Original Article

Associations of decreased serum transthyretin with elevated high-sensitivity CRP, serum copper and decreased hemoglobin in ambulatory elderly women

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Background: Transthyretin (TTR), a sensitive indicator of malnutrition and inflammation, has been shown to be associated with mortality in elderly population. **Methods:** We examined relationships between serum TTR and a range of risk factors for mortality in 185 free-living elderly women. Blood was drawn between breakfast and lunch. **Results:** TTR was correlated negatively with age (r= -0.30, p<0.001). After controlling for age, TTR was negatively associated with log high-sensitivity CRP (hsCRP) and serum copper. It was positively associated with albumin, serum iron and hemoglobin. In addition, TTR was positively correlated with systolic and diastolic blood pressure and postprandial triglyceride (TG). In multiple regression analysis for TTR as a dependent variable, hemoglobin (standardized β, 0.244), serum copper (standardized β, -0.134), postprandial TG (standardized β, 0.223) and log hsCRP (standardized β, -0.190) emerged as determinants of TTR independently of age, albumin, serum iron, systolic and diastolic blood pressure, and explained 22.8% of TTR variability. **Conclusions:** Subclinical low-grade inflammation, elevated serum copper and decreased hemoglobin were associated with decreased serum TTR in community-living elderly Japanese women and may represent important confounders of the relationship between low TTR and mortality in the elderly. The positive association of TTR with postprandial TG warrants further investigation.

Key Words: copper, low-grade inflammation, hemoglobin, postprandial triglyceridemia, transthyretin

INTRODUCTION

The rapid increase in the prevalence of older persons in the general population has been accompanied by substantial interest in identifying those biomarkers which are able to predict functional decline and mortality in the elderly.[1] Among the biomarkers which predict mortality in the elderly population, C-reactive protein (CRP), an inflammatory marker, and serum albumin, a laboratory variable commonly used to assess nutritional status, seem to play a major role.[2-4]

Transthyretin (TTR), formerly referred to as prealbumin, is known as a sensitive indicator of inflammation and malnutrition.[5-7] Previous studies have demonstrated that decreased TTR levels were associated with mortality in dialysis patients.[8-12] It has been shown that decreased TTR levels were strongly associated with an increased risk of early death in apparently healthy community-dwelling older persons as well.[13] Women compared with men and older compared with younger persons had lower TTR.[6,14] We, therefore, examined relationships between TTR and traditional and non-traditional risk factors for mortality in community-living Japanese elderly women.

PARTICIPANTS AND METHODS

We examined 185 women, in whom TTR data were available, out of 202 free-living elderly Japanese women whose details have recently been reported.[15] They were all Japanese, were able to walk freely and were residents in Nishinomiya, Hyogo, Japan. There was no difference in anthropometric, hematological and biochemical variables between the 185 and the remaining 17 women (data not shown). None of the subjects had cancer, or clinical diagnosed acute or chronic inflammatory diseases. This research followed the tenets of the Declaration of Helsinki. The design of this study was approved by the Ethical Committees of Mukogawa Women's' University and written informed consents were obtained from all participants.

Anthropometric indices and blood pressure were measured between breakfast and lunch and following which

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Manuscript received 30 June 2014. Initial review completed and accepted 03 July 2014.
doi: 10.6133/apjcn.2015.24.1.18

blood samples were obtained from the cubital vein. Fat mass, grip strength and blood pressure were measured, as previously reported.[15] Plasma glucose, serum insulin, lipids and lipoproteins were assayed as previously reported.[16,17] Serum levels of albumin, TTR, zinc, iron and copper were measured as previously reported.[11] Adiponectin, leptin and hsCRP were assayed by respective commercially available kits as previously reported.[16,17] Complete blood cell count was analyzed using an automated blood cell counter (Sysmex XE-2100, Sysmex, Kobe, Japan).

