ORIGINAL

Body fat mass is correlated with serum transthyretin levels in maintenance hemodialysis patients

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Abstract : Serum transthyretin (TTR), also known as prealbumin, is a reliable nutritional indicator and an independent prognostic factor for maintenance hemodialysis patients. However, we recently reported that serum TTR levels did not affect protein–energy wasting (PEW). In this study, we investigated factors affecting serum TTR levels in 60 maintenance hemodialysis patients. The patients were divided into High-TTR and Low-TTR groups according to the median serum TTR level. Albumin levels were significantly higher and C-reactive protein (CRP) levels were significantly lower in the High-TTR group than in the Low-TTR group. Although body fat mass was significantly higher in the High-TTR group than in the Low-TTR group, no significant difference in body fat ratio were observed. These findings suggest that body fat mass is related to serum TTR levels, apart from factors such as albumin and CRP levels, which showed correlations with serum TTR levels. Because body fat mass is related to better survival in maintenance hemodialysis patients, it may contribute to the prognostic value of serum TTR levels. In addition, in such patients, it may be important to evaluate body fat mass rather than body fat ratio and to maintain the minimum necessary body fat mass. J. Med. Invest. 64 : 222-227, August, 2017

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INTRODUCTION

The number of maintenance hemodialysis patients continues to increase and has become a major problem worldwide. Initiation of hemodialysis not only significantly decreases the patient's quality of life (1) but also increases national medical expenditure. One of the major factors contributing to high mortality in maintenance hemodialysis patients is malnutrition (2-4). Approximately 18%–75% maintenance dialysis patients show evidence of malnutrition, muscle wasting, body fat loss, and inflammation (5, 6).

Various terms, such as uremic malnutrition, protein–energy malnutrition, malnutrition–inflammation–atherosclerosis syndrome, and malnutrition –inflammation complex syndrome, have been used for malnutrition in patients with renal disease, resulting in some confusion (7). Therefore, the International Society of Renal Nutrition and Metabolism (ISRNM) proposed the term "protein–energy wasting (PEW)", which refers to the multiple metabolic and nutritional alterations occurring in renal disease patients, and established diagnostic criteria for PEW (7, 8).

Serum transthyretin (TTR), also known as prealbumin, is an acute-phase protein. The Nutritional Care Consensus Group recommended the evaluation of TTR levels in hospitalized patients with malnutrition risk, such as elderly patients (9). Serum TTR levels are regarded as a reliable indicator for evaluating nutritional states and the effect of nutritional intervention in maintenance hemodialysis patients ; in addition, the TTR level is one of the PEW diagnostic criteria (3, 10-12). Several studies report that serum TTR levels correlate well with survival of maintenance hemodialysis patients and provide prognostic value independent of serum albumin levels and other established predictors of mortality in this population (10, 13, 14). However, we recently reported that "decreased muscle mass" and "unintentional low dietary energy intake" were the significant differences between PEW and non-PEW patients, classified according to PEW diagnostic criteria, rather than "serum TTR of < 30 mg/dL" (15). This suggested that serum TTR levels did not affect PEW, or malnutrition status, which is contrary to the widespread belief that the correlation between serum TTR levels and survival is related to the nutritional state, which is reflected in serum TTR levels.

Hence, we speculate that factors other than nutritional status influence the correlation between serum TTR levels and survival. In this study, we investigated factors related with the serum TTR levels of maintenance hemodialysis patients.

PATIENTS AND METHODS

Subjects

All outpatients receiving maintenance hemodialysis at Iga City General Hospital for at least 6 months, and without clinical evidence of edema, ascites, inflammatory diseases, or known malignancies, were included in the study. Patients were dialyzed for 10–14 h/week using bicarbonate buffer. The clinical records of each patient were thoroughly reviewed by the collaborating physician. This study was approved by the ethical committee of Iga City General Hospital, and informed consent was obtained from all patients.

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Anthropometric measurements

Patient's height data were obtained from their clinical records. Body weights in this study refer to dry weight defined as post-dialysis weight in patients without edema. Body mass index (BMI) was calculated as dry weight (kg) divided by the square of height (m^2) and expressed in kg/m^2.

Serum chemistry

Blood samples were obtained at the first dialysis session of May 2012. All assays were performed in the hospital laboratory using routine methods. Complete blood counts were measured using a ADVIA2120 hematology analyzer (Siemens, Munich, Germany). Biochemical parameters were measured using a Hitachi 7600-020 automatic biochemical analyzer (Hitachi Ltd., Tokyo, Japan). Normalized protein catabolic rate (nPCR) (g/kg/day), which is known to be a valid surrogate for dietary protein intake, was measured using kinetic modeling. Urea clearance (Kt/V) was used for evaluation of the adequacy of dialysis.

