multiple regression analysis

Variables	β	SE	<i>p</i>
Intercept	517.444	177.124	0.005
age	1.577	0.625	0.014
γ -GTP	1.362	0.480	0.006
GNRI	-4.291	1.630	0.010
ABI	-103.160	58.916	0.084
Gender (male)	15.580	18.568	0.404

β , partial regression coefficient ; SE, standard error. Adjusted R², 0.300 ; *p*=7.55E-6

healthy subjects.

YKL-40 levels of HD patients have been reported to be related to nutritional parameters, such as serum albumin, hemoglobin and BMI (26, 27). In this study, YKL-40 levels were not significantly associated with these traditional nutritional parameters. This difference may be due to the fact that, unlike previous reports, about half of patients in this study were undernourished by GNRI. Thus, the values for the anthropometric indices MAC (*p*=0.080) and TSF (*p*=0.056) and the nutritional assessment measure GNRI (*p*=0.073) tended to be inversely related to YKL-40. In the multiple regression analysis, GNRI was only independently associated with YKL-40 (Table 5). However, in line with previous reports, YKL-40 was related to nutritional status. In order to clarify the association between YKL-40 and anthropometric indices as markers of nutritional status in HD patients, a cross-sectional study is needed, rather than the longitudinal design of the present study.

Previous studies found YKL-40 to be either moderately or only slightly associated with inflammatory parameters (26, 27, 45, 46). In the present study, YKL-40 showed no significant association with either hs-CRP or IL-6, apparently reflecting differences in the expression or the turn-over of these factors in HD patients. The opposite tendency was observed, i.e., there was no significant difference between the YKL-40 levels in diabetic patients as compared with non-diabetic subjects, despite diabetes being related to atherosclerosis, inflammation and chronic renal failure (22). Furthermore, YKL-40 became increasingly elevated with progression of diabetic nephropathy (23-25). To our knowledge, no studies have measured YKL-40 levels in diabetic HD patients. In HD patients, another factor beyond the pathogenic factors associated with diabetes might be the influence of YKL-40 elevation itself. Previous studies have reported high YKL-40 protein expression within activated macrophages and atherosclerotic lesions, in contrast to the systemic reactions involved in hepatic synthesis of inflammatory mediators (4, 5). Previous reports have also noted that YKL-40 levels in patients on HD fluctuated from normal- to high-range values. Thus, YKL-40 elevation in patients receiving HD, as demonstrated in prior studies might have contributed to the development of hepatic disorders. In the univariate analysis, YKL-40 correlated with ALP, AST and γ -GTP. However, our study criteria specifically excluded patients with hepatic disorders, including fatty liver detected by CT, such that we cannot conclude that the observed correlation is attributable to hepatic dysfunction. Further study is required, with detailed examination and following up of the HD patients with mild forms of liver damage such as fatty liver.

In relation to chronic inflammation, previous studies have suggested that an increase in YKL-40 serum level with HD may indicate unresolved low-grade inflammation and abnormal local

tissue remodeling such as within the vessel wall (47-49). In the present study, the atherosclerosis marker ABI was significantly associated with YKL-40. However, ABI was not independently associated with YKL-40 in the multiple regression analysis. A previous study reported that γ -GTP showed a significant positive association with atherosclerosis in elderly Japanese men (50). In the present study, age and γ -GTP were independently associated with YKL-40 in HD patients. A rise in YKL-40 level with age has been described in the general population, but this is reportedly controversial in HD patients (26, 27, 30, 51). Aging was suggested to increase chronic inflammation in blood vessels (51). Blood vessel inflammation was also reported to be associated with YKL-40 levels (3-5). The precise mechanism(s) underlying the association of YKL-40 with age in the general population and, particularly, in HD patients awaits investigation of age- and inflammation-related cytokines, though it is noteworthy that CRP and IL-6 were not related to YKL-40 in our present study. γ -GTP has been reported to be associated with inflammation in patients with metabolic diseases and hepatitis C virus infections (52-54). Inflammation associated with metabolic disease may be affecting YKL-40 level. Patients in this study had a high prevalence of diabetes ; however, this prevalence was not significantly related to other factors (data not shown).

This study has limitations. First, the sample size was small. However, the size was adequate as the correlation coefficient of *r*=0.431 on the univariate analysis of YKL-40 with age, an association which has already been convincingly demonstrated, requires no more than 50 samples (26, 51). Second, this study was a cross-sectional analysis. Not only the malnutrition status of HD patients, but also the chronic worsening of inflammation and arteriosclerosis were taken into account. It is necessary to consider the relationships between YKL-40 and parameters of arteriosclerosis, including PWV, CAVI, and central blood pressure, in HD patients. A prospective study is required to examine the association of YKL-40 with additional parameters. Furthermore, longitudinal study to examine the relationships of YKL-40 with GNRI, another nutritional parameter, and nutritional disorders would allow for the assessment of a possible correlation with mortality.

In conclusion, this study found that YKL-40 elevation was associated with age, GNRI and γ -GTP in patients on HD. This suggests that YKL-40 may contribute to malnutrition and metabolic disorders such as age-related chronic inflammatory diseases, in HD patients. Further study is needed to elucidate the possible relationships of YKL-40 with other factors in the HD setting.

CONFLICT OF INTEREST

The authors have no conflicts of interest related to the content of this article.

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