Serum creatinine was measured enzymatically using an autoanalyzer (AU 5200, Olympus, Tokyo, Japan). The estimated glomerular filtration rate (eGFR) was determined using the equation recommended by the Japanese Society for Nephrology[18] and participants with eGFR<60 mL/min·1.73 m^2 was considered as having chronic kidney disease (CKD). Women with hemoglobin level<12 g/dL were considered as anemic.[19]

Data were presented as mean±SD unless otherwise stated. Due to deviation from normal distribution, hsCRP was logarithmically transformed for analysis. Differences in frequencies of conditions were analyzed by Chi-square tests. Differences among 3 groups were analyzed using analysis of variance. When *p* values in analysis of variance were $p<0.05$, Bonferroni's multiple comparison procedure was performed. Bivariate correlations were evaluated by Pearson correlation analysis. Stepwise multiple regression analyses were performed to further identify the most significant variables contributing to the variation of TTR. A two-tailed $p<0.05$ was considered statistically significant. All calculations were performed with SPSS system 15.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

As previously reported,[15] participants had a low prevalence of underweight (BMI<18.5 kg/m^2) and hypoalbuminemia (albumin<3.5 g/dL) and they had prevalence of anemia and CKD similar to Japanese women aged 70 and older in the general population. TTR averaged 27.3±5.4 mg/dL, a figure which is within the reference range of women aged 60 years and older.[6]

Serum TTR was associated negatively with age and positively with grip strength, diastolic blood pressure (BP) and total cholesterol (Table 1). In addition, TTR was associated positively with post-meal TG, serum zinc and iron and negatively with serum adiponectin, copper, log hsCRP and TNF-α. Further, it showed positive associations with red blood cell count (RBC), hemoglobin (Hb) and hematocrit (HCT). After adjustment for age (Table 1), the association of Zn with systolic BP became sig-

Table 1. Anthropometric and biochemical characteristics of 185 free-living elderly women studied and correlation coefficients of serum transthyretin

Variables	Mean±SD	Transthyretin	
		Simple	Partial
Age (years)	76.3±8.2	-0.304***	adjusted
BMI (kg/m^2)	22.5±3.1	0.046	-0.015
Body fat percentage (%)	31.8±7.1	0.002	-0.030
Abdominal girth (cm)	86.5±9.3	0.050	-0.002
Handgrip strength (kg)	20.4±5.3	0.312***	0.156
Systolic BP (mmHg)	143±22	0.133	0.202*
Diastolic BP (mmHg)	84±13	0.210**	0.256**
Transthyretin (mg/dL)	27.3±5.4	1.00***	1.00***
Albumin (g/dL)	4.4±0.3	0.377***	0.291**
Plasma glucose (mg/dL)	100±29	-0.051	-0.066
Insulin (μU/mL)	8.3±7.5	-0.001	0.027
Total cholesterol (mg/dL)	219±31	0.158*	0.079
HDL-cholesterol (mg/dL)	64±14	0.099	0.046
Post-meal TG (mg/dL)	142±79	0.260***	0.235**
Serum creatinine (mg/dL)	0.69±0.15	0.001	0.102
eGFR (mL/min·1.73m^2)	65±13	0.050	-0.111
Iron (μg/dL)	94±28	0.227**	0.276**
Copper (μg/dL)	109±15	-0.201**	-0.235**
Zinc (μg/dL)	78±12	0.195**	0.117
hsCRP (μg/dL)	85±109	-0.208**	-0.278**
log hsCRP	1.7±0.4	-0.188*	-0.245**
TNF-α (pg/mL)	1.6±1.0	-0.198**	-0.130
Leptin (ng/mL)	7.7±4.7	0.121	0.086
Adiponectin (μg/mL)	14.1±7.8	-0.190**	-0.070
PAI-1 (ng/mL)	26.5±16.5	0.085	0.095
Leukocytes (×10^3/μL)	6.1±1.6	0.157*	0.107
Red blood cells (×10^4/μL)	424±38	0.339***	0.259**
Hemoglobin (g/dL)	12.9±1.2	0.317***	0.246**
Hematocrit (%)	40.9±3.4	0.302***	0.224*
Platelets (×10^4/μL)	22.9±5.6	0.147*	0.089

BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate; hsCRP: high-sensitivity C-reactive protein; TG: triglyceride; TNF-α: tumor necrosis factor-α; PAI-1:plasminogen activator inhibitor-1. Blood was drawn between breakfast and lunch.
*, $p<0.05$, **, $p<0.01$, ***, $p<0.001$.