Body composition measurements by bioelectrical impedance analysis (BIA)

BIA is a noninvasive and widely used method for measuring body composition. In this study, body composition was measured using Inbody S20 (Inbody Japan Inc., Tokyo, Japan) after dialysis. Inbody S20 is a multifrequency analyzer that uses an eight-polar tactile electrode system.

Survey of dietary intake and physical activity

Survey of dietary intake was performed in individual interviews by dietitian using three-day dietary records self-reported by the patients. The patients did not have dietary restrictions and were asked to follow their usual diet on the day before the date of measurements. Amount of energy and nutrients was calculated by Excel-Eiyokun software (Kenpakusha Co., Ltd., Tokyo, Japan)

Physical activity was assessed using Lifecorder (Suzuken Co., Ltd., Nagoya, Japan). Lifecorder is a commercially available physical activity monitor based on a uniaxial acceleration sensor.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation, and difference in means was evaluated by Student's t-test. Categorical variables were compared among groups by chi-square test. P values of < 0.05 were accepted as statistically significant. All statistical analyses were performed by JMP version 10 (SAS Institute, Cary, NC, USA).

RESULTS

Characteristics of the study population

The characteristics of study population are listed in Table 1. Subjects consisted of 60 maintenance hemodialysis patients with mean age of 66.2 ± 9.5 years, and 73% patients were male (n = 44). The mean duration of hemodialysis was 12.3 ± 8.5 years. Clinical diagnosis of end-stage renal failure was primary renal disease (60%, n = 36) and diabetic nephropathy (40%, n = 24). Ten patients (16%) were diagnosed with PEW according to the ISRNM diagnostic criteria.

Variability of serum TTR level

Figure 1 shows the variability of serum TTR levels. The mean, median, and range of serum TTR levels were 24.8 ± 6.9 mg/dL, 25.5 mg/dL (interquartile range : 20.5–30.2 mg/dL) and 6.5–41.1 mg/dL, respectively. Serum TTR levels did not differ by age, gender, hemodialysis duration, or diabetes status. However, serum TTR levels were positively correlated with serum albumin levels (r = 0.57, P < 0.0001) and were negatively correlated with C-reactive protein (CRP) levels (r = −0.49, P < 0.0001).

To investigate factors affecting serum TTR levels, patients were divided into the following two groups at the median serum TTR level : High-TTR group and Low-TTR group.

Difference of characteristics between High-TTR and Low-TTR groups

The demographic, clinical, and anthropometric characteristics of the High-TTR and Low-TTR groups are shown in Table 2. Mean age, gender, hemodialysis duration, diabetes status, PEW status, and BMI were not significantly different between the groups.

Table 1. Characteristics of the study population

	n = 60
Age (years)	66.2 ± 9.5
Gender (men / women)	44 / 16
Hemodialysis duration (years)	12.3 ± 8.5
Diabetes (diabetes / non-diabetes)	24 / 36
PEW (PEW / non-PEW)	10 / 50
Height (cm)	159.8 ± 8.9
Body weight (kg)	53.3 ± 11.0
Body mass index (kg/m^2)	20.7 ± 3.1
Skeletal muscle ratio (%)	40.3 ± 5.4
Body fat ratio (%)	24.0 ± 9.5
Kt/V	1.44 ± 0.23

PEW : protein-energy wasting
Kt/V : urea clearance

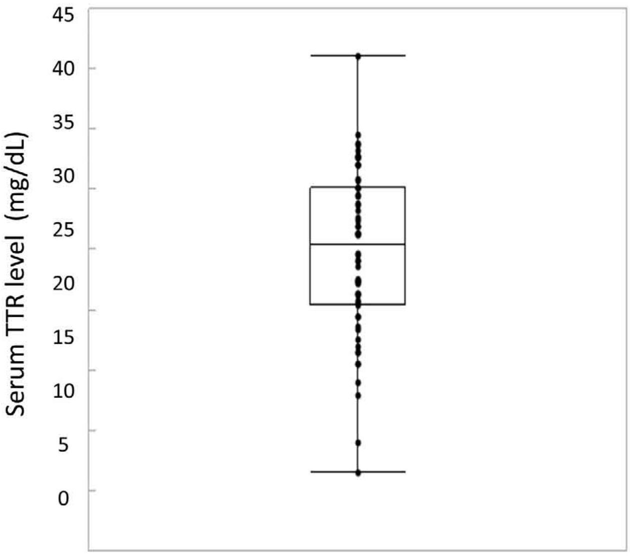

Fig. 1. Variability of serum TTR level
Box plots showing the variability of serum TTR levels in all patients (n = 60). The maximum serum TTR level was 41.1 mg/dL and the minimum was 6.5 mg/dL. The box represents the interquartile range. The upper line represents the upper quartile (75th percentile) and the lower line represents the lower quartile (25th percentile), which were 30.2 mg/dL and 20.5 mg/dL, respectively. The median serum TTR is represented by the line within the box and was 25.5 mg/dL.

However, body weight was significantly higher in the High-TTR group than in the Low-TTR group.

The biochemical characteristics are summarized in Table 3. Serum TTR levels in the High-TTR and Low-TTR groups were 30.5 ± 3.3 mg/dL and 19.2 ± 4.5 mg/dL, respectively. Albumin, blood urea nitrogen, creatinine levels, and nPCR were significantly higher and CRP levels were significantly lower in the High-TTR group than in the Low-TTR group.

Table 4 shows the body composition data. Body fat mass was significantly higher in the High-TTR group than in the Low-TTR group. Dietary intake and physical activity were not different between the High-TTR and Low-TTR groups, as shown in Table 5.

Table 2. Difference of demographic, clinical, and anthropometric characteristics between High-TTR and Low-TTR groups

	High-TTR (n=30)	Low-TTR (n=30)	*P* value
Age (years)	65.2± 6.9	67.2± 11.5	0.42
Gender (men / women)	23 / 7	21 / 9	0.56
Hemodialysis duration (years)	11.7± 7.2	13.0± 9.7	0.55
Diabetes (diabetes / non-diabetes)	12 / 18	12 / 18	1.00
PEW (PEW / non-PEW)	3 / 27	7 / 23	0.17
Height (cm)	162.0± 9.7	157.7± 7.5	0.06
Body weight (kg)	56.5± 12.4	50.1± 8.5	< 0.05
Body mass index (kg/m²)	21.4± 3.2	20.0± 2.8	0.10

PEW : protein-energy wasting

Table 3. Difference of biochemical characteristics between High-TTR and Low-TTR groups

	High-TTR (n=30)	Low-TTR (n=30)	*P* value
Total protein (g/dL)	6.6± 0.4	6.5± 0.6	0.51
Albumin (g/dL)	3.9± 0.3	3.6± 0.4	< 0.01
Transthyretin (mg/dL)	30.5± 3.3	19.2± 4.5	< 0.01
Total cholesterol (mg/dL)	150.1± 28.6	136.7± 35.0	0.12
Aspartate aminotransferase (IU/L)	13.1± 6.0	15.8± 5.5	0.07
Alanine aminotransferase (IU/L)	10.5± 4.0	11.6± 7.4	0.48
Alkaline phosphatase (IU/L)	227.4± 77.3	263.4± 136.9	0.22
Lactate dehydrogenase (IU/L)	205.4± 52.2	194.2± 31.7	0.32
Creatine phosphokinase (IU/L)	124.8± 72.6	99.2± 86.8	0.22
Blood urea nitrogen (mg/dL)	67.0± 15.1	57.3± 13.2	< 0.01
Creatinine (mg/dL)	12.2± 2.4	10.5± 3.1	< 0.05
Sodium (mEq/L)	140.6± 2.4	139.7± 3.1	0.23
Potassium (mEq/L)	4.9± 0.5	4.6± 0.8	0.11
Chloride (mEq/L)	103.9± 2.9	103.4± 3.3	0.49
Calcium (mEq/L)	9.3± 0.6	9.2± 0.5	0.75
Phosphate (mEq/L)	5.8± 1.1	5.6± 1.3	0.49
Magnesium (mg/dL)	2.3± 0.3	2.2± 0.3	< 0.05
Glucose (mg/dL)	139.4± 48.2	134.3± 34.4	0.64
C-reactive protein (mg/dL)	0.18± 0.24	0.76± 1.31	< 0.05
Iron (μg/dL)	58.5± 23.4	49.8± 19.6	0.12
Total iron binding capacity (μg/dL)	276.5± 50.5	262.4± 57.8	0.32
Ferritin (ng/mL)	115.7± 233.4	90.2± 101.9	0.58
Intact parathyroid hormone (pg/mL)	148.2± 81.7	159.8± 109.1	0.64
nPCR (g/kg/day)	0.85± 0.15	0.76± 0.13	< 0.05
Kt/V	1.43± 0.23	1.45± 0.23	0.76