Table 2. Multiple regression analysis for serum transthyretin as a dependent variable in community-dwelling elderly women

	Standardized β	*p* value	Cumulative R^2
Hemoglobin	0.244	0.002	0.096
Serum copper	-0.134	0.066	0.140
Age	-0.185	0.009	0.182
TG	0.223	0.002	0.205
log hsCRP	-0.190	0.012	0.228

As independent variables, age and all parameters were included that showed significant associations with transthyretin in partial correlation analysis in Table 1; hemoglobin, serum copper, age, post-breakfast TG, log hsCRP and serum iron. Abbreviations are the same as in Table 1.

Table 3. Anthropometric, biochemical and hematological characteristics of elderly women grouped according to tertiles of serum transthyretin

	Transthyretin		
	Low	Medium	High
Range (mg/dL)	15.0-25.4	25.5-29.1	29.2-49.0
Variables	n=60	n=62	n=63
Age (years)	79.2±6.3[a]	75.2±8.2[b]	75.0±9.3[b]
BMI (kg/m^2)	22.5±3.4	22.2±3.0	22.7±3.0
Body fat percentage (%)	31.9±7.5	31.5±7.1	31.6±6.8
Abdominal girth (cm)	85.8±10.0	85.3±8.8	87.9±8.8
Handgrip strength (kg)	18.2±4.6	20.9±5.3	21.4±5.6
Systolic BP (mmHg)	141±21[a]	143±23[ab]	149±22[b]
Diastolic BP (mmHg)	83±13[a]	82±13[a]	90±13[b]
Transthyretin (mg/dL)	21.7±2.7[a]	27.2±1.0[b]	32.6±3.5[c]
Albumin (g/dL)	4.3±0.3[a]	4.4±0.2[b]	4.5±0.2[b]
Plasma glucose (mg/dL)	105±43	96±19	98±20
Insulin (µU/mL)	9.4±8.8	7.6±8.3	8.2±5.6
Total cholesterol (mg/dL)	210±32[a]	225±32[b]	220±29[ab]
HDL-cholesterol (mg/dL)	60±13[a]	63±14[ab]	67±15[b]
TG (mg/dL)	119±51[a]	150±89[b]	150±84[b]
Serum creatinine (mg/dL)	0.71±0.17[ab]	0.65±0.11[a]	0.71±0.17[b]
eGFR (mL/min·1.73 m^2)	63±12[a]	68±12[b]	64±14[ab]
Iron (µg/dL)	88±24[a]	91±27[ab]	101±31[b]
Copper (µg/dL)	113±18[a]	109±15[ab]	106±12[b]
Zinc (µg/dL)	73±10[a]	80±12[b]	78±10[b]
hsCRP (µg/dL)	111±142[a]	87±102[ab]	55±68[b]
log hsCRP	1.8±0.5[a]	1.7±0.4[a]	1.6±0.4[b]
TNF-α (pg/mL)	2.0±1.4[a]	1.5±0.7[b]	1.5±0.7[b]
Leptin (ng/mL)	7.3±4.6	6.9±4.0	8.4±5.4
Adiponectin (µg/mL)	15.6±9.0	13.8±7.9	13.0±6.5
PAI-1 (ng/mL)	24.4±11.4	24.0±10.6	26.0±13.1
Leukocytes (×10^3/µL)	5.9±1.7	6.2±1.5	6.3±1.5
Red blood cells (×10^4/µL)	408±30[a]	427±35[b]	434±37[b]
Hemoglobin (g/dL)	12.4±0.8[a]	12.9±1.1[b]	13.2±1.3[b]
Hematocrit (%)	39.5±2.6[a]	41.2±3.4[b]	41.8±3.7[b]
Platelets (×10^4/µL)	22.0±6.5[a]	24.3±5.1[b]	23.1±5.3[ab]