nPCR : normalized protein catabolic rate
Kt/V : urea clearance

Table 4. Difference of body composition data between High-TTR and Low-TTR groups

	High-TTR (n=30)	Low-TTR (n=30)	*P* value
Intracellular water (L)	18.6± 3.5	17.1± 2.7	0.07
Extracellular water (L)	12.0± 2.1	11.5± 1.6	0.36
Protein (kg)	8.0± 1.5	7.4± 1.2	0.07
Mineral (kg)	2.8± 0.5	2.6± 0.3	0.20
Skeletal muscle mass (kg)	22.3± 4.6	20.3± 3.5	0.07
Skeletal muscle ratio (%)	39.8± 5.2	40.8± 5.6	0.45
Body fat mass (kg)	15.2± 7.5	11.5± 6.1	< 0.05
Body fat ratio (%)	25.9± 8.8	22.1± 9.9	0.12
Body cell mass (kg)	26.6± 5.0	24.5± 3.9	0.07

Table 5. Difference of dietary intake and physical activity between High-TTR and Low-TTR groups

	High-TTR (n=30)	Low-TTR (n=30)	*P* value
Dietary intake			
Energy/body weight (kcal/kg)	33.1± 8.4	32.6± 5.2	0.79
Protein/body weight (g/kg)	1.1± 0.3	1.2± 0.3	0.33
Salt (g)	6.5± 1.4	7.1± 1.8	0.13
Physical activity			
Number of steps on the days of hemodialysis session (steps/day)	3797± 3175	3915± 2936	0.91
Number of steps on the other days of hemodialysis session (steps/day)	5920± 4225	6000± 6418	0.96

DISCUSSION

Although serum TTR levels have been reported to be a reliable nutritional indicator and independent prognostic factor for maintenance hemodialysis patients (3, 10, 13, 14), we recently suggested that serum TTR levels did not affect PEW or malnutrition status (15). Therefore, we speculated that factors other than the nutritional status influence the correlation between serum TTR levels and survival. In this study, we divided 60 Japanese maintenance hemodialysis patients into two groups according to the median serum TTR level and investigated factors affecting serum TTR levels. The results suggest that body fat mass is related to serum TTR levels, apart from factors such as albumin and CRP levels, which showed correlations with serum TTR levels.

TTR is a 5.5-kDa homotetrameric protein mainly synthesized in the liver ; it has a rapid turnover rate, short half-life (1.9 days), high tryptophan content, and small pool size (16). TTR is reported to correlate well with albumin and CRP, because its synthesis in the liver decreases in inflammatory states (10, 12, 14). In this study, serum TTR levels were positively correlated with serum albumin levels and were negatively correlated with serum CRP levels, which is consistent with the findings of previous studies.

The main function of TTR is to transport the thyroid hormone thyroxine and retinol (vitamin A) (10). TTR binds thyroxine directly and transports it to target cells. On the other hand, retinol is transported indirectly through retinol-binding protein 4 (RBP4). TTR transports retinol to target cells by binding to retinol–RBP4 complex. RBP4 is 21-kDa protein mainly synthesized in adipocytes. Considering that RBP4 has a lower molecular weight than albumin and is filtered in the glomeruli, serum RBP4 levels increase as renal function decreases (17). Noel *et al.* showed that serum RPB4 levels were approximately three times higher in hemodialysis patients than in healthy controls (18). They also found increased total TTR levels and RBP4-bound TTR levels and decreased free TTR levels in hemodialysis patients than in the control group. The decrease in free TTR levels indicates the reduction in TTR catabolism. Thus, they concluded that combination of increased serum RBP4 levels, increased of RBP4-bound TTR levels, and decreased free TTR levels is related to elevated serum TTR levels in dialysis patients. Recently, Alessio *et al.* reported that there is a strong positive association between serum RBP4 levels and body fat mass, especially the visceral fat mass, in maintenance hemodialysis patients (19). As described above, the relationship between RBP4 and TTR and that between RBP4 and body fat mass has been studied. These previous studies may explain the significantly higher body fat mass of the High-TTR group than that in the Low-TTR group. That is, RBP4 may contribute to the relationship between TTR and body fat mass. In dialysis patients with high body fat mass, serum TTR levels are considered to be increased beyond the typical increase seen in general dialysis patients because of the increased RBP4 production in adipocytes. However, it is unknown whether serum RBP4 levels were higher in the High-TTR group than in the Low-TTR group because serum RBP4 levels were not measured in this study.