Data are means±SD. Abbreviations are the same as in Table 1. Means not sharing common alphabetical letters are significantly different each other at $p<0.05$ or less.

nificant. Associations remained significant with diastolic BP, post-meal TG, serum iron, copper, log hsCRP, RBC, Hb and HCT. There was no association between TTR and BMI, percentage fat mass, abdominal girth and serum leptin.

Stepwise multiple regression analysis for TTR as a dependent variable was conducted which included age (Table 2). The independent variables that showed significant associations with TTR, after controlling for age, included hemoglobin, serum copper, post-breakfast TG, log hsCRP and serum iron (Table 2). Independent determinants of serum TTR were age, Hb, serum copper, postprandial TG and log hsCRP. These 5 variables explained 22.8% of TTR variability.

Elderly women were divided into 3 groups according to tertiles of TTR in order to confirm associations of TTR (Table 3). Women in the lowest compared with the highest third of TTR were older, had lower serum albumin and systolic and diastolic BP. In addition, they had lower serum TG and HDL cholesterol. Further, they had higher log hsCRP, TNF-α and serum copper, and lower serum iron and zinc. Finally, they had lower RBC, Hb, HCT. However, there was no difference in the prevalence of anemia (25.0%, 24.2% and 14.3% in the low, median and high TTR tertile, respectively, p=0.26). After taking into accounting age, differences remained significant in di-