In maintenance hemodialysis patients, mortality risk factors established in the general population, such as overweight (BMI > 25 kg/m^2) and hypercholesterolemia, are related to better survival. This paradoxical phenomenon is referred to as "reverse epidemiology" (20). The relationship between body fat mass and mortality is an example of reverse epidemiology. Kakiya *et al.* measured body fat mass of 808 Japanese maintenance hemodialysis patients using dual-energy X-ray absorptiometry and revealed that higher fat mass index (kg/m^2) was related to lower mortality risk, especially noncardiovascular disease mortality (21). Noori *et al.* and Huang *et al.* reported similar results (22, 23). They evaluated body fat mass measured by near-infrared interactance and triceps skinfold thickness, respectively. Furthermore, Kalantar-Zadeh *et al.* showed that not only a low baseline body fat mass but also fat loss over time was associated with higher mortality (24). The results of these studies, including the Japanese study, consistently show that body fat mass confers a survival advantage in maintenance hemodialysis patients. In this study, body fat mass was related to serum TTR levels. Therefore, the survival advantage of body fat mass may contribute to the prognostic value of serum TTR levels in maintenance hemodialysis patients.

Although the mechanisms by which body fat confers a survival advantage to maintenance hemodialysis patients are unclear, we speculate that the characteristic functions of adipose tissue may play a protective role. One of these functions is energy storage. Maintenance hemodialysis patients are in a sustained inflammatory state as a result of dialysis treatment, and they are exposed to chronic catabolic stress. When a patient is ill, such as infection, energy consumption increases as part of the recovery process. Because fat is a more efficient energy source than carbohydrate and protein, higher body fat mass permits more energy storage in the body. Therefore, maintenance hemodialysis patients with high fat mass seem to have a better chance to survive. Another characteristic function is adipocytokine secretion. Adipose tissue secretes both proinflammatory and anti-proinflammatory cytokines. Proinflammatory cytokines include interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), and anti-proinflammatory cytokines include adiponectin. In the general population, increases in body fat mass causes increases in proinflammatory cytokine levels and decreases in anti-proinflammatory cytokine levels. However, in maintenance hemodialysis patients, it is reported that there is no difference in proinflammatory cytokines based on body fat mass, and the inverse relationship between body fat mass and plasma adiponectin levels are no longer significant (21, 24, 25). Such changes in adipocytokine profile may be related to survival advantage in maintenance hemodialysis patients. Zoccali *et al.* showed that maintenance hemodialysis patients have plasma adiponectin levels that are two to three times higher than the healthy population, and increased plasma adiponectin levels were a significant inverse predictor of cardiovascular disease outcomes (26). Adiponectin is an adipocytokine that protects against atherosclerosis and insulin resistance. Thus, an increase in plasma adiponectin levels appears to play important role in better outcomes for maintenance hemodialysis patients. However, it was recently reported by Rhee *et al.* that higher adiponectin levels are associated with a threefold higher all-cause mortality risk (27). These two findings suggest that although an increase in adiponectin levels has a beneficial effect for maintenance hemodialysis patients, the effects are limited only to cardiovascular system. Further studies are needed to explain the mechanisms by which body fat confers a survival advantage for maintenance hemodialysis patients.

Finally, in this study, a significant difference in body fat mass was observed between the High-TTR and Low-TTR groups, whereas no significant difference in body fat ratio was confirmed. Because body fat ratio (%) is the ratio of body fat mass to body weight, patients with the same body fat ratio but different body weights have different body fat mass (kg). Therefore, it is considered important to evaluate body fat mass rather than body fat ratio and to maintain the minimum necessary body fat mass in maintenance hemodialysis patients.

The present study has some limitations. First, the present study's findings are limited the observational design ; that is, the association can be established but causality cannot be concluded. Intervention studies are needed to demonstrate causality between serum TTR levels and body fat mass. Second, the sample size was small. Although all patients in the dialysis facility were enrolled, patient number was limited because of the use of a single facility. Third, the influences of confounding factors were not excluded. In this study, mean age, gender, and diabetes status were not significantly different between the High-TTR and Low-TTR groups ; however, several studies have reported that these factors affect serum TTR level (3, 14, 28). In addition, nPCR, which is known to be a valid surrogate for dietary protein intake, was significantly different between the High-TTR and Low-TTR groups. On the other hand, protein intake of dietary record was not significant difference between these two groups. The reason for the different findings remains unclear. Thus, to confirm whether the association between serum TTR levels and body fat mass is independent, it is necessary to evaluate more patients and to perform multivariate analyses.

In conclusion, this study showed that body fat mass was correlated with serum TTR levels in maintenance hemodialysis patients. Because body fat mass is related to better survival in maintenance hemodialysis patients, body fat mass may contribute to the prognostic value of serum TTR levels. The results of this study may be important for improving the prognosis of maintenance hemodialysis patients, although this needs to be confirmed by further study.

CONFLICT OF INTEREST STATEMENT

None declared.

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