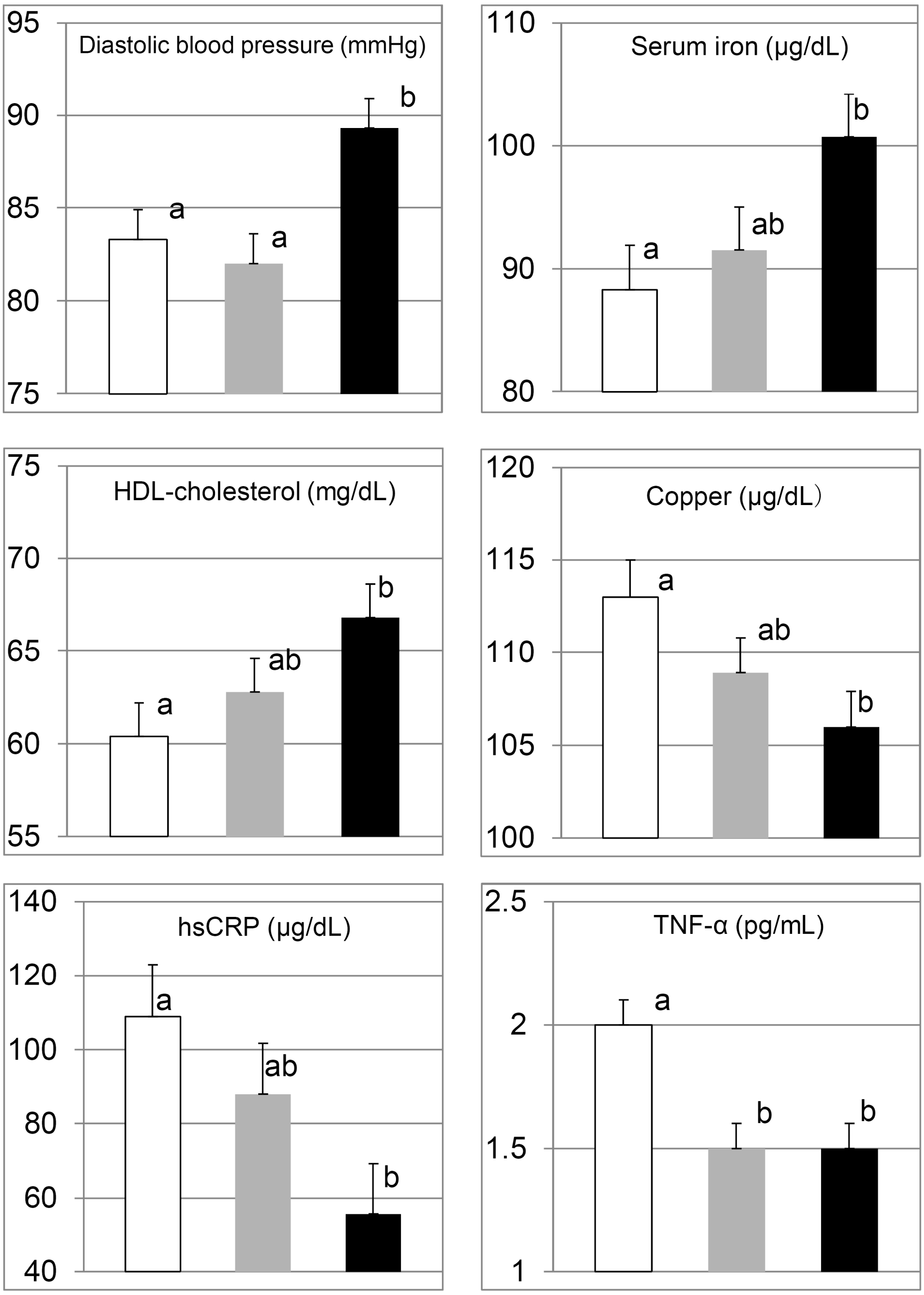

Figure 1. Characteristics of elderly women in the bottom (white columns), median (grey columns) and top (black columns) tertile of transthyretin. Data were adjusted for age and are expressed as mean±SE. Means not sharing common alphabetical letters are significantly different each other at $p<0.05$ or less.

astolic BP, HDL cholesterol, serum iron, copper, log hsCRP and TNF-α (Figure 1).

DISCUSSION

The present study has demonstrated that decreased TTR was independently associated with elevated serum copper, hsCRP and post-meal TG and decreased Hb in apparently healthy ambulatory elderly women. It is noted that these findings were observed in community-living elderly women who had few indicators of disease, such as a low BMI and hypoalbuminemia, which are usually considered hallmarks of malnutrition and frailty[20] and in whom prevalence of anemia and CKD were similar to Japanese women aged 70 and older in the general population.

The plasma concentration of TTR is decreased during clinical inflammation such as infection, and it is a well-characterized, negative, acute-phase protein.[5,6] Inverse association of TTR with CRP has been reported in chronic dialysis patients.[21] In the present study of community-living elderly women where those with cancer, clinical diagnosed acute or chronic inflammatory diseases were excluded, TTR was associated inversely and independently with hsCRP. This finding suggests that TTR may be a very sensitive marker of subclinical low-grade inflammation. Elevated hsCRP has been shown to be associated with higher CVD mortality in Japanese whose median CRP levels are low by western standards.[22]

In the present study, the concentration of TTR was positively correlated to the concentration of Hb independently of hsCRP in community-living elderly women. Although some studies found an association between TTR and Hb in Japanese centenarians[23] and dialysis patients,[24] they did not measure markers of inflammation. As proposed by Hirose et al,[23] TTR has been shown to represent an indicator of total body nitrogen metabolism as well as nutritional status[24] and moderately severe protein deprivation significantly impairs erythropoiesis.[25] Therefore, it may be reasonable to assume that people with decreased TTR may have decreased Hb. Anemia and decreased Hb concentrations were independently associated with increased mortality in the Cardiovascular Health Study, a prospective cohort study with 5888 community-dwelling elderly people.[26]

Serum copper is elevated during aging[27] and in patients with cardiovascular disease.[28] Elevated serum copper is associated with increased risk for cardiovascular mortality.[29]

We and others have shown that serum copper was positively related to hsCRP in community-dwelling elderly people.[15,30] In the present study, serum copper was associated with TTR independently of hsCRP in community-dwelling elderly people. In a population of stable dialysis patients, ceruloplasmin has been re-ported to be related to CRP (r=0.4; p<0.001) and copper (r=0.96; p<0.001), but the authors did not report on the association between serum copper and TTR.[21] No correlation between serum copper and TTR was seen in HIV-infection patients[31] and newborn infants requiring parenteral nutrition.[32] We have no explanation for the association between TTR and serum copper.

TTR, a protein loosely associated with chylomicrons,[33] has been identified as being involved in mediating the stimulatory effect of chylomicrons on production of acylation-stimulating protein (ASP) in adipocytes.[33,34] ASP is a potent stimulator of TG synthesis in human adipocytes,[35] and plays important roles in clearance of TG in chylomicrons from plasma and fatty acid storage in adipose tissue. [33] Previous studies on postprandial TG clearance in normal healthy subjects have indicated that fasting ASP positively correlates with TG area under the curve during a high fat meal, where higher ASP levels are associated with inefficient TG clearance.[36] Taken together, these findings may be in line with our observation that TTR was independently and positively associated with postprandial TG in elderly women.

Several limitations of the present study must be acknowledged. The cross-sectional design did not allow causal relationship. The recruitment procedure may also have some potential impact on the results. As the participation was voluntary, women who pay more attention to health may have been more likely to participate. Participants were recruited from one area in Japan. Those on medication for cardiovascular diseases were excluded. Therefore, the generalization of the results is limited. Biochemical parameters were measured only once and blood was taken between breakfast and lunch, which may have influenced the results. We did not have detailed information on drugs and supplements, which may contain trace element metals.

In conclusion, subclinical low-grade inflammation, elevated serum copper and decreased hemoglobin were associated with decreased serum TTR in community-living elderly Japanese women and may represent important confounders of the relationship between low TTR and mortality in the elderly. Whether decreased serum TTR is related more to nutrition or to disease remains controversial and, especially among older people, it is difficult to distinguish the effects of underntrition from those of disease. Positive association of TTR with postprandial TG warrants further studies.

ACKNOWLEDGEMENTS

We are indebted to all the participants for their dedicated and conscientious collaboration. This study was supported by KAKENHI (21300260) of a Grant-in-Aid for Scientific Research (B) from Japan Society for the Promotion of Science.

AUTHOR DISCLOSURES

No potential conflicts of interest were disclosed.

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老年女性血清甲状腺素降低与升高的高敏 C 反应蛋白和血清铜以及降低的血红蛋白之间的关系

背景：甲状腺运载蛋白（TTR）是反映营养不良和炎症的一个敏感指标，已被证实与老年人口死亡率有关。**方法：**我们研究了 185 名独立生活的老年妇女血清 TTR 和一系列死亡风险因素之间的关系。血液在早餐和午餐之间抽取。**结果：**TTR 与年龄呈负相关（r=-0.30，*p*<0.001）。在控制了年龄因素后，TTR 与高敏 C 反应蛋白（hsCRP）的对数和血清铜呈负相关，与白蛋白、血清铁、血红蛋白呈正相关。此外，TTR 与收缩压、舒张压、餐后甘油三酯（TG）呈正相关。在以 TTR 为因变量的多元回归分析中，独立于年龄、白蛋白、血清铁、收缩压和舒张压，血红蛋白（标准化 β，0.244）、血清铜（标准化 β，- 0.134）、餐后 TG（标准化 β，0.223）和高敏 C 反应蛋白对数（标准化 β，0.190）解释了 TTR 变率的 22.8%。**结论：**亚临床轻度炎症，升高的血清铜和降低的血红蛋白可能与日本社区老年妇女血清 TTR 下降有关，并且有可能是老年人低浓度 TTR 和死亡率关系的混杂因素。TTR 与餐后 TG 值的相关性有待进一步研究。

关键词：铜、轻度炎症、血红蛋白、餐后甘油三酯血症、甲状腺素